Chapter 19

SEXUALLY TRANSMITTED DISEASES

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INTRODUCTION

Field medical officers are likely to encounter sexually transmitted diseases (STDs)—a diverse group of infections caused by bacterial, chlamydial, and viral pathogens—in an active-duty population of men and women. Worldwide, STDs account for millions of patient visits to health clinics and serious perinatal complications, and expose sexual partners to the risk of infection with the human immunodeficiency virus (HIV). STDs share several common characteristics[1]:

- they are infectious,
- they spread predominately by sexual activity,
- the usual presentation is in the anogenital area, and
- infection does not confer lifelong immunity.

Genital ulcer disease is a subset of STD in which patients present with ulcers on the genitalia or perineum. This subset includes syphilis, chancroid, granuloma inguinale, lymphogranuloma venereum, and genital herpes. In the United States, genital herpes is the most common cause of genital ulcer disease, accounting for 60% to 70% of ulcer disease in patients attending an STD clinic. In 1991, there were more than 250,000 visits to healthcare providers for genital herpes. Syphilis, the second-most-common cause of genital ulcer disease, was responsible for 10% to 20% of visits to STD clinics. In 1991, approximately 43,000 cases of primary and secondary syphilis were reported. Fewer than 10% of STD visits were for chancroid, with the remaining visits due to infection with lymphogranuloma venereum, granuloma inguinale, and miscellaneous conditions.[2]

Elsewhere in the world, chancroid accounts for more than half of all cases of genital ulcer disease, and the disease is closely linked to prostitution and drug abuse. Syphilis accounts for 10% to 20% of cases; genital herpes for fewer than 10%; and lymphogranuloma venereum, granuloma inguinale, and others account for the remainder.[2]

The evaluation of genital ulcer disease is difficult even for experienced clinicians, and the limited diagnostic tests and laboratory support in dispensaries and field medical units make accurate diagnosis even more difficult. However, important clinical clues can enable medical officers to be more certain of their diagnoses (Table 19-1 and Figure 19-1).

Many of the bacterial and vial pathogens involved in STDs are able—by mechanisms that remain to be elucidated—to successfully evade the host's (ie, the individual human's) immune system. This may lead to chronic, progressive disease, as in lymphogranuloma venereum or tertiary syphilis; recurrent episodes of disease, as in genital herpes; or asymptomatic carrier states, as in gonorrhea and chancroid. Additionally, persistence of infection my be due to many factors, including antibiotic resistance, ineffective or inappropriate treatment, an immunologically impaired host, or lack of available treatment.

Risk factors and *risk behavior* have replaced the term *risk groups* to describe an activity or behavior that has a significant association with the acquisition of STD (Exhibit 19-1). The worldwide spread of infection with HIV has focused much attention on these behaviors because unprotected sexual intercourse, multiple sexual partners, prostitution, and intravenous drug abuse significantly increase the risk of transmission of the HIV virus.[1] It is the responsibility of healthcare providers to do more than simply treat STDs. Not only individual soldiers but also the chain of command must be educated and reeducated on risk factors and behaviors and, when necessary, must make attempts to modify them.

International travel permits rapid mobility of large groups of individuals, with the result that diseases previously thought to be local or regional phenomena suddenly appear in areas far removed from the source. Likewise, microorganisms carry their antibiotic susceptibility profiles with them; as a result, an antibiotic-resistant strain of diseases such as gonorrhea or chancroid from the Philippines or the Middle East may appear abruptly. Clearly, a thorough history, careful contact tracing, laboratory confirmation of antibiotic sensitivities, and follow-up cultures are essential to ensure that appropriate therapy is provided and that the disease is eradicated.

This chapter does not address acquired immunodeficiency syndrome (AIDS) and HIV infection as STDs per se for the following reasons:

TABLE 19-1

RELATIVE FREQUENCY OF CLINICAL FEATURES OF GENITAL ULCER DISEASE

1+: 0%–25%; 2+: 25%–50%; 3+: 50%–75%; 4+: 75%–100%; 1°: primary; 2°: recurrent.

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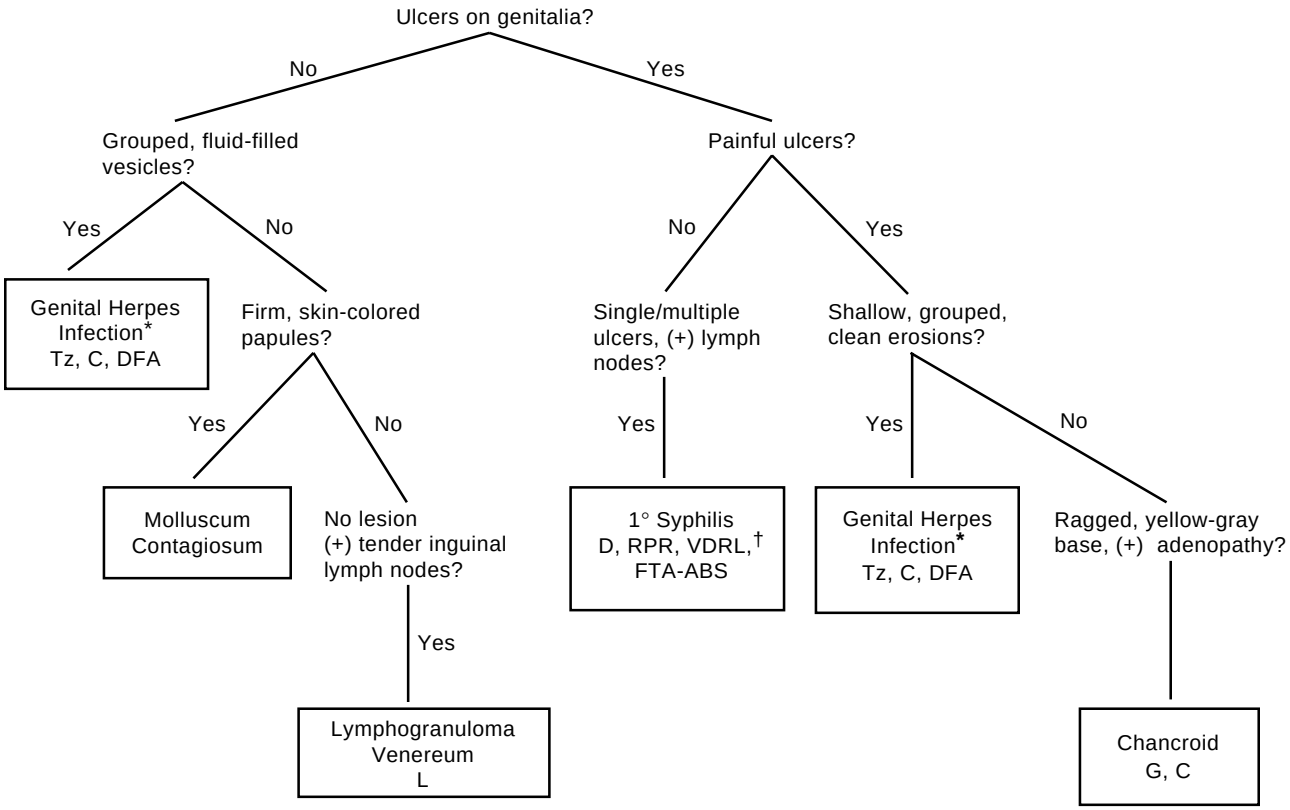

*patients with genital herpes infection can present both with and without ulcers
†RPR and VDRL may be negative in early syphilis
(+): positive
C: culture
D: dark-field microscopy
DFA: direct fluorescent antibody
FTA-ABS: fluorescent treponemal antibody absorption
G: Gram's stain
L: serology for lymphogranuloma venereum
RPR: rapid plasma reagin test
Tz: Tzanck prepreparation
VDRL: Venereal Disease Research Laboratory test

Fig. 19-1. A field algorithm for diagnosing genital ulcer disease.

EXHIBIT 19-1

RISK FACTORS AND RISK BEHAVIORS FOR SEXUALLY ACQUIRED DISEASES

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- HIV-positive military personnel are not deployed;
- there are no recognizable cutaneous signs and symptoms of early HIV infections;
- the cutaneous manifestations of AIDS are usually late signs (this chapter focuses on acute, treatable STDs that have signs and symptoms that allow the medical officer to make a definite or probable diagnosis); and
- because HIV infection and AIDS are complicating and exacerbating factors in other STDs and also in other cutaneous diseases (eg, tuberculosis and leprosy), they are discussed briefly in this and other chapters throughout the book.

MILITARY IMPACT OF SEXUALLY TRANSMITTED DISEASES

Among U.S. Army personnel during World War I, STDs accounted for 6,804,818 lost duty days and the discharge from active duty of more than 10,000 men.[3] As a cause of disability and absence from duty, STDs ranked second only to influenza in this conflict. During World War II, the different theaters varied widely in the impact of STDs on military personnel. Worldwide, between the years 1941 and 1945, the incidence of STDs in U.S. Army personnel was about 43 cases per 1,000 individuals.[4] The impact of these figures can be appreciated in a report issued early in World War II that addresses the critical problem of sulfonamide-resistant gonorrhea among U.S. military personnel during the early period of the war:

> Circular Letter No. 86, Office of The Surgeon General, 18 August 1942, … designated eight named general hospitals as fever therapy centers....
>
> These eight hospitals soon proved to be insufficient to care for the mounting load of patients with sulphonamide-resistant gonorrhea. The average rate of cure with the sulphonamides was falling below 75 percent, owing to the development of sulphonamide-resistant strains of the gonococcus and to the substantial number of chronic cases that probably represented relapse after inadequate self-administered treatment. Every station and general hospital had a mounting backlog of patients with chronic gonorrhea for whom the only prospect of cure and return to duty at that time lay in treatment with fever [therapy].[4(p412)]

During the years 1946 to 1950, the incidence of STDs doubled to more than 82 cases per 1,000 service personnel. During the years 1951 to 1955 of the Korean conflict, the case rate more than doubled again to 184/1,000.[3]

During the Vietnam conflict, STDs were the number one medical diagnosis in the theater, and approximately 90% of this caseload was caused by gonorrhea. The overall incidence of STDs exceeded 260/1,000/y during the period 1963 to 1972. De-

spite the high prevalence of STDs, however, fewer than 1% of individuals required admission to the hospital for therapy.[3]

Much has changed since World War I, when patients with STDs were admitted to hospitals and treated with painful and often dangerous medications. Treatment now is rational and safe, state-of-the-art medical facilities can be transported quickly to the front, and hospitalization with prolonged convalescence is almost never necessary. Nonetheless, the inability of the military's extensive public health procedures to curb the enormous incidence of STDs among its personnel, especially in wartime, means that military physicians need to attain and maintain clinical competence in the diagnosis and treatment of STDs.

SYPHILIS

Syphilis is a venereal disease that is caused by the bacterial spirochete *Treponema pallidum* and is transmitted by direct contact, usually sexual intercourse. Among the STDs, syphilis has occupied a unique place in medical literature and lore since the late 15th century. Various theories attempt to explain the origins of syphilis and reasons for the rapid spread and increased severity of the disease among European populations, who knew the disease as the "Great Pox." The Columbian theory proposes that, on returning to Europe in 1493, Columbus's crew brought syphilis with them, having acquired it from natives in the West Indies. However, there are inconsistencies in this theory: syphilis has not been described in early Native Americans, and ancient Chinese writings are known that describe an illness similar to late cutaneous syphilis. Others postulate that syphilis was endemic to European populations during the time of Columbus. At that time, Europe was embroiled in long, protracted wars and syphilis, already present at a low background level, may have become epidemic as a result of the movement of troops and the migration of civilian populations.[5,6]

A newer idea, known as the environmental or unitarian theory, proposes that syphilis, yaws, pinta, and nonvenereal endemic syphilis (ie, bejel) are all variants of the same disease and that they arose from a single ancestral saprophytic treponeme (Figure 19-2). According to this theory, the various expressions of spirochetal disease reflect the influence of temperature, environment, and other factors on pathogenicity and clinical manifestations.[7,8] The relatively benign African diseases yaws and bejel may have been transformed in the susceptible population of Europe into a highly virulent disease with high mortality rates.[9,10]

The venereal nature of the transmission of syphilis was not recognized until the 18th century, and confusion reigned whether gonorrhea and syphilis represented different manifestations of the same disease or were two different diseases. To resolve the issue, in 1767, John Hunter inoculated himself with urethral exudate from a patient with gonococcal urethritis. In fact, the patient had both syphilis and gonorrhea. Hunter developed both a chancre and urethritis, and he erroneously concluded that the two diseases were disparate manifestations of the same infection.[11] Not until 1838 was the separate nature of gonorrhea and syphilis established.

A dramatic increase in the incidence of primary, secondary, and congenital syphilis in the United States has prompted a resurgence of interest in this ancient disease. The populations most at risk—urban, heterosexual, black and Hispanic men and women with limited access to medical care—are the

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Fig. 19-2. Syphilis, yaws, pinta, and nonvenereal syphilis may all have evolved from one ancestral saprophytic spirochete. This photomicrograph of *Treponema pallidum*, the spirochete that causes syphilis, shows the characteristic helical coils. These thin, highly motile microorganisms must be viewed through a dark-field microscope, which uses light reflected off the specimen. Photograph: Reprinted with permission from Smith JL. *Spirochetes in Late Seronegative Syphilis, Penicillin Notwithstanding*. Springfield, Ill: Charles C Thomas; 1969: 317.

same groups experiencing a dramatic increase in the rates of HIV infection as a result of intravenous drug use and sex-for-drugs prostitution.[12] In addition, syphilis in individuals who are infected with HIV may behave in a biologically different manner resulting in serologic aberrations,[13] an increased risk of symptomatic neurosyphilis,[14] and failures with traditional antibiotic regimens.[15]

Syphilis, the "great imitator," will continue to present clinicians and public health officials with major diagnostic and therapeutic challenges in this decade. The medical officer in a field unit or on board a ship may find himself or herself with a lack of resources and trained personnel to accurately diagnose syphilis in any stage of the disease. Dark-field microscopy, the principal means of diagnosing primary syphilis, is usually unavailable. A new test utilizing direct immunofluorescent staining of dried ulcer exudate (discussed later in this chapter) may allow more accurate and timely diagnosis. The cutaneous and mucosal lesions of secondary and tertiary stages of syphilis may be confused with numerous similar skin eruptions. Pitfalls in the interpretation of serologic tests cause a small but significant number of false-positive and false-negative test results. The legal requirement to report syphilis and the potential embarrassment of contact tracing may lead to less-than-honest answers by patients regarding their sexual exposure and sexual behavior.

A rational approach to the clinical and laboratory diagnosis of primary and secondary syphilis will be presented, geared to the resources available to the field medical officer. Late, or tertiary, syphilis will be discussed briefly; congenital syphilis and syphilis during pregnancy will not; interested readers can find several excellent discussions[16,17] of these subjects. Lastly, the impact of HIV infection on the current syphilis epidemic will be discussed as it relates to changes in diagnosis and treatment.

Magnitude of the Problem

In 1990, the Centers for Disease Control (CDC), Atlanta, Georgia, reported that between the years 1981 to 1989 the incidence of primary and secondary syphilis increased an alarming 34% in the United States.[12] This represents the highest incidence of syphilis in the general population since 1949. In 1993, there were 26,279 projected cases of primary and secondary syphilis (10.6/100,000) reported to the STD Surveillance Department of the CDC. In reviewing the data among various population groups, several striking trends are apparent[12]:

- Among white men, the incidence of syphilis actually decreased by 69% during this period, to 3.2/100,000.
- However, among heterosexual black men and women, the incidence of syphilis approached 122/100,000. This is almost a *50-fold* difference between black and white populations.
- Incidence rates for Hispanic men and women were intermediate between the rates for whites and blacks.
- The increase in syphilis is most acute for women, regardless of their racial or ethnic background.
- The male-to-female ratio has declined to just below 2:1.

This shift of disease—from homosexual men in the 1970s to heterosexual black men and women in the 1980s—foreshadows a potential public health catastrophe with regard to human HIV infection. Several reports from Africa[18,19] demonstrate that genital ulcer disease, including syphilis, facilitates the sexual transmission of HIV infection. This suggests that segments of the population in the United States, especially urban blacks, may be at great risk of suffering the rapid spread of HIV disease that has been seen among heterosexuals in Africa.

As a result of changes in sexual practices between 1981 and 1989, the largest decrease in syphilis rates occurred among white homosexual and bisexual men (Figure 19-3). However, among black

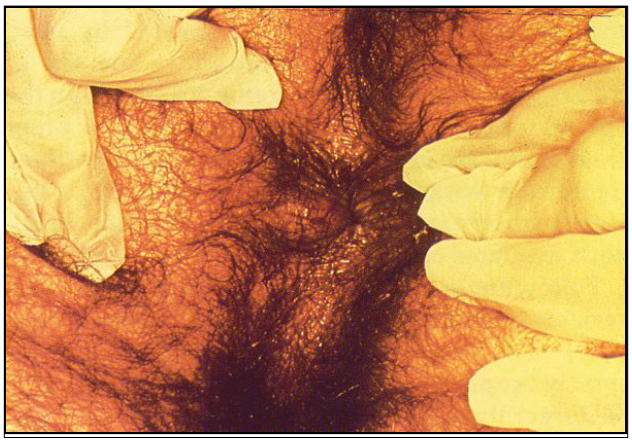

Fig. 19-3. Anal chancre in a man who is also infected with the human immunodeficiency virus. Primary lesions of syphilis are usually asymptomatic and are frequently overlooked by the patient. Such a lesion might mimic a perirectal abscess.

heterosexuals, especially black women, the enormous increase in rates of syphilis and gonorrhea can be traced to the use of illegal drugs—in particular, crack cocaine.[12]

There has also been a resurgence in cases of congenital syphilis that parallels the increase in syphilis among women. During 1989, for example, 1,747 cases of congenital syphilis were reported to the CDC. The majority (1,017 cases) were reported from New York City.[20]

Clinical Manifestations

Syphilis is not a highly contagious STD. About 30% of individuals exposed to an infected partner will develop syphilis, based on a study[21] that determined the efficacy of antibiotics to abort syphilis infections in individuals exposed to known contacts. Another study[22] demonstrated that about one half of the contacts of individuals with early syphilis developed infection. Transfusion-associated syphilis has been virtually eliminated in the United States as a result of serologic screening of all blood prior to transfusion. However, in developing countries where screening of donated blood is inconsistent, transfusion-associated syphilis still occurs. The practice in the United States of using refrigerated stored components is also advantageous, as *T pallidum* is killed by storage at 4°C.[11]

Syphilis is almost exclusively sexually transmitted and direct contact with skin or mucous membranes, from an infected to an uninfected person, is required for transmission. The organism will pass through mucous membranes and abraded skin. However, it is quite sensitive to a variety of physical and chemical agents and is inactivated by heat, cold, drying, and soap and water.[23] The site of inoculation is usually on the genitalia, although the lips may be involved through kissing, and other areas of the skin may be infected through abrasions. Healthcare workers can be infected if they fail to use gloves when examining lesions or handling infectious exudates or specimens.[9]

Following exposure, *T pallidum* incubates for a variable period ranging from 10 to 90 days (average 21 d). The length of the incubation period is inversely proportional to the size of the inoculum (eg, the larger the inoculum, the shorter incubation period).[24] In the primary stage of syphilis, a chancre develops at the site of inoculation. If untreated, the chancre spontaneously resolves within 3 to 6 weeks. In 60% to 90% of patients, secondary syphilis develops, typically 4 to 10 weeks following the development of primary syphilis. A chancre is still present in 18% to 34% of patients who present with secondary syphilis.[11] Almost 25% of patients with secondary syphilis do not recall a primary lesion: lesions are often on the cervix or vaginal wall in women, or in the anal canal in women and homosexual men.[23]

With resolution of the secondary stage, the patient enters the latent phase, where there are no clinical signs or symptoms of the disease. For treatment purposes, the U.S. Public Health Service defines *early* latent syphilis as syphilis of less than 1 year's duration after the primary lesion, and *late* latent syphilis as syphilis of longer than 1 year's duration after the onset of the chancre.[25]

After a period ranging from 2 to more than 40 years, clinical signs of late, or tertiary, syphilis may develop in about one third of untreated patients.[11] Tertiary syphilis is now rare in this country because of widespread serologic testing and the availability of antibiotics. However, infection with HIV appears to alter the biological behavior of the spirochete and its responsiveness to therapy.[26] Persistence of spirochetes has been reported[27] in the cerebrospinal fluid of patients who (*a*) are infected with HIV and (*b*) have been treated with the doses of penicillin recommended for early syphilis. The treatment guidelines for managing all stages of syphilis in the HIV-infected population will undoubtedly change.

Primary Syphilis

The primary lesion of syphilis is the chancre, which develops 10 days to 3 months (average 3 wk) after exposure to the spirochete. The classic chancre begins as a painless, firm, rubbery, elevated papule that progresses to develop a central ulceration (Figure 19-4). The base of the ulcer is clean and smooth with a thin, serous exudate present. In men, the chancre is found on the inner aspect of the foreskin, near the frenulum, in the coronal sulcus, and occasionally on the glans or penile shaft. In women, the primary lesion may go unnoticed. It occurs on the cervix, vaginal wall, vulva, and periurethral and perianal areas. Although they are classically described as nontender, occasional chancres are painful owing to secondary infection with bacteria.[28]

Atypical lesions commonly occur. Multiple chancres may be found in up to 25% of patients.[29] In the perianal area, the primary lesion may resemble an anal fissure. Extragenital chancres may be found on the oral mucosa, lips, tonsils, and pharynx of homosexual men or individuals who practice orogenital sex. Anal and rectal chancres also occur and may be asymptomatic, may present as an acute proctitis, or

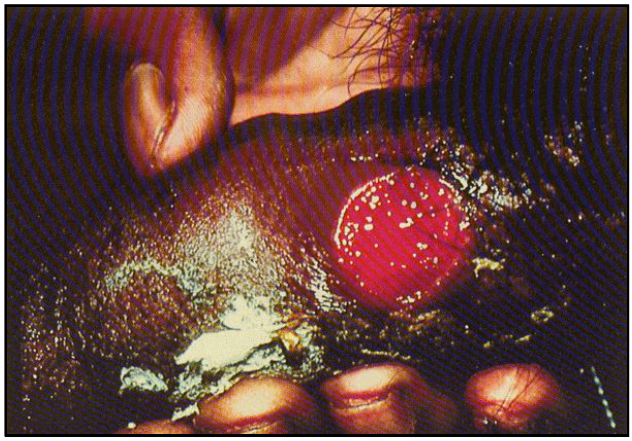

Fig. 19-4. This painless, clean-based ulcer with rolled borders is typical of primary syphilis.

may be misdiagnosed as a carcinoma. Intraurethral chancres may produce signs and symptoms of urethritis. Lesions in other areas such as fingers are rare (Figure 19-5).[10]

Inguinal lymphadenopathy usually develops within a few days of the appearance of the chancre, if it is located on the external genitalia. Lymphadenopathy may be unilateral or bilateral. The lymph nodes are firm, discrete, and painless unless the chancre is secondarily infected. With extra-genital infection, the lymphadenopathy is more commonly unilateral.[10]

If no treatment is sought or if the chancre is inconspicuous, it heals uneventfully in 3 to 6 weeks.

Secondary Syphilis

Secondary syphilis develops in 60% to 90% of untreated patients from 4 to 10 weeks after the initial appearance of the chancre. As noted previously, up to one third of patients may still have a chancre present at the time of onset of lesions of secondary disease.[11,30] The characteristic rash, present in 75% to 100% of patients, is typically found on the trunk, extremities, palms, and soles. Condylomata lata lesions are found on mucous membranes and other moist areas such as the inframammary and axillary areas. The cutaneous lesions are polymorphous, and numerous colorful terms have been used to describe the clinical findings. Lesions may be macular, papular, papulosquamous, follicular, annular, pustular, or nodular—the most common presentations are variants of papular lesions. Vesiculobullous lesions do not occur in adults but are frequently seen in congenital syphilis. Pruritus is usually absent but has been reported in a minority of patients; the presence or absence of pruritus is not a reliable clinical sign in the evaluation of possible syphilitic exanthems.[28]

Papular lesions are dull red-to-ham colored but may only appear as elevated areas of hyperpigmentation in dark-skinned patients. Macules and papules are often found together as symmetrically distributed, discrete lesions with a predilection for the palms and soles (Figure 19-6). Various investigators have emphasized the "uniqueness" of palmar and plantar lesions. However, dermatologists are well aware that drug eruptions, viral illnesses, and rickettsial infections (ie, Rocky Mountain spotted fever) may also be important causes of lesions in these areas. Scaling overlying the lesions may be (*a*) minimal to absent, (*b*) suggestive of psoriasis, or (*c*) very thickened and keratotic (ie, lues cornee). Central clearing of papular lesions results in annular lesions (also called annular syphilid) that are commonly seen on the face of dark-skinned individuals. Split papules are common, especially at the corners of the mouth and nostrils in dark-skinned individuals.[31] Less-common secondary lesions include pustules; acneform lesions; follicular or miliary syphilid consisting of small, discrete follicular papules; corymbose (ie, bombshell) syphilid with a large central papule surrounded by smaller lesions (Figure 19-7); and a highly destructive, necrotic, ulcerative form known as lues maligna, which is associated with fever and malaise (Figure 19-8).[28]

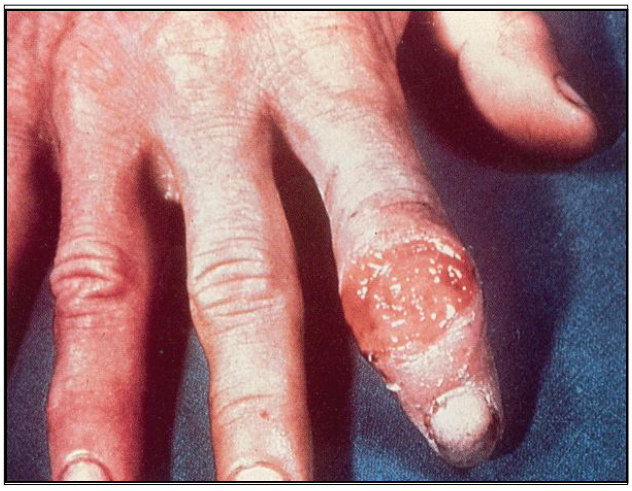

Fig. 19-5. Syphilitic chancre on a patient's index finger. This chronic, ulcerative lesion mimics many other infectious and inflammatory processes such as tuberculosis, deep fungal infections, or malignancy.

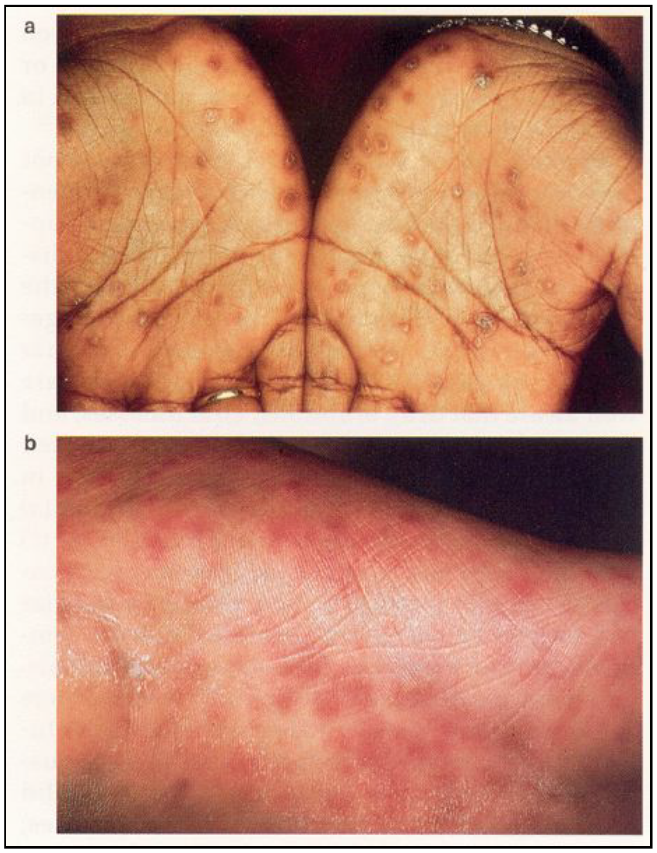

Fig. 19-6. Papulosquamous lesions of secondary syphilis on (**a**) the hands and (**b**) the feet, which are frequently involved in secondary syphilis. The lesions are asymp-tomatic, pink-to-red papules with slight overlying scale. These eruptions are frequently overlooked by the patient or misdiagnosed as viral exanthems or drug eruptions. Photograph: Courtesy of C. Kalter, MD, Bethesda, Md.

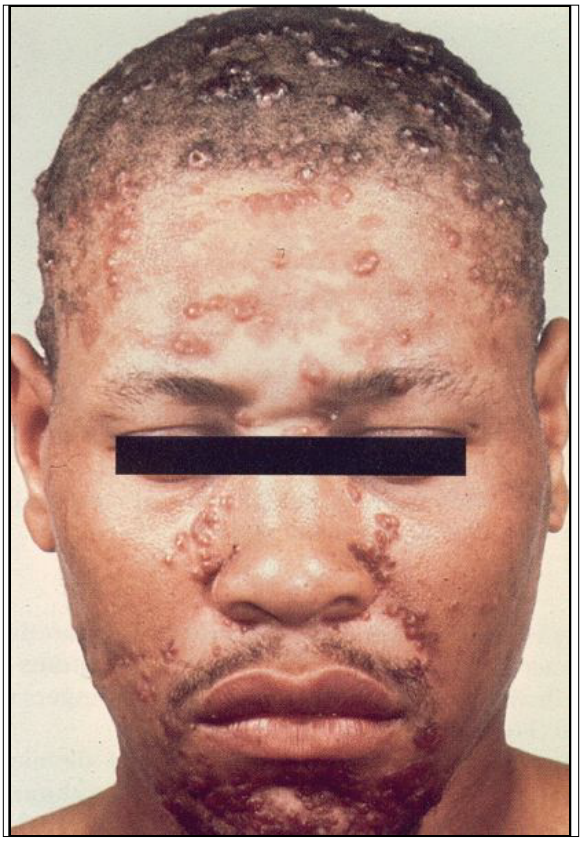

Fig. 19-8. Lues maligna showing destructive papulo-necrotic lesions of the face and scalp. This rare, destructive form of secondary syphilis is associated with severe constitutional symptoms and ulcerative lesions. Photograph: Courtesy of Walter Reed Army Medical Center Dermatology Service slide file, Washington, DC.

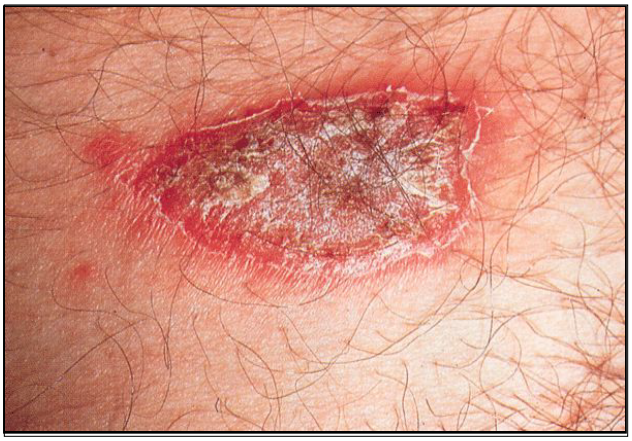

Fig. 19-7. Rupial lesions are uncommon manifestations of secondary syphilis. They are elevated, often with thick, overlying scale-crust. Photograph: Courtesy of C. Kalter, MD, Bethesda, Md.

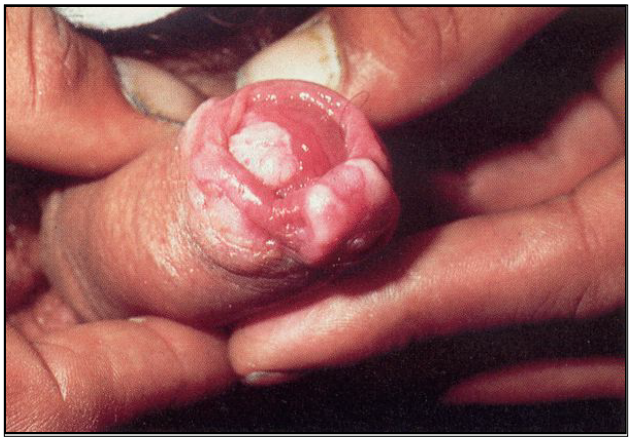

Fig. 19-9. These grayish white, smooth papules of condylomata lata of the glans penis resemble genital warts. When lesions like this are seen, healthcare personnel should look elsewhere on the patient's body for telltale signs of secondary syphilis. Photograph: Courtesy of C. Kalter, MD, Bethesda, Md.

Lesions in the mucous membranes are common and are known as (*a*) condylomata lata when found in moist intertriginous areas (eg, groin and perianal area) and (*b*) mucous patches when located in the mouth or on the lips. The lesions are asymptomatic, white-to-grayish, flat-topped papules or plaques, with a mucoid exudate on the surface (Figure 19-9). The lesions may become large, malodorous vegetations. The moist environment in which they develop permits large numbers of spirochetes to survive, and the lesions are highly infectious.[28]

Other reported cutaneous findings include a "moth-eaten," patchy alopecia, or a diffuse hair loss; hyperpigmentation and hypopigmentation, often as a result of previous inflammation; and syphilitic paronychia.[28]

Constitutional signs and symptoms are variable, although generalized, asymptomatic, nontender lymphadenopathy is present in virtually every patient with secondary syphilis. Signs and symptoms vary from mild to severe and include low-grade fever, headache, myalgias, sore throat, and loss of appetite. Anemia, elevated sedimentation rate, and lymphocytosis may be found on routine blood tests. Almost any organ may be involved during the second stage of syphilis, and clinical and laboratory findings referable to this involvement should be sought. Major organ involvement includes the following[31]:

- syphilitic hepatitis (elevated alkaline phosphatase, rarely jaundice);
- renal involvement (proteinuria, nephrotic syndrome, glomerulonephritis);
- ocular disease (anterior uveitis, photophobia, lacrimation, and rarely chorioretinitis);
- syphilitic myocarditis with electrocardiographic abnormalities; and
- central nervous system involvement, which, although uncommon, may include cranial nerve palsies, acute meningitis, transverse myelitis, neural deafness, or thrombosis of spinal arteries.

Recently, patients with HIV infection have been reported to develop lesions of secondary syphilis in the absence of confirmatory serologic tests (eg, the Venereal Disease Research Laboratory [VDRL] test and the fluorescent treponemal antibody absorption [FTA-ABS] test).[13] Therefore, in any patient with clinical signs or symptoms that may be those of syphilis, laboratory tests—and even skin biopsy—should be done early and routinely.

If secondary syphilis is not treated, the lesions spontaneously resolve in 1 to 3 months, with secondary relapses occurring in as many as 25% of patients,[32] usually during the first year after infection. After resolution of the secondary lesions, the patient enters either the early or the late latent disease phase. This division has important medical implications, as patients with early latent disease (*a*) may have relapses of secondary lesions during this time and (*b*) are potentially infectious to their sexual partners. Individuals in the late latent phase are generally not infectious.[11]

Tertiary Syphilis

Tertiary syphilis is now a rare disease in the United States. About 70% of patients with untreated syphilis will remain asymptomatic; the remainder will progress to tertiary disease and may present with late benign gummata (16%), cardiovascular syphilis (9.6%), neurosyphilis (6.5%), or involvement of bone or virtually any other organ.[28]

Gummata (ie, superficial or deep, destructive granulomatous lesions that involve skin, subcutaneous tissues, or bone) tend to occur on the extremities, especially at the sites of trauma and in the head and neck. The lesions, which are asymptomatic, begin as nodules or subcutaneous masses that often ulcerate and coalesce to form large irregular plaques with annular borders. The skin may be secondarily involved by direct extension from underlying bony gummata. The lesions heal slowly with atrophy and pigmentary changes. Differential diagnosis includes malignancy, tuberculosis, leprosy, cutaneous lymphomas, and deep mycoses, among others.[11,28]

The clinical presentation of syphilitic involvement of the central nervous system has changed recently, for unknown reasons. General paresis and tabes dorsalis are much less common than in previous times and seizure disorders and neuro-ophthalmic findings are more often encountered.[28] A discussion of neurosyphilis is beyond the scope of this chapter; however, recent experiences with late syphilis in patients infected with HIV suggest that current treatment regimens are inadequate to prevent this complication in this population. Two groups of investigators[26,33] have reported development of symptomatic neurosyphilis in patients infected with HIV despite treatment with recommended doses of benzathine penicillin.

Laboratory Diagnosis

Culture

Culture of treponemes is both unavailable and impractical for the rapid diagnosis of syphilis. However, the recent confirmation that *T pallidum* can successfully be propagated in vitro will undoubtedly increase knowledge of both the molecular biology and the spirochete–host interaction that leads to infection.

T pallidum, a spirochete, the causative organism of syphilis, is a motile, flexible, rod-shaped bacterium with 8 to 14 helical coils that gives the treponeme its characteristic shape. The genus *Treponema* (from the Greek words *trepo* and *nema* meaning "turning thread") contains the spirochetes that cause syphilis, yaws, pinta, and nonvenereal syphilis; the species are indistinguishable both morphologically and serologically. Differentiation of the pathogenic spirochetes is based solely on their mode of infection, the severity of the infection, and the infectivity for laboratory animals. As a result, the nomenclature has been changed to reflect the close relatedness of the treponemes[9]:

- *Treponema pallidum* (which causes syphilis) is now called *T pallidum* (subspecies *pallidum*);
- *Treponema pertenue* (which causes yaws) is now called *T pallidum* (*pertenue*); and
- the *Treponema pallidum* variant that causes endemic syphilis is now called *T pallidum* (*endemicum*).

In the laboratory, *T pallidum* is usually maintained in rabbit testes. Until recently, the spirochete had never been cultured outside a human or animal host. Using special tissue culture techniques, the organism has been shown to multiply through several generations in rabbit epithelial cells. Treponemes were found to attach and replicate on the surface of tissue culture cells—tissue culture appears to be essential for successful in vitro cultivation. However, although virulence has been maintained in culture, it has not been possible to pass the organisms serially.[9,34]

Dark-Field Microscopy

T pallidum is too narrow to be seen well by ordinary light microscopy, and dark background illumination (ie, dark-field microscopy) is necessary to visualize the organism (see Figure 19-2). Dark-field microscopy is the principal means of diagnosing primary syphilis, as serologic tests are often negative when patients are first seen.[10] Except from the moist condylomata lata, organisms are difficult to obtain from lesions of secondary syphilis. Nonpathogenic treponemes are found in the mouth and along the gingival margins in normal individuals. Therefore, dark-field microscopy is unreliable for diagnosis of primary or secondary lesions occurring in the oropharynx.

Dark-field microscopy requires a dark-field condenser, trained personnel, and knowledge of the technical difficulties in preparing a specimen and interpreting the findings. Pitfalls often encountered include (*a*) the age or condition of the lesion, (*b*) inadequate or improper collection of specimens, (*c*) recent use of topical or oral antibiotics by the patient, and (*d*) failure to distinguish artifacts and nonpathogenic treponemes from *T pallidum.*

For those interested in the technique and materials required for dark-field microscopy, the CDC has an excellent publication available free of charge.[35]

Direct Fluorescence Microscopy

A fluorescein-tagged monoclonal antibody that is specific for *T pallidum* has been developed and can be used to detect the presence of the organism on dried exudate from lesions. A smear of lesional material is applied to a glass microscope slide, air-dried, fixed in acetone, and sent to the laboratory. The slide can be sent by mail to a reference laboratory if the test cannot be done locally. If specimens are to be mailed, the smears should be air-dried only and not fixed.[36] Initial results of the fluorescein-tagged monoclonal antibody indicate that it is both sensitive and specific.[10,37]

Lesional material may also be collected in heparinized, microhematocrit capillary tubes, then sealed and stored at 4°C to 8°C until slides are to be prepared. Capillary tubes may be mailed to a reference laboratory without refrigeration.[36]

Serologic Tests

Serologic testing, despite its limitations and pitfalls, remains the workhorse for the laboratory diagnosis of syphilis. Unfortunately, these tests are neither inexpensive nor rapid, and delays of days to a week or more may cause treatment to be delayed in a potentially infectious individual. Two types of serologic tests for syphilis are currently in use or are being evaluated for use: the nontreponemal tests, which are discussed below, and treponemal tests. Treponemal tests employ spirochetal antigen and

are reliable indicators of syphilitic infection, present or past. However, they do cross-react with other treponemes and therefore are not entirely specific.[9] It is incumbent on the medical officer to appreciate the sensitivity and specificity of the test that is being ordered, and to consider false-negative and false-positive results, prior infection (serofast), possible reinfection or relapse, and treatment failures in the evaluation of the patient (Exhibit 19-2).

Nontreponemal Tests. The word *nontreponemal* means that the test antigen is derived from a source other than a spirochete. This test antigen is cardiolipin-lecithin-cholesterol (reagin), which is a beef-heart extract. Reagin is a phospholipid also found in human tissue and is present in minor amounts in spirochetal membranes.[36] Nontreponemal tests currently available include the standard VDRL microscopical flocculation test and various modifications including the rapid plasma reagin (RPR) 18-mm–circle card test; automated reagin test (ART); unheated serum reagin (USR); and toluidine red unheated serum test (TRUST), which is an investigational test.

All nontreponemal tests measure antilipid immunoglobulin (Ig) G and IgM antibodies. The test antigen is mixed with the patient's serum on a card, rotated for a specified number of minutes, and then read. The tests are reported as either reactive or nonreactive; the VDRL and USR tests are also reported as weakly reactive (Table 19-2).[36]

In general, quantitative tests indicating tube dilutions (ie, 1:32) are more useful in evaluation of serologic status and response to treatment. Active disease will show a rising titer, adequately treated disease will show a drop in titer, and serofast patients will have no change in titer on serial testing.[28]

The nontreponemal tests usually become positive within 10 to 14 days after the chancre has appeared, but up to 4 weeks may be required in some individuals.[10] In primary syphilis, the titers may be negative, low, or occasionally 1:32 or higher. They are usually high (> 1:32) in secondary syphilis.[28] Sera from about 30% of patients with cardiovascular syphilis or with neurosyphilis are nonreactive with the VDRL test.[38] In a small number of patients with secondary syphilis, a false-negative or weakly reactive test (ie, the prozone phenomenon) may occur in the presence of high antibody titers. Most laboratories perform dilutions on specimens to distinguish false-negative results from this phenomenon.[17]

Biological false-positive reactions occur in 1% to 2% of the population and increase to more than 10% of intravenous drug abusers. Most titers are usually 1:8 or less; however, low titers may also be seen in the later stages of syphilis. All reactive nontreponemal tests must be confirmed with a treponemal test.[36]

Treponemal Tests. Patients with reactive nontreponemal tests must have the reactivity confirmed with one of the four currently available treponemal antibody tests: (1) fluorescent treponemal antibody absorption (FTA-ABS); (2) fluorescent treponemal antibody absorption double-staining (FTA-ABS DS), a recent modification using a fluorochrome-labeled counterstain; (3) hemagglutination treponemal test for syphilis (HATTS); and (4) microhemagglutination assay for antibodies to *T pallidum* (MHA-TP).

The FTA-ABS is still the most widely used test and is an indirect immunofluorescent technique

EXHIBIT 19-2

DIAGNOSTIC TESTS FOR SYPHILIS

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Adapted with permission from Larsen SA, Hunter EF, Creighton ET. In: Holmes II, Mardh P-A, Sparling PF, et al, eds. *Sexually Transmitted Diseases*. New York: McGraw-Hill; 1990: 928.

TABLE 19-2

SENSITIVITY OF SEROLOGIC TESTS IN UNTREATED SYPHILIS

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VDRL: Venereal Disease Research Laboratory
FTA-ABS: fluorescent treponemal antibody absorption
MHA-TP: microhemagglutination assay for antibodies to *Treponema pallidum*
Adapted with permission from Jaffe HW, Musher DM. In: Holmes II, Mardh P-A, Sparling PF, et al, eds. *Sexually Transmitted Diseases*. New York: McGraw-Hill; 1990: 935.

that utilizes a fluorescein-labeled antihuman antibody to detect host antibodies against *T pallidum*. A *sorbent*, which removes antibodies to nonpathogenic Reiter treponemes (hence the word "absorption"), is first utilized.[36]

The other two tests, the HATTS and MHA-TP, do not require a fluorescent microscope and can be performed more quickly. However, they are less sensitive in primary syphilis and cross-reactions may occur.[36]

The treponemal tests become reactive earlier in primary syphilis than the nontreponemal tests. Still, approximately 20% of patients who present with primary syphilis will be nonreactive on the FTA-ABS test. Therefore, the FTA-ABS test should be performed and may provide important information in suspect cases where the RPR test is negative. The treponemal tests remain positive throughout an individual's life. However, the CDC reports[25] that 15% to 25% of patients who are treated during the primary stage may revert to being seronegative on the treponemal tests after 2 to 3 years. The false-positive rate in the general population is about 1% (Exhibit 19-3).[11]

The FTA-ABS test has several drawbacks: it requires special equipment and trained personnel, is time-consuming to perform and technicians find the repetitive reading of tests tiresome, and is somewhat expensive. It should be used principally as a confirmatory test.[39]

Treatment

Penicillin, the treatment of choice for all patients in any stage of syphilis today, is a considerable improvement over the treatment used during the Civil War by Assistant Surgeon E. A. Tompkins, Fourth Cavalry, Fort Yamhill, on 1 April 1863:

> The patient contracted syphilis ... a short time before I arrived at this post. He was relieved by the use of iodide of potassium in syrup of sarsaparilla. Small doses of corrosive sublimate were given and lunar caustic was applied to the chancres. A continuance of this treatment for three weeks enabled him to return to duty, although not entirely well.[40(p893)]

T pallidum has remained sensitive to penicillin since the drug was first used for the treatment of syphilis in 1943. However, because of the organism's long dividing time, prolonged, moderately low levels are required for complete killing of the organisms present.[11] The current treatment guidelines for adults recommended by the CDC are presented below. Controversy exists regarding therapy of patients with HIV infection, and they may require alternative regimens. Consultation with an infectious disease specialist is advised, as numerous investigational protocols are currently underway. The treatment of syphilis in pregnant women and children is not discussed in this chapter.

Primary, Secondary, and Early Latent Syphilis

The recommended regimen for treatment of primary, secondary, and early latent syphilis[25] is benzathine penicillin G 2.4 million units, administered intramuscularly, in one dose. There are two alternative regimens for nonpregnant, penicillin-allergic patients:

EXHIBIT 19-3

FALSE-POSITIVE REACTIONS TO NONTREPONEMAL AND TREPONEMAL TESTS FOR SYPHILIS

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Adapted from (1) Hutchinson CM, Hook EW. Syphilis in adults. *Med Clin N Am*. 1990;74(6):1405. (2) Rhodes AR, Luger AFH. Syphilis and other treponematoses. In: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF, eds. *Dermatology in General Medicine*. 3rd ed. New York, NY: McGraw-Hill; 1987: 2424, 2426.

1. doxycycline 100 mg, administered orally twice daily for 2 weeks, or
2. tetracycline 500 mg, administered orally four times daily for 2 weeks.

There is less clinical experience with doxycycline than with tetracycline, but compliance may be better with doxycycline.

Similarly, two options are available for treating patients who are unable to tolerate tetracycline or doxycycline[25]:

1. the patient should have skin-testing for penicillin allergy and be desensitized, if necessary; or
2. erythromycin 500 mg should be administered orally four times daily for 2 weeks.

Erythromycin is less effective than other recommended regimens. Single-dose ceftriaxone *is not effective* for treating syphilis.[25] Optimal dose and duration have not been established for ceftriaxone.

Persons Exposed to Syphilis. Persons who have been exposed to syphilis within the preceding 90 days should have clinical and serologic examinations, and the patient should be treated presumptively even if seronegative. Evidence of other STDs should be sought in every individual.[25]

Follow-Up. Following treatment, the CDC recommends that patients be reexamined clinically and serologically at 3 and again at 6 months. Treatment failures can occur with any regimen. The CDC currently recommends that patients who are infected with HIV, and who are also being treated for syphilis, should have more frequent serologic testing at 1, 2, 3, 6, 9, and 12 months.[25]

Latent Syphilis of Unknown Duration, Late Latent Syphilis, and Tertiary Syphilis

Patients with late latent or symptomatic tertiary syphilis need more extensive evaluation that is beyond the scope of this discussion. For therapeutic guidelines, see the CDC guidelines for dosage and routes of administration of penicillin or alternative regimens.[25]

GONORRHEA

Gonorrhea, caused by the Gram-negative diplococcus bacterium *Neisseria gonorrhoeae*, is the most commonly reported communicable disease in the United States. In 1993, there were 419,711 projected cases (169/100,000) reported to the CDC,[41] although many more cases go unreported. Important shifts in the epidemiology, populations at risk, and antibiotic susceptibility of the organism have resulted in significant and rapid changes in treatment guidelines and strategies for public health intervention. The military has figured prominently in epidemiological studies of gonorrhea because of the large numbers of young, sexually active individuals who can be followed prospectively for long periods of time.

Gonorrhea is transmitted almost exclusively by sexual contact and is common in both developed and developing countries. Globally, almost 200 million cases are reported annually, evidence of the enormity of the problem and the necessity for improved public health measures for control. Early and accurate diagnosis of gonococcal infection followed by an effective treatment that ensures a high level of patient compliance are crucial to any successful control program.[42]

The spectrum of disease caused by *N gonorrhoeae* includes[42]:

- genital infection including acute anterior urethritis in men, acute endocervicitis in women, and asymptomatic urethral infections;
- rectal infection;
- pharyngeal infection;
- local complications including acute salpingitis (pelvic inflammatory disease) and Bartholin's gland abscess in women; and epididymitis, prostatitis, and other perineal complications in men;
- disseminated gonococcal infection, including the arthritis-dermatitis syndrome and meningitis; and
- infections in infants and children, frequently a sign of sexual abuse (although gonorrhea can be acquired during birth).

Clinical Manifestations

Acute Anterior Urethritis in Men

Epidemiological studies have revealed that following a single exposure to an infected woman, about 20% of exposed men will become infected.[43] The incubation period for acute gonococcal urethritis averages 2 to 5 days following exposure, with a range of 1 to 14 days.

Approximately 85% of infected men will develop an acute urethritis syndrome consisting of pain, dysuria, and a urethral discharge (Figure 19-10).[44] The discharge is initially scant and mucoid to mucopurulent, but within 24 hours becomes frankly purulent and profuse.[45] The urethral discharge has been reported to be purulent in 75% of cases, white or cloudy in 20%, and clear to mucoid in the remaining 5%.[46] Recent voiding will temporarily eliminate a discharge in more than one half of patients and will reduce it to cloudy or white in another one third.[46]

Signs and symptoms of untreated gonococcal urethritis in men peak within 2 weeks, with spontaneous resolution occurring in more than 95% of patients within 6 months.[45]

Asymptomatic Infections in Men

Of infected men, 15% will have only mild symptomatic urethritis, and a minority (1%–2%) will be asymptomatic.[28,47] The actual figures cited in the literature vary due to the types of populations studied and how carefully the individuals were questioned and examined regarding the presence of symptoms. The existence of the asymptomatic man was considered but was not verified until 1974, when researchers demonstrated that male carriers of the organism could be identified.[48] Two groups of U.S. Army personnel were surveyed to assess the incidence of asymptomatic urethral carriage of gonococci. From a group of 2,628 asymptomatic men who had sexual intercourse either in Vietnam or in the Fort Lewis, Washington, area, the investigators recovered gonococci from the urethras of 59 (2.2% of the total), of whom 40 (68%) were asymptomatic. Additionally, 28 asymptomatic men were followed without treatment for periods ranging from 7 to 165 days and were found to be culture positive for gonococci until the time of treatment, indicating that asymptomatic infections in men may be chronic.[48]

Acute Endocervicitis in Women

The cervix is the most common site of infection in women, although the urethral canal, periurethral glands, or Bartholin's gland may be primarily or secondarily involved. Within about 10 days following a single exposure to an infected partner, about one half of women will become infected with *N gonorrhoeae*, and most become infected after multiple exposures.[49] Symptoms include purulent cervical discharge, dysuria, lower abdominal discomfort, menstrual irregularities, and uterine bleeding that varies from minimal to severe. Although 60% to 70% of women will have these nonspecific symptoms, only 10% to 20% of infected women will have an obvious purulent cervical discharge or a purulent vaginal discharge that clearly originates from the cervix. Women may remain asymptomatic and infectious for many months before a spontaneous cure occurs.[50] Female prostitutes constitute an important reservoir of the disease. The reported prevalence of gonorrhea in this group varies from one study to another—from 5.2% to 11.2%—with the higher rates seen in developing countries.[51] In a 1991 study of 757 female prostitutes in Madrid, Spain, 89 were infected with *N gonorrhoeae*. Of these, 48 (54%) were asymptomatic.[51]

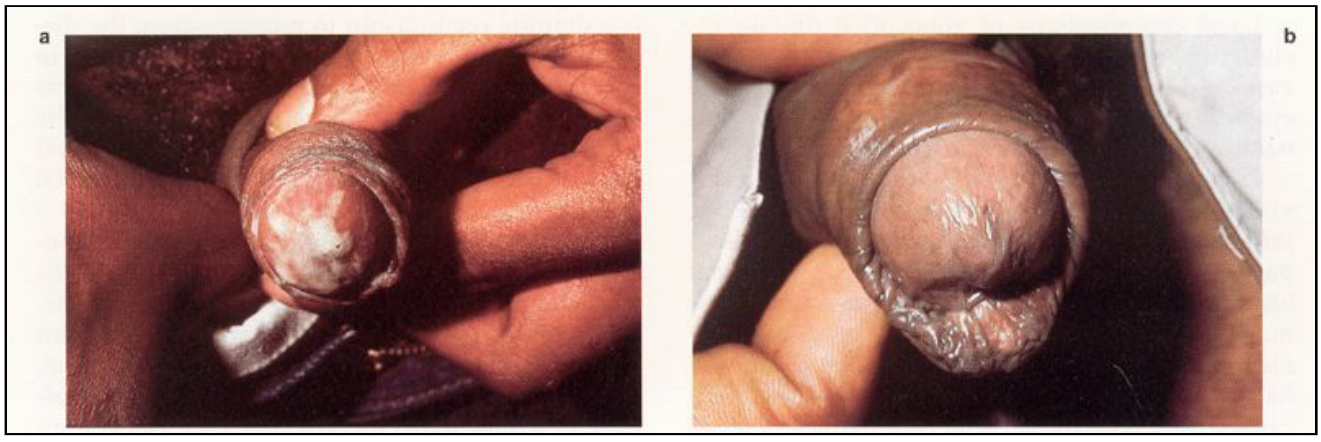

Fig. 19-10. (**a**) This thick, purulent, urethral discharge is typical of primary gonorrhea. (**b**) In nongonococcal urethritis, in contrast, the discharge is clear and mucoid. Photograph: Courtesy of C. Kalter, MD, Bethesda, Md.

Rectal Infection

The rectal mucosa may be the primary site of infection in 40% of homosexual men and in 5% of women. Of women with gonococcal infections of the cervix, one third to one half will also have infection of the rectum, which is mainly due to contamination of the anus by infected cervical secretions but may also result from anal intercourse.[42] In most women, rectal infection is asymptomatic. However, as a result of receptive anal intercourse, a syndrome of acute proctitis occurs in homosexual men with pain, tenesmus, purulent rectal discharge, and constipation. Physical examination reveals perianal erythema and discharge. Anoscopy shows inflammatory mucosal changes consisting of a purulent exudate, erythema, friability, and bleeding.[45]

Pharyngeal Infection

Infection of the pharynx most commonly occurs as a result of orogenital intercourse, although occasional cases develop as a result of autoinoculation from infections at other sites. More than 90% of pharyngeal infections are asymptomatic. In the remaining 10%, however, an acute pharyngitis or tonsillitis develops associated with cervical lymphadenopathy and fever. The significance of pharyngeal infection is uncertain and epidemiological studies have shown that without treatment, spontaneous cure occurs in 100% of affected individuals within 3 months.[45] The prevalence of pharyngeal infection is highest among homosexual men.[42] Transmission of pharyngeal infection to sexual partners appears to be rare.

Complicated Infections

Local complications of gonococcal disease include acute salpingitis (ie, pelvic inflammatory disease) and Bartholin's gland abscess in women and epididymitis, penile lymphangitis, prostatitis, seminal vesiculitis and urethral strictures in men.[42]

Of women with gonococcal infection of the cervix, approximately 15% will develop acute pelvic inflammatory disease with pelvic and abdominal pain, cervical discharge, dyspareunia, abnormal bleeding, and constitutional signs and symptoms including fever, leukocytosis, and elevated sedimentation rate.[49] In the United States, about one half the cases of pelvic inflammatory disease are caused by *N gonorrhoeae*, with chlamydia and other non-STD organisms responsible for the remaining cases. Long-term complications of pelvic inflammatory disease include sterility and the risk of ectopic tubal pregnancy.

Bartholin's gland abscess is also common, and patients present with enlargement of the gland and tenderness. Gonococci may be isolated from the Bartholin's glands in a significant number of women who have no symptoms of bartholinitis.[45]

In men, infection of the urethra may uncommonly progress to involve the epididymis, prostate, testicle, preputial glands (Tyson's glands), bulbourethral glands (Cowper's glands), the median raphe of the penis, and the glans penis.[10] Epididymitis is uncommon, probably because (*a*) gonococci have difficulty traversing a long urethra and vas deferens and (*b*) men often seek early treatment for symptomatic urethritis.[50] Infection is usually unilateral, with patients complaining of a painful and swollen testicle. Physical examination reveals scrotal erythema and an enlarged and tender epididymis; the testicle is usually normal. A secondary hydrocele is frequently found.

Gonococcal prostatitis and seminal vesiculitis are rare complications. Signs and symptoms include urinary urgency, vague pelvic discomfort, hematuria, fever, and painful erections. Infection of the median raphe of the penis is also rare; patients present with a small papule from which pus may be expressed (Figure 19-11).[10] As a result of early and effective treatment, urethral strictures are now an uncommon complication in the United States. However, in parts of the world with inadequate medical facilities, urethral strictures and fistula formation are frequent.[42]

Disseminated Gonococcal Infection

Disseminated gonococcal infection occurs with 6-fold greater frequency in women than men. There is a definite relationship to menstruation: the disease occurs within 1 week of the onset of menses in more than half the cases. Disseminated gonococcal infection is also more common in women during the third trimester of pregnancy and in homosexual men. This complication occurs in 1 in 300 to 1 in 600 patients with genital gonorrhea.[47]

Patients present with the dermatitis-arthritis syndrome, which consists of fever, chills, acute arthritis, tenosynovitis, and tender, erythematous pustules located on the distal extremities. Any joint may be involved but most frequently the wrist, metacarpophalangeal, ankle, or knee joints are affected. Frank pyogenic arthritis may cause joint destruction if not recognized and promptly treated.[45] The characteristic skin lesions usually number fewer

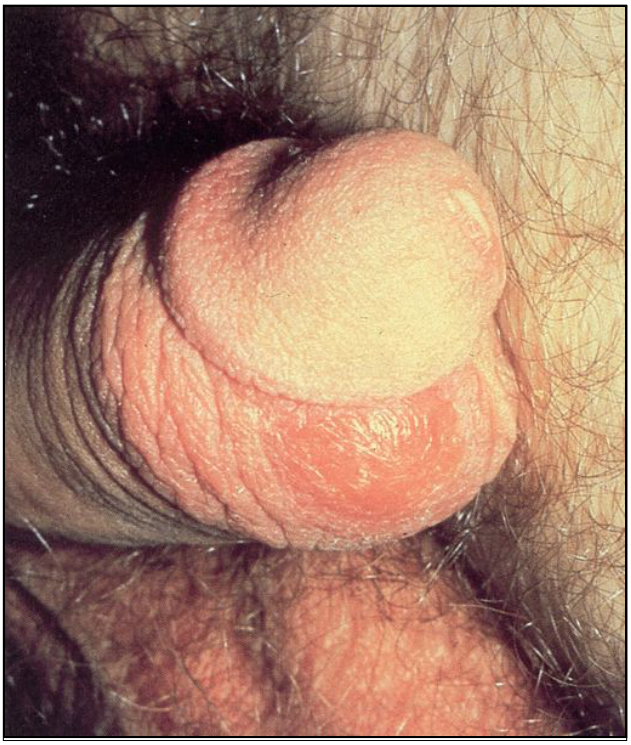

Fig. 19-11. Uncommonly, patients with gonococcal infection may present with a painful abscess of the median raphe of the penis. Gram's stain of the expressed pus would show typical intracellular gonococci. Photograph: Courtesy of the Walter Reed Army Medical Center Dermatology Service slide file, Washington, DC.

than 12 and are concentrated on the extremities, around the joints. They are typically tender vesiculopustules on an erythematous base, which may become hemorrhagic (Figure 19-12).[44]

Infections in Infants and Children

Gonococcal infections in infants and children are the result of sexual abuse, with the exception of gonococcal conjunctivitis (ophthalmia neonatorum), which is acquired from an infected birth canal. This subject is not discussed in this chapter; readers are referred to excellent reviews[52,53] in the literature.

Laboratory Diagnosis

The present approach to the evaluation of a patient with suspected gonococcal infection consists of (*a*) obtaining Gram-stained smears of exudate, (*b*) culture on gonococcal media, and (*c*) determination of antibiotic susceptibility (Table 19-3). Newer methods, such as monoclonal or polyclonal antibody tests to detect gonococcal antigens in cultures or exudate, gonococcal complement fixation tests, and gonococcal deoxyribonucleic acid (DNA) hybridization probes, are available to diagnose the infection rapidly. Whenever possible, culture and sensitivity testing should be obtained.

Gram's Stain

Staining the genital secretions with Gram's stain is the most widely accepted procedure for the immediate diagnosis of gonococcal infection. In men with urethral symptoms, the test is both highly specific and highly sensitive; approximately 90% to 98% of culture-positive men with a purulent discharge have a positive smear. On urethral smears from men, the Gram's stain is considered positive when Gram-negative diplococci of typical morphology are found within or closely associated with neutrophils. It is equivocal if only extracellular organisms or atypical, intracellular, Gram-negative diplococci are seen. Nonpathogenic *Neisseria* organisms are usually not cell-associated (Figure 19-13).[9]

In women, Gram-stained smears from the endocervix are relatively insensitive (30% to 60%)[50] and interpretation is difficult and time-consuming. However, the test may permit rapid diagnosis and treatment in the presence of pelvic inflammatory disease, acute endocervicitis with a purulent discharge, or a history of exposure to gonorrhea.[50] It is important to avoid mistaking morphologically similar saprophytes of the normal flora for *N gonorrhoeae*,

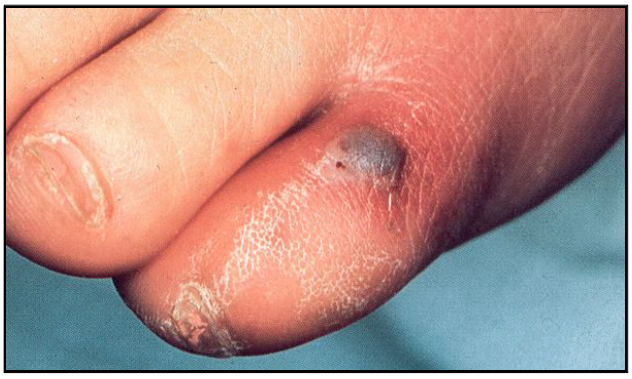

Fig. 19-12. This hemorrhagic pustule, when seen in a sexually active individual in association with acute arthritis and tenosynovitis, should elicit a high degree of suspicion of disseminated gonorrhea. The patients, usually women, may have mild preceding symptoms and are usually unaware that they have gonorrhea prior to the onset of their illness.

TABLE 19-3

SENSITIVITY OF GRAM'S STAIN AND CULTURE IN DIAGNOSING GONORRHEA

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*These specimens are often contaminated with local flora
Reprinted with permission from Judson FN. Gonorrhea. *Med Clin N Am*. 1990;74(6):1358.

and only those smears that contain several polymorphonucleocytes with multiple, intracellular, Gram-negative diplococci with typical morphology should be considered positive.[9]

Gram-stained smears of pharyngeal and rectal exudate are not helpful and the diagnosis rests principally with a culture.

Culture

In men, culture of exudates adds little (2%) to the yield and considerable cost but is often employed when the Gram-stained specimen is negative for *N gonorrhoeae*. However, the CDC currently recommends that all cases of gonorrhea be diagnosed or confirmed or both by culture.[25] The susceptibility of *N gonorrhoeae* to antibiotics changes over time in a locality, and routine culture facilitates antimicrobial susceptibility testing.

In women, cultures obtained from multiple sites provide better yields and a greater chance for isolating the organism than does a single endocervical culture. Ideally, specimens for culture should be obtained from the endocervix, urethra, rectum, and pharynx.[42]

Blood cultures are often positive both early in the course of disseminated disease and when taken from synovial fluid of patients with acute purulent gonococcal arthritis. In disseminated gonococcal infection, culture of skin lesions is usually negative, although Gram's staining and fluorescent-antibody testing of smears from pustules often demonstrates organisms. Culture requires viable organisms, whereas stains and fluorescent antibody testing do not.[44,54]

Immediately after the specimen is collected, it should be plated on an enriched, selective medium

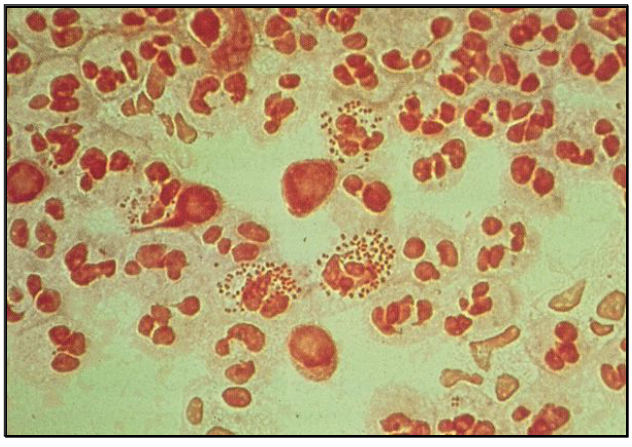

Fig. 19-13. Gram-negative intracellular diplococci are the hallmark of gonococcal infection. Photograph: Courtesy of M. Mulvaney, MD, Albany, NY.

and incubated in an atmosphere containing 5% carbon dioxide (eg, a candle-extinction jar) at 37°C.[55]

Treatment

Treatment guidelines for the management of gonococcal infections have changed dramatically during the last decade. Several factors, including resistance to penicillin, coinfection with gonococci and chlamydia, and the anatomical site of infection, are responsible for the shift in therapeutic approaches.

Resistance to penicillin was first noted in the 1950s, with increasing doses required to cure infection.[56] Penicillinase-producing *N gonorrhoeae* (PPNG) were first reported from Southeast Asia and West Africa during the mid-1970s. Infected military personnel returning from Southeast Asia introduced PPNG to the United States.[49] Resistance is conferred by plasmid-mediated transfer of the genes responsible for production of β-lactamase.[57] During the next several years, only isolated outbreaks associated with prostitution in urban areas were reported.[58] Since 1980, however, the incidence of PPNG has risen significantly, and infection with PPNG is now firmly established in the United States.[58] Additionally, plasmid-mediated, high-level resistance to tetracycline was first reported in the mid-1980s, resulting in outbreaks of tetracycline-resistant strains of *N gonorrhoeae* (TRNG).[59]

There is a high incidence of coinfection with gonococci and chlamydia. Experimental data have demonstrated that simultaneous infection with *N gonorrhoeae* and chlamydia results in a 100-fold increase in the replication of chlamydia in cervical epithelium, and current recommendations encourage the use of single or multiple agents that are effective against both organisms.[60]

The anatomical site of infection has a significant bearing on the choice and efficacy of antibiotics. When caused by susceptible strains of *N gonorrhoeae*, uncomplicated gonococcal infections of the urethra and cervix will respond to single-dose therapy. On the other hand, not all cases of gonococcal pharyngitis or proctitis in a homosexual man will respond to single-agent therapy regimens. Patients whose symptoms persist after treatment should be recultured for *N gonorrhoeae*, and the gonococci should be tested for antibiotic susceptibility. Invasive gonococcal disease (eg, pelvic inflammatory disease, disseminated gonococcal infection) usually requires multiple-dose parenteral therapy.[61]

Other factors to consider in the selection of appropriate antibiotic regimens for gonococcal disease include safety of the drug, incidence of adverse reactions, patient compliance, ease of administration, and cost (Exhibit 19-4).

Uncomplicated Gonococcal Infections

In 1993, the CDC recommended the following regimen for treating uncomplicated gonococcal infections[25]:

- ceftriaxone 125 mg, administered intramuscularly in a single dose, or
- cefixime 400 mg, administered orally in a single dose, or
- ciprofloxacin 500 mg, administered orally in a single dose, or
- oflaxicin 400 mg, administered orally in a single dose;

EXHIBIT 19-4

ANTIBIOTIC SELECTION CRITERIA FOR GONORRHEA

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Adapted with permission from Moran JS, Zeligman JM. Therapy for gonococcal infections: Options in 1989. *Rev Infect Dis*. 1990;12(Suppl 6):S633.

- plus a regimen that is effective against possible coinfection with *Chlamydia trachomatis*, such as doxycycline 100 mg, administered orally twice daily for 7 days.

In clinical trials, these recommended regimens cured more than 95% of anal and genital infections; any of the regimens may be used for uncomplicated anal and genital infection. Published studies indicate that ceftriaxone 125 mg and ciprofloxacin 500 mg can cure more than 90% of pharyngeal infections. If pharyngeal infection is a concern, one of these two regimens should be used.[25]

No ceftriaxone-resistant strains of *Neisseria gonorrhoeae* have been reported. The drawbacks of ceftriaxone are (1) it is expensive, (2) it is currently unavailable in vials smaller than 250 mg, and (3) it must be administered by injection. Some healthcare providers believe that the discomfort of the injection may be reduced by using 1% lidocaine as a diluent. Ceftriaxone also may abort incubating syphilis, a concern when gonorrhea treatment is not accompanied by a 7-day course of doxycycline or erythromycin for the presumptive treatment of chlamydia.[25]

Cefixime has an antimicrobial spectrum similar to that of ceftriaxone. Cefixime appears to be effective against pharyngeal gonococcal infection, but few patients with pharyngeal infection have been included in studies. No gonococcal strains resistant to cefixime have been reported. The advantage of cefixime is that it can be administered orally. Whether the 400-mg dose can cure incubating syphilis is not yet known.[25]

Ciprofloxacin, at a dose of 500 mg, provides sustained bactericidal levels in the blood. Ciprofloxacin can be administered orally and is less expensive than ceftriaxone. No resistance has been reported in the United States, but strains with decreased susceptibility to some quinolones are becoming common in Asia. Quinolones are contraindicated for pregnant or nursing women and for persons younger than 17 years of age, on the basis of information from studies with animals. Quinolones are not active against *Treponema pallidum*.[25]

Many other antimicrobials are active against *Neisseria gonorrhoeae*. These guidelines are not intended to be a comprehensive list of all effective treatment regimens.

Follow-Up. Patients with uncomplicated gonorrhea who are treated with any of the regimens in these guidelines need not return for a test of cure. Patients whose symptoms persist after treatment should be evaluated by culture for *N gonorrhoeae*, and any gonococci isolated should be tested for antimicrobial susceptibility. Persistent urethritis, cervicitis, or proctitis also can be caused by *Chlamydia trachomatis* and other organisms.

Management of Sexual Partners. Patients should be instructed to refer their sexual partners for evaluation and treatment. Sexual partners of *symptomatic* patients who have gonorrhea should be evaluated and treated for both *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections if their last sexual contact with the patient was within 30 days of onset of the patient's symptoms. If the index patient is asymptomatic, sexual partners whose last sexual contact with the patient was within 60 days of diagnosis should be evaluated and treated.

Disseminated Gonococcal Infection

The 1993 CDC recommendations also specify the following treatment for patients with disseminated gonococcal infection[25]:

- Recommended initial regimen:
  - ceftriaxone 1 g, administered intramuscularly or intravenously every 24 hours.
- Alternative initial regimens:
  - cefotaxime 1 g, administered intravenously every 8 hours, or
  - ceftizoxime 1 g, administered intravenously every 8 hours, or,
  - for persons allergic to β-lactam drugs, spectinomycin 2 g, administered intramuscularly every 12 hours.

All regimens should be continued for 24 to 48 hours after improvement begins; then therapy can be switched to one of the following regimens to complete one full week of antimicrobial therapy[25]:

- cefixime 400 mg, administered orally twice daily, or
- ciprofloxacin 500 mg, administered orally twice daily.

Ciprofloxacin is contraindicated for children, adolescents younger than 17 years of age, and pregnant and lactating women.

Hospitalization is recommended for initial therapy, especially for patients who cannot be relied on to comply with treatment, for those whose

diagnosis is uncertain, and for those who have purulent synovial effusions or other complications. Patients should be examined for clinical evidence of endocarditis and meningitis. Patients treated for disseminated gonococcal infection should be treated presumptively for concurrent *Chlamydia trachomatis* infection.[25]

Pregnant Women

Pregnant women should not be treated with quinolones or tetracyclines. They should be treated with a recommended or alternative cephalosporin, following the regimen for disseminated gonococcal infection, above.[25]

CHANCROID

Chancroid is an STD caused by the Gram-negative coccobacillus *Haemophilus ducreyi*. Worldwide, chancroid is a more important cause of genital ulcers than syphilis, and there is a clear association between chancroid, poverty, and poor hygiene. This association is reflected in the incidence of the disease, which is highest in underdeveloped tropical and subtropical countries.

Chancroid was well known during the Civil War, as Surgeon J. G. Bradt of the 26th Massachusetts Volunteers, New Orleans, Louisiana, reported on 1 January 1863:

> Of the various forms of venereal disease, chancre of the non-indurated variety is the most common. It is accompanied in a majority of cases with bubo. The sores yield readily to cauterization with acid nitrate of mercury and applications of black wash, the bowels meanwhile being regulated and the patient kept on a low diet.[40(p892)]

There is ample epidemiological evidence that the incidence of chancroid increases dramatically during wartime.[10] Among U.S. troops in the Korean conflict, chancroid was 14- to 21-fold more common than gonorrhea.[62] A study conducted in 1969 found that among troops in Vietnam, chancroid was second only to gonorrhea in the total reported cases of venereal disease (Figure 19-14).[63]

Chancroid is more common in uncircumcised men, and the disease is more often reported in men, as well. However, women may have inapparent or mildly symptomatic infections for which they do not seek medical care. In addition, female prostitutes constitute an important reservoir of infection.[64] Of prostitutes who were implicated as sources of chancroid infection, only 10% had genital ulcers, and 4% were either transient or persistent asymptomatic genital carriers.[10]

Recent epidemiological studies have noted an association between the presence of genital ulcer disease and a significant risk of acquiring HIV infection. In both men and women who are exposed to partners who are infected with HIV-1, those who develop genital ulcer disease are at increased risk of HIV-1 seroconversion.[18] In developing countries, from 10% to 30% of patients presenting with STDs may have genital ulcer disease, of which chancroid is the most commonly reported.[65] In a study of female prostitutes in Nairobi with genital ulcer disease, HIV-1 could be isolated from the ulcer exudate in 11% of these patients.[66] In another study of 19 men presenting with confirmed chancroid, HIV-1 could be isolated by viral culture from the ulcers of two of seven HIV-1–positive patients.[67] Polymerase chain reaction confirmed the presence of the virus in genital exudate in six of the same seven men. The fact that it was possible to culture virus from these chancroidal ulcers suggests that a concentration of virus sufficient to result in transmission from such lesions is possible.[67] Not surprisingly, uncircumcised men are at greater risk of acquiring both chancroid and HIV-1 infection.[68]

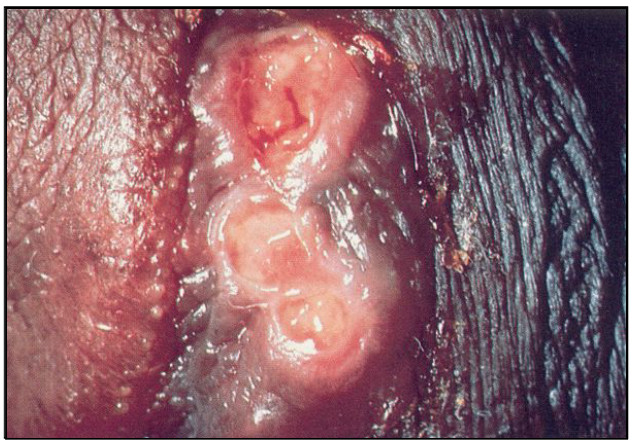

Fig. 19-14. A painful, ragged, necrotic, undermined ulcer of chancroid in the coronal sulcus of the penis. The yellowish pseudomembrane is characteristic of chancroid, but can be confused with herpes simplex or other secondarily infected penile ulcerations.

Clinical Manifestations

Following an incubation period that varies from 2 to 35 days (average 7 d), a small papule develops at the site of initial infection.[69] This rapidly becomes pustular and then ulcerates as a result of thrombotic occlusion of the underlying dermal vessels. The ulcer enlarges, rapidly forming a crater with ragged, undermined borders surrounded by a thin rim of erythema. The ulcer floor is covered by a grayish membrane; removal of this membrane reveals a glistening base of granulation tissue. Unlike the chancre of primary syphilis, the chancroidal ulcer is painful and the border is not indurated. Autoinoculation of surrounding areas results in multiple ulcers in various stages of evolution, which is a more common finding than a solitary lesion (Figure 19-15). Ulcers may range from a few millimeters to more than 2 cm in diameter. There are no constitutional symptoms.[10]

In men, the foreskin is the region most commonly affected, with lesions found less frequently on the glans or penile shaft. In women, the labia majora, introitus, vagina, and perianal areas are involved. Homosexual men may present with chancroidal lesions in the perianal area, as well. Extragenital lesions are rare, and disseminated infection with *H ducreyi* has not been reported.[10]

In about 50% of cases, unilateral, occasionally bilateral, tender, inguinal lymphadenitis (ie, a bubo) develops and is characteristic of chancroid. The overlying skin may vary from erythematous to a dusky violaceous color. If untreated, buboes progress to form soft, fluctuant abscesses that often rupture spontaneously, leaving large, nonhealing, serpiginous ulcers.[70] Aspiration of fluctuant buboes before they rupture will promptly relieve discomfort and prevent this complication (Figure 19-16). There is no permanent immunity following chancroid infection.

There are several clinical variants of the chancroidal ulcer:

- Patients with transient chancroid present with a small, evanescent ulcer that remains for less than 1 week. Rapid healing is followed by painful inguinal lymphadenitis that must be differentiated from lymphogranuloma venereum.
- Patients with follicular chancroid present with small, follicular ulcerations in the perineum, which resemble bacterial folliculitis.[71]
- Patients with phagedenic chancroid present with large, rapidly spreading, necrotic ulcerations, which may result in extensive destruction or formation of a urethral fistula. Superinfection with anaerobic bacteria such as *Treponema vincentii*, *Fusobacterium nucleatum*, and *Leptotrichia buccalis* are responsible for the massive ulceration.[10]
- Other uncommonly reported clinical variants include dwarf chancroid, papular chancroid, and giant chancroid.[71]

Laboratory Diagnosis

Gram's Stain

A Gram-stained smear of a specimen taken from a penile ulcer or bubo aspirate may allow a preliminary diagnosis of chancroid in approximately half the patients. To properly obtain a specimen, the ulcer should first be cleaned with physiological saline and then dried. The specimen is obtained with a cotton-tipped applicator from the undermined edge of the ulcer, and then carefully rolled across a glass microscope slide in one direction only (this is important, as it will preserve the morphologic appearance of the organism). The Gram-negative coccobacilli are found in small clusters or parallel chains of organisms described as "school-of-fish" or "railroad-track" patterns (Figure 19-17). Routine light microscopy lacks both sensitivity and specificity because Gram-negative coccobacilli that are morphologically similar to *Haemophilus ducreyi* are present. As a result, Gram-stained smears from

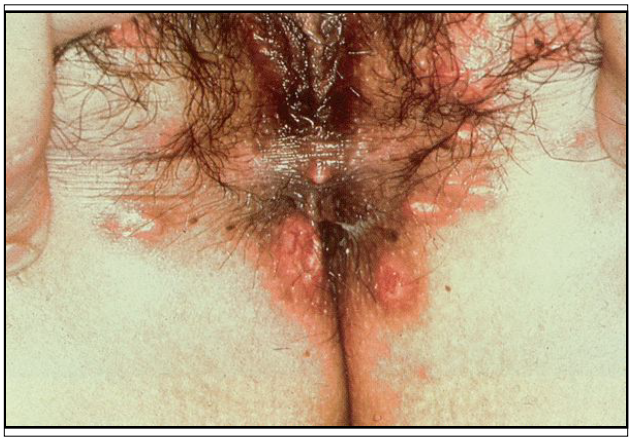

Fig. 19-15. Multiple, small, vulvar erosions of chancroid can easily be confused with lesions of genital herpes infection. Smears and culture are required to distinguish the two. Compare with the lesions shown in in Fig. 19-26.

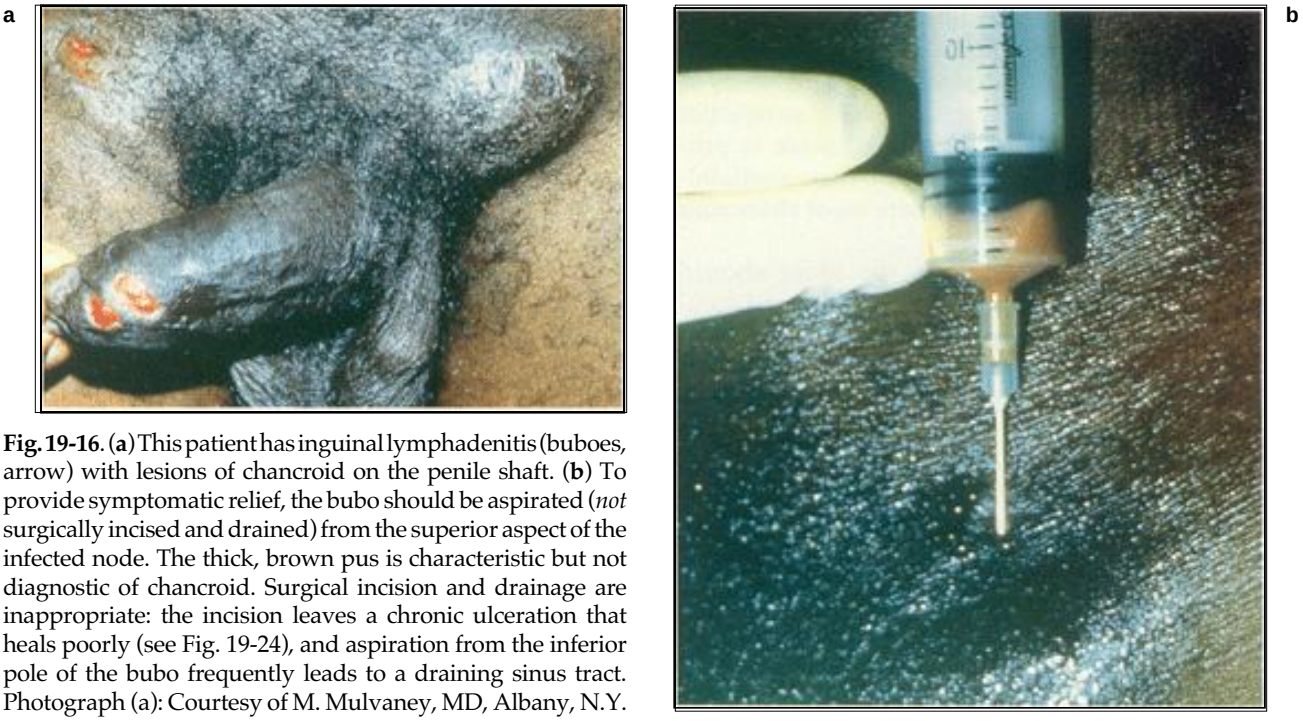

Fig. 19-16. (**a**) This patient has inguinal lymphadenitis (buboes, arrow) with lesions of chancroid on the penile shaft. (**b**) To provide symptomatic relief, the bubo should be aspirated (*not* surgically incised and drained) from the superior aspect of the infected node. The thick, brown pus is characteristic but not diagnostic of chancroid. Surgical incision and drainage are inappropriate: the incision leaves a chronic ulceration that heals poorly (see Fig. 19-24), and aspiration from the inferior pole of the bubo frequently leads to a draining sinus tract. Photograph (a): Courtesy of M. Mulvaney, MD, Albany, N.Y.

genital ulcers or bubo aspirates are often inconclusive. When available, culture confirmation is preferable to Gram-stained smears.[72]

Culture and Serology

Epidemiological studies and laboratory isolation of *H ducreyi* from suspected cases of chancroid have been hampered by (*a*) the lack of reliable, inexpensive culture media and (*b*) the absence of a typing system to assist in contact tracing. Additionally, *H ducreyi* is nearly biochemically inert (ie, nonreactive) on a variety of standard in vitro bacteriological tests, a characteristic that has hindered the development of serologic tests. Recent improvements in culture media have replaced the liquid- or clotted-blood–based media of the past. Currently, gonococcal agar base and Mueller-Hinton agar base are

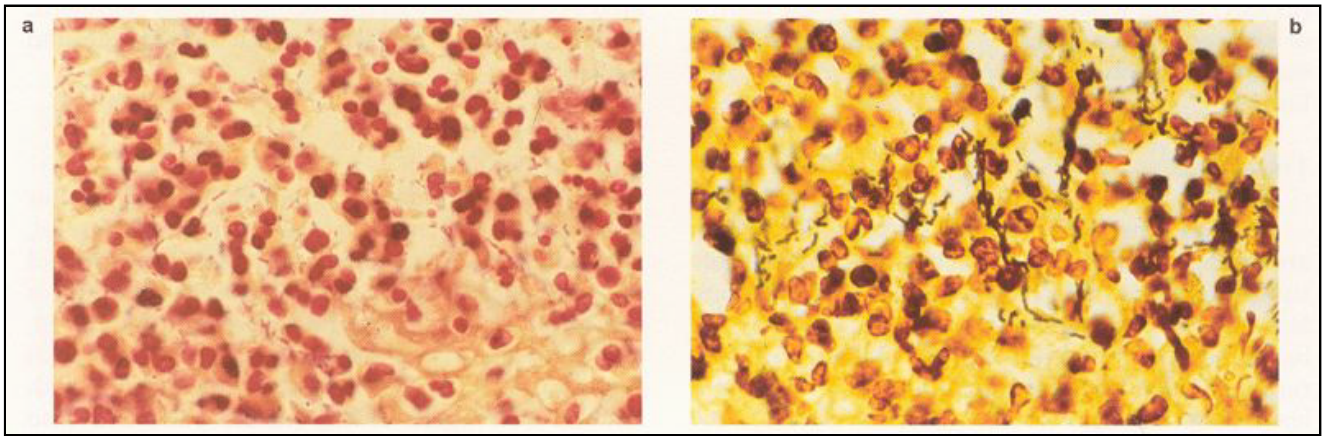

Fig. 19-17. (**a**) This biopsy specimen from a vulvar lesion shows Gram-negative rods, some in chains (Brown and Hopf stain, original magnification 290X). (**b**) The same biopsy specimen is stained with Warthin-Starry silver stain to demonstrate numerous organisms (Warthin-Starry stain, original magnification 290X). Photographs: Courtesy of R. C. Neafie, Armed Forces Institute of Pathology, Washington, DC.

two selective media that are used to culture *H ducreyi*. Unfortunately, these media, which consist of gonococcal chocolate agar, supplemented with blood or serum and vitamins, amino acids, and antibiotics (vancomycin), are expensive and difficult to produce commercially. Consequently, their availability in developing countries, where most chancroid is reported, is limited.[73]

Material from the base of the ulcer should promptly be inoculated on suitable media and incubated at a reduced temperature (33°C–35°C) in a moist, carbon dioxide–rich (5%–10%) chamber. Small, yellow-gray, semiopaque or translucent colonies develop in 2 to 4 days, but may require up to 7 days after inoculation for growth. The colonies have a characteristic adherence and can be moved as an entire colony across the culture plate with an inoculating loop.[10] Confirmatory identification utilizes the porphyrin test, which demonstrates a requirement for hemin (the X factor) for growth, and the oxidase test demonstrates the absence of a requirement for nicotinamide adenine dinucleotide (NAD, the V factor).[70]

Serologic tests and specific monoclonal antibodies based on mouse and rabbit systems are still experimental and are currently unavailable. Several promising antisera without cross-reactivity with other *Haemophilus* species may be available in the future. Monoclonal antibodies specific for *H ducreyi* have been produced[74] and used to detect the antigen in lesional material from experimental animals and from material in patients with chancroid. Serologic tests such as complement fixation, precipitin, and agglutination tests may be positive in some patients with *H ducreyi* infections. A recently described enzyme-linked immunosorbent assay (ELISA) using whole, lysed *H ducreyi* as the source of antigen is promising.[70,75] The nature and duration of the antibody response to *H ducreyi* is unknown.

Treatment

As with other STDs caused by bacteria, strains are emerging worldwide that are resistant to multiple antibiotics. The 1993 CDC recommendations for treatment of chancroid in the United States are listed below. Susceptibility of *H ducreyi* to the recommended and alternative antimicrobials varies throughout the world. Clinical efficacy, relapses, and treatment failures should be carefully monitored—with laboratory determination of antibiotic susceptibility patterns, if available.

Recommended Regimens

The following are the CDC's 1993 recommended regimens for the treatment of chancroid[25]:

- azithromycin 1 g, administered orally in a single dose, or
- ceftriaxone 250 mg, administered intramuscularly in a single dose, or
- erythromycin base 500 mg, administered orally four times daily for 7 days.

All three recommended regimens are effective for the treatment of chancroid in patients without HIV infection. Azithromycin and ceftriaxone offer the advantage of single-dose therapy. Antimicrobial resistance to ceftriaxone and azithromycin has not been reported. Although two isolates resistant to erythromycin were reported from Asia during the 1980s, similar isolates have not been reported.

Alternative Regimens

The following are the CDC's alternative regimens for the treatment of chancroid[25]:

- amoxicillin 500 mg and clavulanic acid 125 mg, administered orally three times daily for 7 days, or
- ciprofloxacin 500 mg, administered twice daily for 3 days.

Ciprofloxacin is contraindicated for pregnant and lactating women, children, and adolescents younger than 17 years of age.

These alternative regimens have not been evaluated as extensively as the recommended regimens. Neither regimen has been studied in the United States.

Follow-Up

Patients should be reexamined 3 to 7 days after initiation of therapy. If treatment is successful, ulcers improve symptomatically within 3 days and improve objectively within 7 days after therapy is initiated. If no clinical improvement is evident, the medical officer must consider whether (*a*) the diagnosis is correct, (*b*) coinfection with another STD agent exists, (*c*) the patient is also infected with HIV, (*d*) the treatment was not taken as instructed, or (*e*) the strain of *H ducreyi* causing the infection is resistant to the prescribed antimi-

crobial drug. The time required for complete healing is related to the size of the ulcer; large ulcers may require more than 2 weeks. Clinical resolution of fluctuant lymphadenopathy is slower than that of ulcers and may require needle aspiration through adjacent intact skin—even during successful therapy.

Management of Sexual Partners

Persons who have had sexual contact with a patient who has chancroid within the 10 days before the onset of the patient's symptoms should be examined and treated. The examination and treatment should be done even in the absence of symptoms.

GRANULOMA INGUINALE

Granuloma inguinale (also called Donovanosis) is a sexually transmitted disease caused by the Gram-negative encapsulated bacillus *Calymmatobacterium granulomatis*. In 1905, C. Donovan described intracellular organisms with peculiar clumping of chromatin at either end that produce a "closed–safety pin" morphology on Giemsa stain.[76] The disease is rare in the United States, although sporadic cases are reported from southern states. In certain parts of the world, especially New Guinea, central Australia, India, the Caribbean countries, and Africa, the disease is endemic and may be among the most prevalent STDs. The disease is reported more often among groups with lower socioeconomic status, and poor hygiene may play a role in transmission and susceptibility to infection.[77]

Significant controversy exists regarding the mode of transmission of the organism. The primary mode appears to be through sexual contact. The disease is considered to be only mildly contagious and repeated exposure is necessary for clinical infection to occur. However, the disease is only rarely reported in prostitutes and is uncommon in sexual partners of clinically infected individuals.[78] The frequent occurrence of perianal and penile lesions in homosexual men who practice anal intercourse has focused attention on colonization of the intestinal tract by organisms resembling *C granulomatis*. Auto-inoculation of fecal material onto traumatized or diseased skin may result in clinical infection. It is possible that transmission occurs by both sexual and nonsexual modes: perineal contamination with fecal organisms may precede transfer by sexual intercourse.[10,79] The disease has been reproduced only by introducing infected material from the granuloma inguinale lesion into an uninfected human. Transfers of organisms grown on tissue or bacterial cultures have not produced clinical disease.[80]

Clinical Manifestations

The incubation period following exposure is unknown although it has been estimated to range from weeks to months. The primary lesion is an intensely pruritic papule that occurs in the anogenital area in more than 90% of cases. Less commonly, the initial lesion may be a firm, subcutaneous nodule that later suppurates, rupturing through the skin to produce an ulcer. In women, the primary lesion is frequently overlooked by the patient.[10] The ulcers are clean, sharply defined, granulomatous, usually painless lesions (Figure 19-18). Secondary infection may, however, result in painful lesions or large, mutilating, necrotic ulcerations.[80] Autoinoculation may cause multiple primary lesions. These often coalesce into a large, irregular ulcer that enlarges slowly and bleeds easily on contact; the base is covered by abundant, beefy-red, granulation tissue.[81] Over time, the edge of the ulcer becomes elevated, thickened, and grayish in color. There are no constitutional symptoms in the absence of secondary infection.

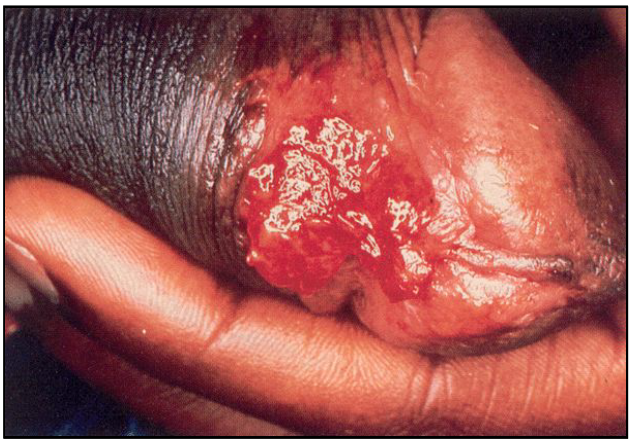

Fig. 19-18. This ulcer of granuloma inguinale is covered by exuberant, beefy-red, granulation tissue The disease is asymptomatic and rare, and patients may have multiple lesions as a result of autoinoculation. The diagnosis is difficult to make clinically; a biopsy is usually necessary.

Bacterial spread through subcutaneous tissues in the inguinal region may lead to large subcutaneous granulomas known as pseudobuboes, which can mimic lymphogranuloma venereum or metastatic squamous cell carcinoma. These granulomas can rupture, leading to typical granulomatous ulcers of the overlying skin. True inguinal lymphadenopathy in granuloma inguinale is rare, except when extensive secondary infection[77] or coexistent involvement of the lymph nodes with syphilis, lympho-granuloma venereum, or malignancy are present.[10]

In addition to the classic large, exuberant, beefy-red ulcer with rolled borders (ie, the ulcerovegetative type), other clinical variants occur, albeit less frequently (Figure 19-19):

- In 1975, a case of extensive necrosis of the penis and perineum with production of a large, mutilating lesion and destruction of most of the penile tissue was reported.[80] This patient had no systemic involvement.
- Patients with a rare hypertrophic form present with two types of ulcers: (1) the large, vegetative masses and (2) the *cicatricial* type, which produces extensive, spreading scar formation as the primary disease process, rather than healing.[82]

Lesions often continue to expand for years and spontaneous healing is slow to occur. Healing generally occurs with extensive fibrosis and significant deformity, and functional disability can occur.

Complications

Complications of extensive or untreated granuloma inguinale include

- scarring and strictures of the anus, urethra, and vagina, with deformity of the external genitalia;
- elephantiasis of the penis, scrotum, or vulva secondary to destruction of the lymphatics; and

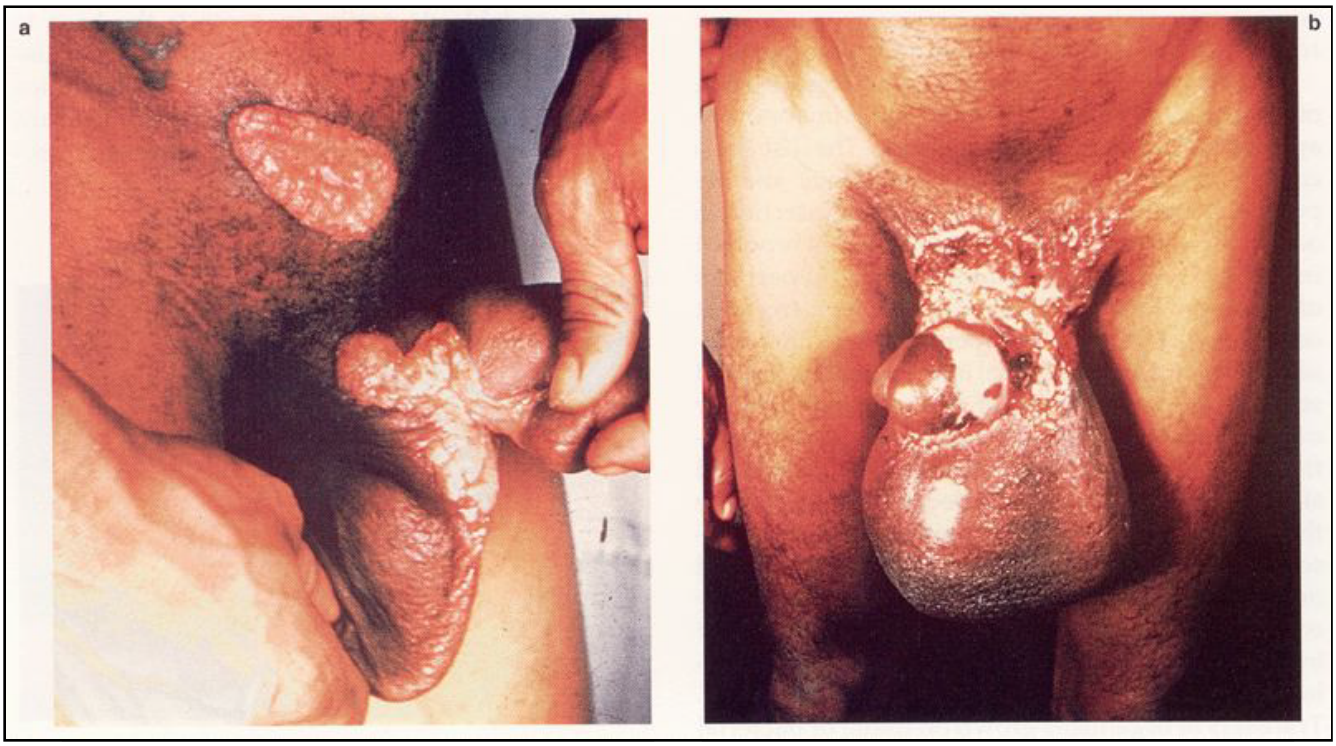

Fig. 19-19. Granuloma ingunale often causes large, ulcerative lesions. (**a**) This patient has a destructive lesion of the penile shaft and a large, exophytic lesion of the lower abdomen. (**b**) Undiagnosed, untreated granuloma inguinale may lead to massive scrotal and inguinal lymphedema. Photographs: Courtesy of Walter Reed Army Medical Center Dermatology Service slide file, Washington, DC.

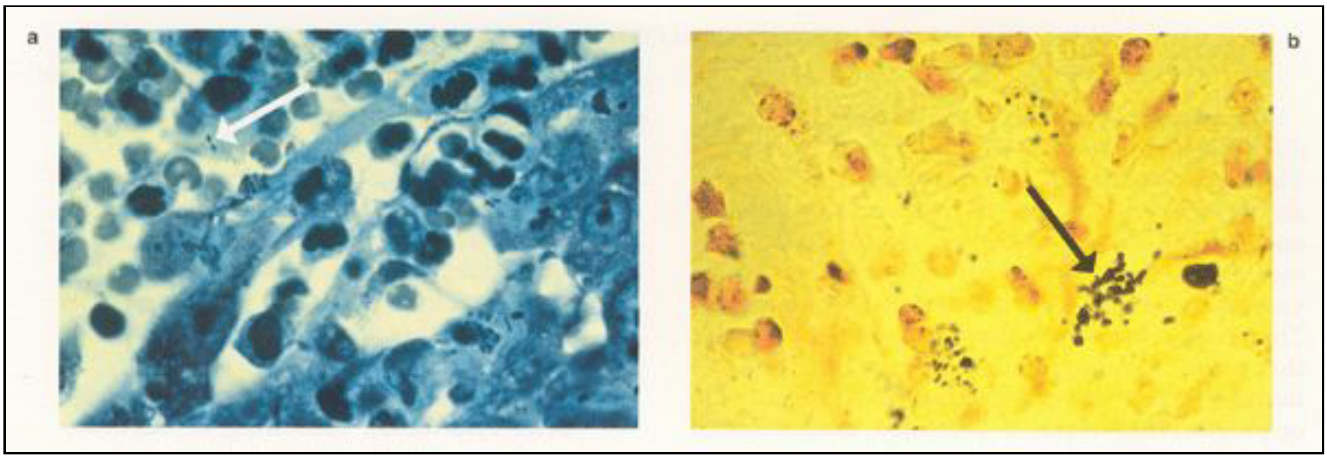

Fig. 19-20. (**a**) This Wright-Giemsa stain of a crush preparation of tissue shows intracellular bacilli (Donovan bodies) (arrow). (**b**) The organisms (arrow) appear black in the Warthin-Starry stain. Photographs: Courtesy of Walter Reed Army Medical Center Dermatology Service slide file, Washington, DC.

- systemic spread of the disease to visceral organs, resulting in death.[83]

Malignancy, either basal cell or squamous cell carcinoma, has been reported to arise in long-standing lesions of granuloma inguinale. Extragenital lesions have been reported in a small number of patients, with occasional involvement of the intestinal tract, bone, orbit, liver, spleen, and oral mucosa.[82]

Laboratory Diagnosis

The diagnosis of granuloma inguinale is based primarily on stained smears of crushed tissue obtained from the ulcer. The bacterium is an intracellular parasite of macrophages; therefore, swabs or superficial scrapings from the lesion are apt to be nondiagnostic. The lesion is first cleaned with normal saline on a cotton gauze pad and then wiped dry. Under local anesthesia, a punch biopsy, curettage, or thin wedge of the ulcer base or margin is obtained. The tissue is placed between two glass slides and crushed; the slides are separated and then air-dried. Wright-Giemsa stain is used to demonstrate clusters of blue-to-black organisms that resemble safety pins within the vacuoles of enlarged macrophages.[77,84] Additionally, the Warthin-Starry stain has been used to demonstrate the intracytoplasmic organisms (Figure 19-20).[80]

Donovan bodies may be difficult to find in formalin-fixed, hematoxylin-eosin–stained sections. However, thin, plastic-embedded sections permit easy identification of the rod-shaped encapsulated organisms within macrophages.[80]

Culture of the organism is beyond the capabilities of most laboratories,[81] as the organism fails to grow on conventional solid media. Only 14 isolates have been reported—the latest in 1962. Isolation is hampered by the need to eliminate the contaminants frequently present in genital ulcers.[85]

Complement-fixation serologic tests and skin testing are not routinely available because the disease is rare and a suitable source of antigen is lacking.

Treatment

Numerous antibiotic regimens have been proposed for the treatment of granuloma inguinale. Tetracycline is the most effective, administered orally as a dose of 500 mg every 6 hours for 21 days. Treatment should be continued until all lesions have completely resolved.[77] Other tetracyclines (eg, doxycycline and minocycline) have also been used successfully.[86]

Alternative regimens include erythromycin 500 mg, administered orally every 6 hours for 12 weeks, or, in cases of treatment failure with tetracycline and erythromycin, ampicillin 500 mg, administered orally every 6 hours for the same duration. Lincomycin, chloramphenicol, and gentamicin are also effective.[77] In 1991, successful treatment was reported in India with norfloxacin.[85]

Inguinal pseudobuboes may require surgical excision if they fail to resolve with antibiotic therapy.[80]

LYMPHOGRANULOMA VENEREUM

The various serotypes of the bacterium *Chlamydia trachomatis* cause a wide spectrum of serious diseases (Table 19-4).[87] Infections caused by chlamydia, which includes pelvic inflammatory disease and nongonococcal urethritis, are the most common STDs; they account for millions of cases per year and a significant incidence of sterility in women. This chapter focuses on the serotypes of chlamydia that cause lymphogranuloma venereum, a condition characterized by painful inguinal lymphadenitis or proctocolitis which, if untreated, may result in scarring and chronic lymphatic obstruction.

Cases of lymphogranuloma venereum are uncommon in the United States and Europe, with only a few hundred cases reported annually; but the disease is endemic in Africa, India, parts of Southeast Asia, South America, and the Caribbean region.[88] In the United States, a number of outbreaks have been reported among sailors, soldiers, and travelers returning from endemic areas. In a study conducted in 1968 of 20 military patients with lymphogranuloma venereum, 19 were either returning from Vietnam or were sexual partners of a person returning from Southeast Asia.[89] Clusters of cases in the United States occur in Washington, D. C., and the southeastern states, particularly affecting the poor, urban, black population.[90] This parallels epidemiological data gathered from overseas, where lymphogranuloma venereum is found to be more common in urban areas, in particular among the sexually promiscuous and the lower socioeconomic classes.

Clinical Manifestations

Lymphogranuloma venereum demonstrates three typical stages, although not every patient will manifest signs and symptoms of each stage[88]:

1. the primary stage, consisting of a small, inconspicuous, transient papule or ulcer;
2. the secondary stage, consisting of acute inguinal lymphadenitis with bubo formation (ie, the inguinal syndrome), associated with fever and other constitutional symptoms; and
3. the uncommon third stage (ie, the anogenitorectal syndrome), consisting of subacute to chronic infection leading, in any combination, to (*a*) chronic ulceration, (*b*) fistulae and strictures of the rectum, vagina, or urethra, and (*c*) lymphatic obstruction.

Following an incubation estimated to be between 3 and 12 days, a primary lesion develops at the site of inoculation. The primary lesion, found in fewer than one half of patients,[91] is most often a herpetiform ulcer, although a small papule, a shallow ulcer or erosion, or symptoms of nonspecific urethritis can also occur. The primary lesion often goes unnoticed by the patient, particularly in women. In men, it is most commonly found in the coronal sulcus and, in a minority of patients, elsewhere on the external genitalia (Figure 19-21).[88]

After a latent period of 1 to 4 weeks following the primary lesion, regional lymph node involvement develops (ie, the inguinal syndrome). The site of the primary lesion determines which group of lymph nodes will be affected, which, in turn, affects the clinical presentation (Table 19-5). In men, painful, regional lymphadenopathy—usually unilateral—develops, with enlargement of nodes above and below the inguinal ligament. This produces the

TABLE 19-4

SEROTYPES OF *CHLAMYDIA TRACHOMATIS* AND HUMAN DISEASE

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Adapted with permission from from Schachter J. Chlamydial infections. Part 1. *N Engl J Med*. 1978;298(8):429.

TABLE 19-5

SITE OF PRIMARY INFECTION AND LYMPHATIC INVOLVEMENT IN LYMPHOGRANULOMA VENEREUM

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Reprinted with permission from Perine PL, Osoba AO. Lymphogranuloma venereum. In: Holmes II, Mardh P-A, Sparling PF, et al, eds. *Sexually Transmitted Diseases*. New York, NY: McGraw-Hill; 1990:197.

"groove" sign, which is virtually pathognomonic of lymphogranuloma venereum. The nodes enlarge and become fluctuant, developing a striking bluish red hue (ie, the characteristic "blue balls") in the overlying skin (Figure 19-22). They subsequently rupture through the skin to form deep ulcerations with draining sinus tracts.[10] Only 20% to 30% of women will present with acute inguinal lymphadenitis. Patients complain of deep pelvic, abdominal, or low back pain.[88]

Hematogenous dissemination of the organism results in clinical signs and symptoms of malaise, fever, hepatitis, pneumonitis, arthritis, conjunctivitis, and even encephalitis. Erythema multiforme, erythema nodosum, photosensitivity, and scarlatiniform eruptions may be seen in association with acute infection.[77,86]

Long-standing, untreated disease leads to the development of deep ulcerations, secondary infection with purulent discharge from the anorectal area (proctocolitis) or vagina, and, ultimately, fistulae and scarring. In the anorectal region, strictures and fibrosis of the bowel wall cause fever, constipation, diminished caliber of stools, cramping abdominal pain, and weight loss. Bowel perforation and peritonitis leading to death have been reported.[77]

Following an outbreak of lymphogranuloma venereum in a university, a 1976 report[92] estimated that significant penile deformity in chronic lymphogranuloma venereum occurred in fewer than 5% of infected men. Elephantiasis of the penis and scrotum and chronic penile ulcerations were also reported. However, serious genitourinary deformity occurs in nearly 25% of all untreated women. Anal and rectovaginal fistula formation with fibrosis are reported complications. *Esthiomene* is a deforming vulvar elephantiasis characterized by edema, fibrosis, chronic ulceration, and scarring of the external female genitalia.[92]

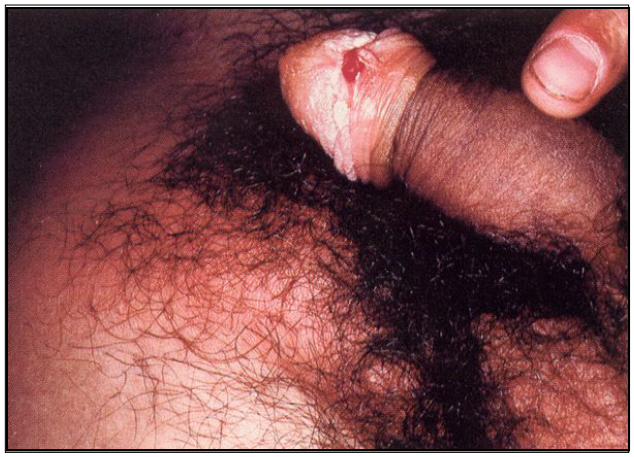


Fig. 19-21. A rarely seen primary lesion of lymphogranuloma venereum on the penile frenulum. This small, shallow erosion is easily confused with a traumatic injury, genital herpes infection, or syphilis. The penis was rotated upward and to the right to show the lesion.

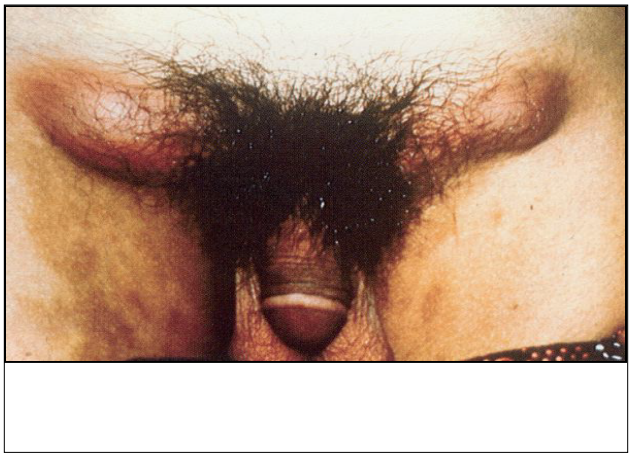


Fig. 19-22. Massive, bilateral, inguinal lymphadenopathy of lymphogranuloma venereum with large, fluctuant nodes. Spontaneous rupture, which is imminent, may lead to chronic ulcers that heal poorly. Photograph: Courtesy of Walter Reed Army Medical Center Dermatology Service slide file, Washington, DC.

Laboratory Diagnosis

The diagnosis of lymphogranuloma venereum rests principally on (*a*) the exclusion of other STDs in which patients present with lymphadenopathy (primarily syphilis, chancroid, and genital herpes infections) and (*b*) the lymphogranuloma venereum complement-fixation test. Complement-fixation titers of 1:64 or greater are considered positive for the disease. There is cross-reactivity with other chlamydial infections, and high complement-fixation titers have been found in asymptomatic individuals and in those with other chlamydial infections. Titers of less than 1:64 are equivocal and should be interpreted with care.[88]

Several newer tests have been developed, but these are not widely available. The microimmunofluorescent test detects type-specific antibody (L-1, L-2, or L-3) in the serum of infected individuals.[93] IgG antibody titers greater than 1:1,000 or IgM titers greater than 1:32 on the microimmunofluorescent test are seen in most patients with lymphogranuloma venereum.[94] A direct fluorescent antibody technique has been introduced to detect the presence of antigen in biopsy specimens or, in a recent case, of smears prepared from lymph node aspirate.[95]

Culture of the organism on mouse brain, yolk sac, or tissue culture (ie, McCoy cells) is the definitive diagnostic test but is generally unavailable.[77] The Frei test, which involved the intradermal injection of sterilized bubo aspirate, is no longer performed and is mentioned only for historical interest.

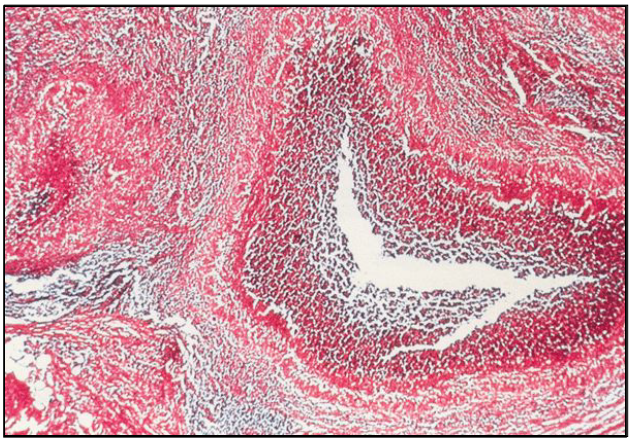


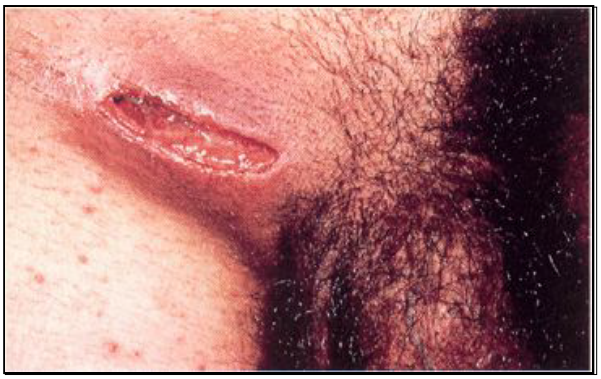
Fig. 19-23. This histological section through an excised lymph node shows triangular stellate abscesses of lymphogranuloma venereum (hematoxylin-eosin stain, medium-power magnification).

Histological sections of involved lymph nodes show characteristic stellate abscesses surrounded by a palisading arrangement of epithelioid cells. No organisms can be seen in histological sections (Figure 19-23).[54]

Treatment

The CDC's 1993 recommended regimen for treatment of lymphogranuloma venereum is doxy-

a



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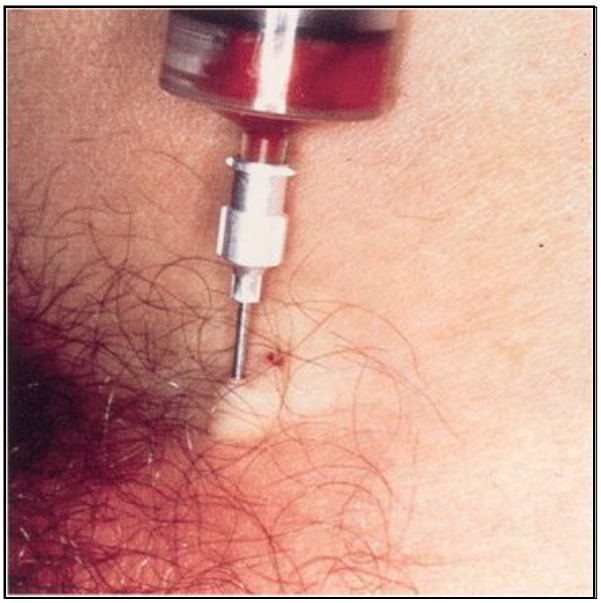


Fig. 19-24. (**a**) Surgical incision and drainage, as were inappropriately done in this patient with lympho-granuloma venereum, cause chronic, nonhealing, inguinal ulcers. (**b**) As seen in a different patient, the proper treatment is aspiration from the superior aspect of the node, which reduces pain and the risk of spontaneous rupture, and allows the lymphadenitis to resolve (also see Fig. 19-16).

cycline 100 mg, administered orally twice daily for 21 days.[25] The alternative regimens are the following[25]:

- erythromycin 500 mg, administered orally four times daily for 21 days; or
- sulfisoxazole 500 mg, administered orally four times daily for 21 days; or
- an equivalent course of sulfonamide.

Response to therapy is usually better in acute cases. Many cases require two or more 21-day courses of antibiotic before a clinical response is observed. Aspiration of fluctuant inguinal lymph nodes may speed recovery when rupture of those nodes is imminent. Incision and drainage is contraindicated, as complications such as scarring and delayed healing may occur (Figure 19-24).[96]

Follow-Up

Patients with lymphogranuloma venereum should be followed clinically until signs and symptoms have resolved.[25]

Management of Sexual Partners

Persons who have had sexual contact with a patient who has lymphogranuloma venereum within the 30 days before the onset of the patient's symptoms should be examined, tested for urethral or cervical chlamydial infection, and treated.[25]

Pregnant Women

Pregnant and lactating women should be treated with the erythromycin regimen.[25]

GENITAL HERPES INFECTION

Although public awareness of genital herpes infection (caused by herpes simplex viruses [HSVs]) has been eclipsed by the AIDS epidemic, infections caused by HSVs continue to be an enormous public health problem (Figure 19-25). Although genital herpes infection is not a reportable disease and therefore exact figures are not available, various estimates of its incidence in the United States suggest that (*a*) 5 to 20 million persons are infected, with 260,000 to 500,000 new cases per year; and (*b*) the incidence appears to be increasing.[97] This makes genital herpes infection the most common cause of genital ulceration in the industrialized nations.[98] The increase in this disease may be attributable to an increase in the number of sexual partners; earlier sexual activity among adolescents; and the introduction of oral contraceptives and other forms of contraception, which has led to earlier and more frequent casual sexual encounters.[99] Additionally, genital ulcer diseases, including genital herpes infection, have been linked to transmission of HIV to sexual partners.[100]

Fig. 19-25. Genital herpes infection was the "social disease" of the 1970s and 1980s. Drawing: Courtesy of B. E. Benson, Silver Spring, Md.

Clinical Manifestations

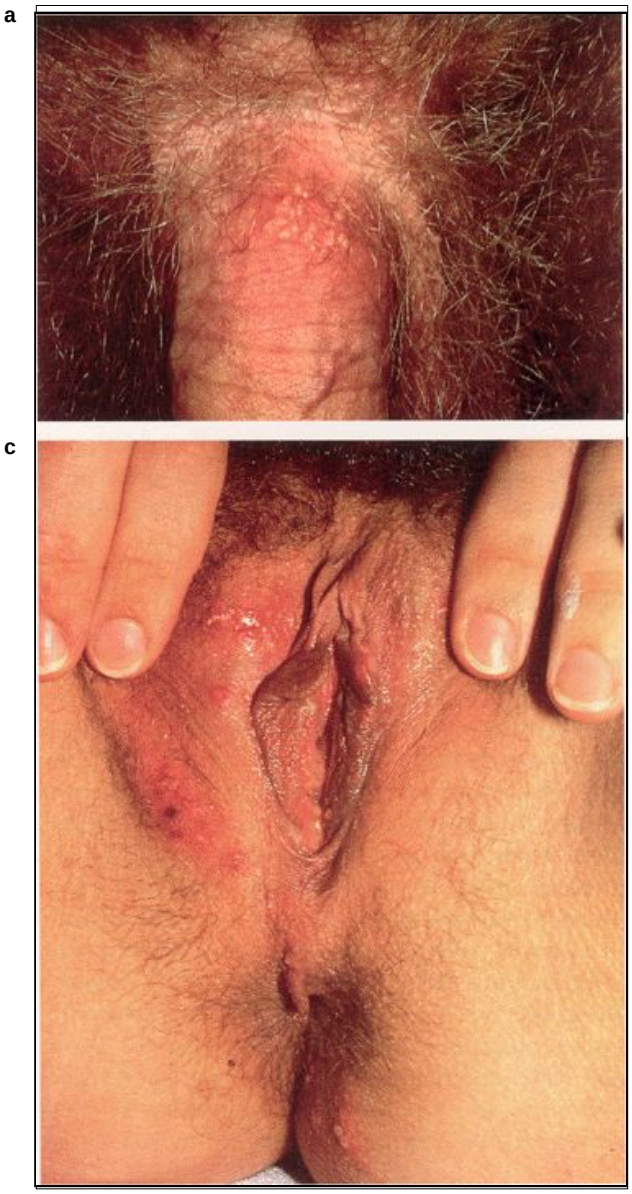
Primary Genital Herpes Infection

Following contact with an infected sexual partner, an incubation period of 3 to 7 days, rarely up to 3 weeks, ensues before clinical signs and symptoms appear.[101] Grouped vesicles on an erythematous, edematous base quickly develop and may cover extensive areas of perineal skin. Pain and itching, severe in some individuals, are reported by almost all patients with primary infection. First-episode infections are more severe in women. This may be due to cervical involvement as well as a greater total surface area of infection.[102] The vesicles rupture and coalesce into areas of extensive erosions associated with pain and tenderness. In women, lesions are found on the vulva (the most common location),

labia majora, labia minora, and the perianal skin (Figure 19-26). Women with involvement of the cervix or vagina present with erosions and a profuse, watery vaginal discharge. In men, vesicles are found most frequently on the glans, foreskin, and penile shaft. Autoinoculation may lead to extensive erosions and vesiculation of the penis and the pubic area. In homosexual men, primary herpetic lesions may be seen in the anus or the perianal area.[101] Signs and symptoms of herpes proctitis include rectal pain and discharge, tenesmus, constipation, fever, and malaise. A study published in 1983[103] reported that about one half of patients experience sacral paresthesias, impotence, urinary retention, and perianal vesicles; these findings are absent in patients with proctitis caused by *Neisseria gonorrhoeae* or chlamydia.

Tender inguinal lymphadenopathy develops during the second or third week of primary infection. Nodes are enlarged, firm, and nonfluctuant. HSV has been isolated from inguinal aspirates of affected nodes.[102]

Complications of primary infections are most common in women and include local extension of the lesions, extragenital involvement secondary to autoinoculation, and various neurological manifestations. Up to one third of patients develop complaints consistent with aseptic meningitis: stiff neck,



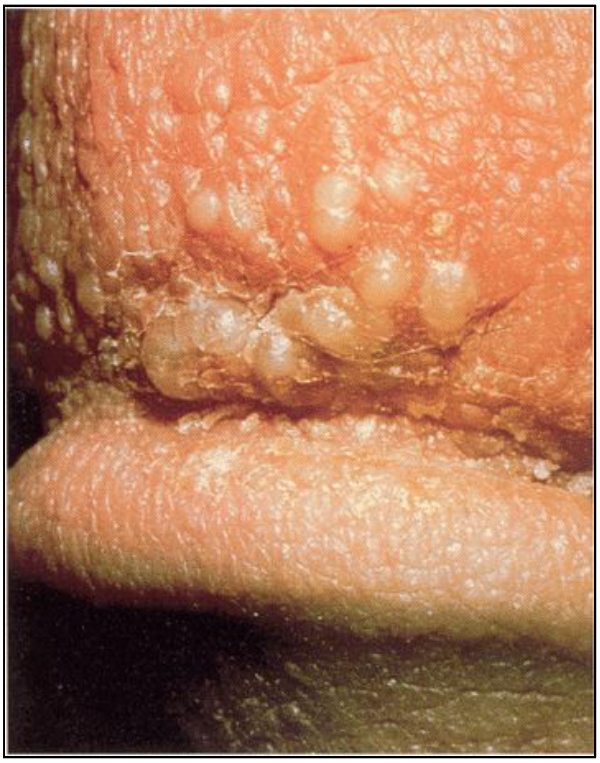


Fig. 19-26. A cluster of small herpetic blisters on (**a**) the penile shaft and (**b**) near the coronal sulcus (in a closer view of the blisters on a different patient). The patient in (**c**) has small blisters and shallow erosions at multiple sites on the right labial mucosal surface. In both males and females, clusters of small, painful erosions—which are actually ruptured vesicles—are often seen instead of intact vesicles. Compare with the erosions of chancroid in Fig. 19-16. Photograph (b): Courtesy of Colonel William D. James, Medical Corps, US Army, Walter Reed Army Medical Center, Washington, DC.

headache, and photophobia.[102] Encephalitis is a rare complication of genital herpes infection and is more often reported with HSV type 1 (HSV-1), although a fatal case of meningoencephalitis caused by HSV-2 in an individual infected with HIV was reported in 1990. (HSV-1 is more frequently associated with mucocutaneous infections, and HSV-2 with genital lesions; however, either type can be isolated from either location.) Notable findings in this case were (*a*) the development of an acyclovir-resistant strain of virus during therapy and (*b*) isolation of the same viral isolate from both a herpetic perirectal abscess and brain tissue.[104]

Other reported complications include temporary sacral anesthesia, urinary incontinence, and impotence. Cutaneous or visceral dissemination or thrombocytopenia may also occur.[105]

In both men and women, lesions persist for 2 to 6 weeks and then resolve, usually without scarring.

Nonprimary Genital Herpes Infection

In 1984, when evaluating patients with clinical primary genital herpes infection for the presence of antibody to HSV-2, researchers found that more than 50% of patients with *primary* genital herpes had antibodies to HSV-2 by Western blot analysis. This unexpected finding suggests that a significant number of patients have had asymptomatic or subclinical infections at an earlier time; therefore, this category of clinical infection is called *nonprimary*. The existence of this nonprimary genital herpes infection is important to remember when counseling patients or attempting contact tracing to identify the source of the virus.[106]

Recurrent Genital Herpes Infection

Within a year after the first episode, about two thirds of patients will have recurrent episodes of genital herpes infection. In one study, approximately 50% of these patients had monthly recurrences, 33% had recurrences every to 2 to 4 months, and 15% had recurrences fewer than 3 times in the first year.[107] Recurrent lesions are frequently inconspicuous, especially those localized to the cervix. In men, asymptomatic urethral infections are thought to occur at an incidence of approximately 1%.[101]

The clinical manifestations of recurrent disease are usually less severe and of shorter duration than primary infections. The risk of recurrence is influenced by (*a*) the type of herpes virus and (*b*) the host immune response to the viral infection. There is a lower rate of recurrence with HSV-1 compared to HSV-2. Researchers have hypothesized that the frequency of sacral ganglionic latency is lower in HSV-1 infections than in HSV-2, resulting in lower rates. Their evaluation of host cellular-immune factors demonstrated that high titers of neutralizing antibody after primary infection correlates with an increased risk of recurrent disease.[102]

The clinical presentation of recurrent disease differs considerably from that of primary infection. Approximately 50% of patients experience prodromal symptoms—tingling, itching, or pain—for a few hours to 1 to 2 days preceding the attack. The lesions tend to be unilateral and fewer in number, and are grouped vesicles on an erythematous base. Viral shedding averages only 4 days and healing is complete in about 10 days.[99] There is usually no lymphadenopathy or systemic symptoms associated with recurrent disease.

Two theories attempt to explain the reactivation of HSV from sacral ganglia[101]:

1. The ganglionic trigger theory proposes that a triggering stimulus (eg, menstruation, fever, or stress) reactivates the virus, which then travels down the peripheral nerve to epidermal cells, causing a skin lesion.
2. The skin trigger theory proposes that within epithelial cells there is a low level of viral replication that is eliminated by the host immune response. Injury to the skin (eg, trauma, sunburn) results in clinical disease by either suppressing local defenses or stimulating viral replication.

Complications of recurrent genital herpes infection are few. Erythema multiforme may develop in young patients 10 to 14 days following recurrent disease. The erythema multiforme may present as typical target lesions on the extremities or may develop into severe mucocutaneous involvement. Spontaneous improvement is the rule, although patients often have recurrent episodes for 5 to 6 years.[108]

Genital Herpes Infections in Immunocompromised Patients

Genital herpes infections in immunocompromised patients (eg, patients who are receiving chemotherapy, have received bone marrow transplants, or are infected with HIV) are more severe and more prolonged than in immunocompetent patients (Figure 19-27). Lesions are deep, necrotic, and painful; viral shedding persists for months in some patients with AIDS. In patients infected with HIV, lesions

are most commonly located in the perianal area, followed by the buttocks, scrotum, penis, and the orolabial area. Although there is an increased risk of dissemination in these patients, most untreated infections do not disseminate.[99]

Laboratory Diagnosis

Numerous laboratory techniques are currently available for the diagnosis of genital herpes infections, although only a few are in routine clinical use. These include viral culture, Tzanck and Papanicolaou smears, direct immunofluorescence staining, and viral serology. Other less frequently employed or research methods include immunoperoxidase staining, ELISA, electron microscopy, and tests to type and subtype virus isolates.

Viral Culture

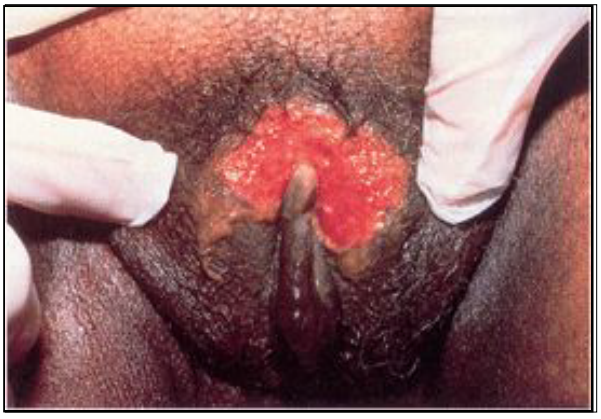
Isolation by tissue culture is the most sensitive method for the detection of HSV. The success of viral isolation depends on the type of lesion cultured (ie, intact vesicle or erosion), the age of the lesion, the size of the inoculum, the immune status of the patient, and the sensitivity of the cell culture (human foreskin fibroblast, monkey kidney, or primary rabbit kidney).[109] Viral cultures obtained from intact vesicles or pustules in patients with primary genital herpes infections are positive in almost 90% of patients, compared to less than 30% if crusted lesions are cultured.[99] In one large series, HSV was cultured from 94% of vesicles, 87% of pustules, 70% of ulcers, and only 27% of crusted lesions.[98]

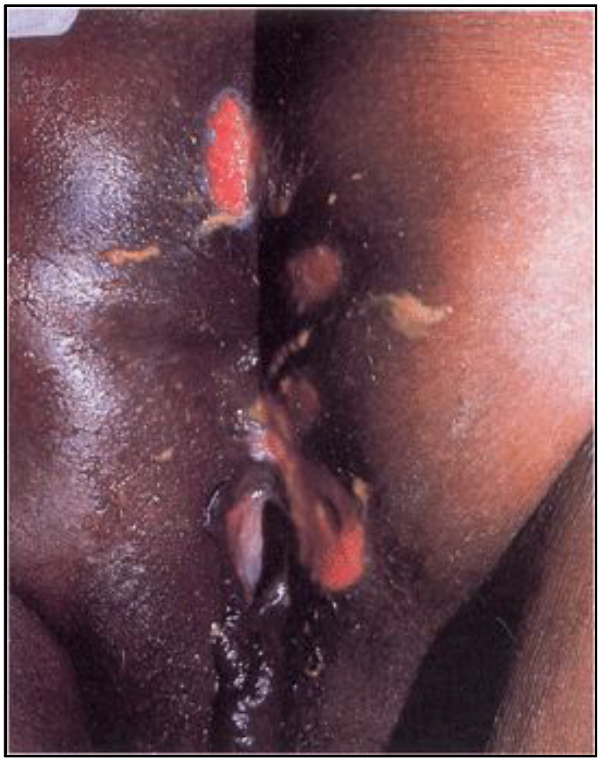
The ideal lesion for culture is an intact vesicle or pustule. The lesion should be unroofed and the base swabbed with a synthetic polyester– or cotton-tipped applicator. The material is then placed into a suitable viral transport medium (ie, Hank's balanced salt solution with antibiotics or veal infusion broth). Under refrigeration, the virus can survive in transport material without loss of infectivity for 72 hours at 4°C.[98] The average replication time of HSV is 12 to 18 hours; typical cytopathic effects of the virus in culture are seen in 1 to 3 days, although it may take 6 or 7 days for smaller inocula. Confirmation that HSV is responsible for the cytopathic effect is done using type-specific antisera, direct immunofluorescence, or nucleic acid hybridization.[110]

Cytologic Diagnosis

Cytologic diagnosis can be made using the Tzanck (Wright-Giemsa) or Papanicolaou stains of smears

a





b

Fig. 19-27. Immunosuppressed patients (ie, those infected with the human immunodeficiency virus, undergoing chemotherapy, or with advanced malignancy) may present with chronic ulcerations that in no way resemble the typical lesions of genital herpes. A high index of suspicion and a history of previous episodes of genital herpes are often helpful in making the diagnosis. The patient shown in (**a**) has an ulcerated herpetic lesion in the suprapubic area. The patient shown in (**b**), who has advanced acquired immunodeficiency syndrome, presented with multiple, painful, deep perinanal ulcerations.

of material taken from the base of lesions. These are rapid, bedside, diagnostic tests that provide information quickly, especially when the test is positive. Cells infected in vivo with HSV show intranuclear inclusions, balloon giant cells, and multinucleated giant cells similar to those seen in tissue culture. Both tests are less sensitive than viral culture and neither differentiates among HSV-1, HSV-2, or herpes zoster infections. With either test, greater sensitivity is seen when intact vesicles or pustules are present than when erosions or ulcers are sampled.[101]

The Tzanck smear is performed by scraping the base and margins of an unroofed vesicle or pustule, or the base of an erosion or ulcer, and spreading the material on a glass slide. After fixation in absolute alcohol, the material is stained with Wright-Giemsa stain and examined for typical balloon and multinucleated giant cells (Figure 19-28). The Papanicolaou smear is especially useful for asymptomatic herpes infections of the cervix. On staining, both multinucleated giant cells and intranuclear viral inclusions are visible, making this test more sensitive than the Tzanck smear.

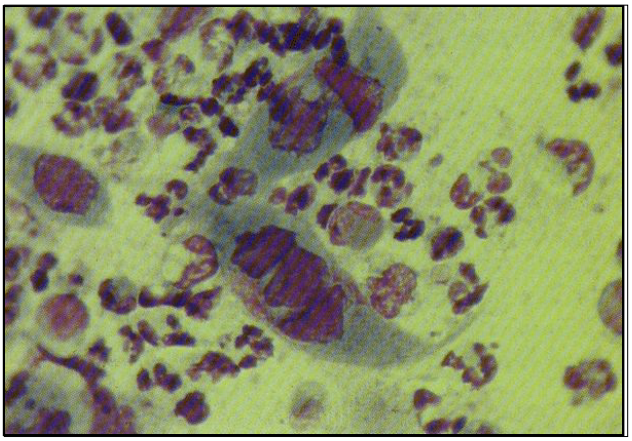


Fig. 19-28. This Tzanck preparation of a herpetic lesion shows several multinucleated giant cells. Photograph: Courtesy of Colonel Purnima Sau, Medical Corps, US Army, Walter Reed Army Medical Center, Washington, DC.

Antigen Detection Using Direct Immunofluorescence

One of the tests most commonly used to detect the presence of HSV antigen is the fluorescein-conjugated anti-HSV monoclonal antibody test (also called the direct immunofluorescence antibody test). The sensitivity of the test is approximately 70% to 95% compared to viral culture. The accuracy of the test depends on the presence of sufficient numbers of cells to be studied (Table 19-6).[111]

To prepare a specimen for the direct immunofluorescence antibody test, the base of the lesion is either scraped with a scalpel blade or swabbed with an applicator. The scrapings are placed on a glass slide and transported to the laboratory, where the specimen is fixed and stained. If a swab is used, it is placed in transport medium and sent to the laboratory. There, the cells are

TABLE 19-6

SENSITIVITY OF DIAGNOSTIC TESTS TO HERPES SIMPLEX VIRUS

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Adapted with permission from Moseley RC, Corey L, Benjamin D, Winter C, Remington ML. Comparison of viral isolation, direct immunofluorescence, and indirect immunoperoxidase techniques for detection of genital herpes simplex virus infection. *J Clin Microbiol*. 1981;13:915.

concentrated and spotted onto glass slides; the stained slides are then examined under a fluorescence microscope (Figure 19-29). Using monoclonal, fluorescein-tagged antibodies, the determination can be made quickly whether the virus is HSV-1 or HSV-2, which provides important prognostic information.[110]

Two other diagnostic methods are available for antigen detection: the ELISA and the immuno-peroxidase tests. These have similar sensitivities as the immunofluorescence stain; they will not be discussed further here.

Serologic Tests

Serologic testing for the presence of antibodies to herpes viruses has limited clinical value except in primary infections. Once an individual becomes seropositive, antibody titers persist for life, and the titers do not correlate with the timing or severity of recurrent disease. Currently available tests do not differentiate between HSV-1 and HSV-2, and patients should not be told they have had prior HSV-2 infections based on the results of routine antibody screening.[99]

When primary genital herpes infection is suspected, blood samples for antibody testing should be taken on the first visit, and then 10 to 14 days later, for a complement-fixation test. Anti-HSV antibody of the IgM class is produced during a primary infection, but is generally not detected in recurrent cases.[10]

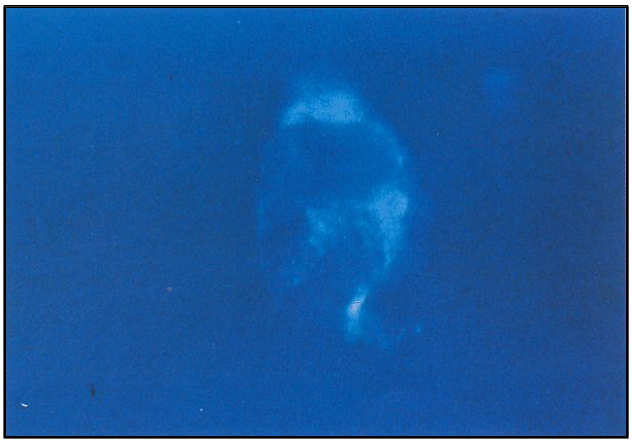

Fig. 19-29. Direct immunofluorescence test showing positive fluorescence in a herpes simplex–infected cell. Photograph: Courtesy of Burroughs Wellcome, Research Triangle Park, NC.

Treatment

Over the last decades, many therapies have been attempted for the management of genital herpes infections. The introduction of acyclovir in oral, topical, and intravenous formulations has revolutionized the management of patients with primary and recurrent disease. However, chronic use of the drug, especially in patients with HIV infections, has led to the emergence of acyclovir-resistant strains.

Primary Genital Herpes Infections

Primary genital herpes infections are often quite severe, prolonged, and associated with constitutional symptoms in many patients, especially women. Acyclovir, administered orally in a dose of 200 mg five times daily for 7 to 10 days, is considered the treatment of choice for first-episode primary genital herpes infections in immunocompetent individuals. Treatment with oral acyclovir in this population significantly reduces viral shedding, shortens the time to healing, and often reduces the duration of pain and new lesion formation.[112]

In patients with complications (eg, dehydration, severe dysuria, inability to tolerate oral medications) intravenous acyclovir (5 mg/kg infused over 1 h, administered every 8 h) may be initiated. When pain and discomfort have subsided, the patient can be discharged to complete the 10-day course of therapy as an outpatient.[99]

Side effects associated with acyclovir therapy, although uncommon, include the following[113]:

- nausea, vomiting, diarrhea, and headache with oral and intravenous acyclovir;
- agitation, altered mental status, and obtundation with more-serious central nervous system toxicity; and
- reversible renal dysfunction with intravenous administration (which may be prevented by increasing the infusion time to 1 h and adequately hydrating the patient).

Unfortunately, regardless of the route of administration, acyclovir treatment of primary genital herpes infection does not prevent the development of recurrent disease.[112,114]

Recurrent Disease

Treatment guidelines for recurrent genital herpes infection vary depending on the frequency of recur-

rent episodes, duration and severity of the episodes, and the presence of complications, especially herpes-associated erythema multiforme. Treatment is divided into episodic and long-term suppressive modes.

Episodic Treatment. Oral acyclovir, in a dose of 200 mg administered five times daily for 5 days, is the most consistently effective therapy for episodic treatment of recurrent genital herpes infection in immunocompetent individuals. Studies have focused on patient-initiated and physician-initiated therapy, and its impact on duration and severity of recurrences. Patient-initiated therapy, in which the patient begins treatment at the onset of prodromal symptoms, tends to offer greater benefit than physician-initiated regimens. Studies have demonstrated a statistically significant reduction in viral shedding and healing times with episodic treatment but less-than-convincing reduction in local pain and discomfort.[115] In recurrent herpes labialis, higher doses of patient-initiated acyclovir (400 mg administered five times daily for 5 d) have been suggested to improve response and decrease symptoms. Likewise, refractory cases of recurrent genital herpes infection may respond to higher doses.[116]

The CDC suggests that acyclovir 400 mg, administered three times daily for 5 days or 800 mg, administered twice daily for 5 days; might be effective.[25]

Long-Term Suppressive Therapy. Rates of recurrent genital herpes infection vary considerably—from 1 or 2 to more than 12 recurrences per year. Most patients who seek therapy for recurrent disease have 5 to 8 recurrences per year.[115] Suppressive therapy is also indicated for the treatment of patients with recurrent herpes-associated erythema multiforme.[99]

Numerous dosing regimens have been proposed; however, the two most effective are 400 mg, administered twice daily, and 200 mg, administered three to five times daily. Once-daily therapy in any dose is less effective than twice-daily regimens but should be considered in poorly compliant patients. There appears to be little, if any, long-term toxicity and no reason that long periods of use are not safe. However, patients should be encouraged to interrupt therapy after 1 year of continuous therapy to determine if the frequency of recurrences still justifies the continued use of the drug.[25,117]

Treatment of Immunocompromised Patients

Treatment of recurrent genital herpes infections in compromised hosts, particularly patients with HIV infection, is complicated by persistent viral shedding, the necessity in some patients for indefinite suppressive therapy, and the emerging problem of acyclovir-resistant strains of HSV. In *outpatient* immunocompromised patients (eg, those with HIV infection, bone marrow–transplant recipients) with recurrent mucocutaneous disease, higher doses of oral acyclovir (400 mg administered five times daily for 10 d) have been shown to be effective.[118] Enthusiasm for topical acyclovir ointment has diminished. However, the topical preparation applied 6 times daily for 10 days significantly reduces viral shedding, pain, and healing times.[113] The treatment of hospitalized, immunocompromised patients with genital herpes infections is beyond the scope of this discussion.

GENITAL WARTS

Anogenital warts (also called condylomata acuminata and venereal warts) are an ancient disease, with the earliest references to them in literature as *condylomata* (figs). It was well known during the Roman Empire that promiscuous sexual behavior and anal intercourse were implicated in the spread of this disease. An early reference to condyloma acuminata is found in this satirical poem written in the first century AD by Martial in his *Epigrammata Medicae Philosophicae* (XII:3), as translated by J. D. Oriel:

> In order to buy some slave boys
> Labienius sold his gardens,
> But now the poor man has
> Only an orchard of figs.[119(p99)]

Genital warts result from infection by a group of DNA-containing human papillomaviruses (HPVs). Recent investigations of the epidemiology and natural history of human papillomavirus infections have shed light on the transmission, infectivity, and probable oncogenic potential of these agents. Advances in molecular biology have clearly demonstrated the role of certain HPV subtypes in Bowenoid papulosis, cervical dysplasia, and cervical carcinoma. In particular, subtypes 16, 18, 31, and 33 are most often implicated in these conditions; many other HPV subtypes have been found in genital wart tissue and in premalignant and malignant lesions of the genitalia.

The HPV organism consists of circular, double-stranded DNA enclosed in a protein shell (ie, a

capsid) (Figure 19-30). The absence of a lipid envelope renders the virus resistant to drying, freezing, and inactivation by ether. HPVs have never been propagated successfully in tissue culture, which has hindered laboratory studies and vaccine development. By DNA hybridization techniques, at least 55 subtypes of HPV are currently known, with more certain to be discovered (Table 19-7).[120]

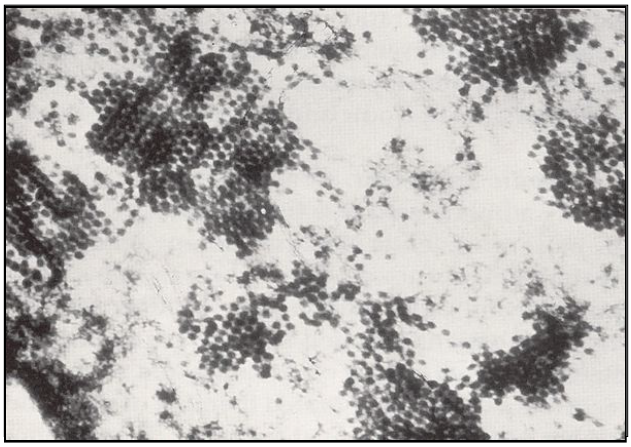

Fig. 19-30. This electron micrograph shows clusters of human papillomavirus. Photograph: Courtesy of Walter Reed Army Medical Center Dermatology Service slide file, Washington, DC.

TABLE 19-7

TYPES AND CLINICAL ASSOCIATION OF HUMAN PAPILLOMAVIRUS (HPV)

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Clinical Manifestations

Clinical signs of genital human papillomavirus infection vary from latent infection, to extensive cauliflower-like vegetations, to frank neoplasia such as cervical carcinoma. The typical lesions are soft, grouped, skin-colored-to-pink papules with a smooth or filiform surface; they occur on moist surfaces of the external genitalia, cervix, or perianal area (Figure 19-31). Although lesions usually are asymptomatic, some patients complain of itching, local irritation, or bleeding, especially in the perianal area.[121] Applying 3% to 5% acetic acid to clinically normal penile or vulvar skin and then examining with magnification may demonstrate areas of flat, whitish epithelium or punctate, fine-caliber, vascular patterns that are subclinical foci of infection with HPV.[122]

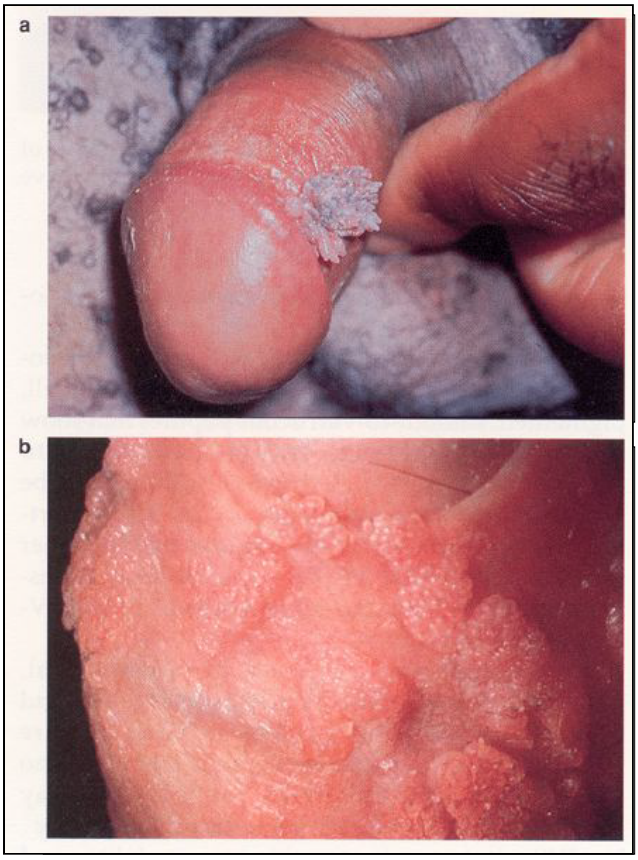

Fig. 19-31. (**a**) Filiform condylomata in the coronal sulcus. (**b**) Grouped and confluent sessile genital warts on the penis. These are different expressions of the same viral infections, (a) being filiform warts, and (b) less-obvious sessile genital warts on the penile shaft.

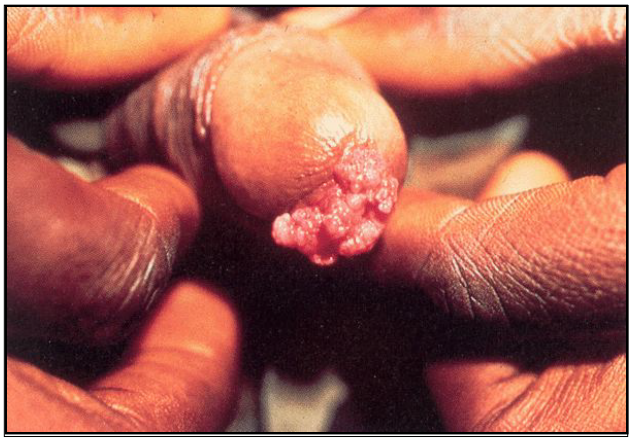

Fig. 19-32. Exophytic mass protruding from the urethral meatus. The lesions may extend proximally to involve the urethral mucosal surface. Intraurethral condylomata may be better seen with urethroscopy.

Most genital warts are seen in young men and women between the ages of 16 and 25. The virus spreads primarily via sexual transmission, with a high rate of infectivity. Nearly two thirds of individuals with infected sexual partners developed genital warts within 2 to 3 months.[123]

In men, condyloma acuminata are most commonly found on the glans, coronal sulcus, and foreskin—moist areas that are prone to trauma and therefore vulnerable to the subsequent entry of the virus during sexual intercourse. The urethral meatus and the urethra itself may be involved with exophytic condylomata, producing dysuria and urethral discharge (Figure 19-32). Papular or flat warts may involve the penile shaft, scrotum, or inguinal folds.[123] Large, exophytic, perianal condyloma may also occur.

Women with genital human papillomavirus infection may present with multiple papular sessile lesions, filiform growths, or vulvar papillomatosis (ie, numerous, small, coalescing papules over the entire vulvar vestibule, giving the area a "cobblestone" appearance) (Figure 19-33). Lesions of the vagina occur in about one third of patients. Subclinical involvement of the cervix is more common than is frank condyloma acuminata. Up to 3% of routine Papanicolaou smears show changes typical human papillomavirus infection: koilocytosis, atypia, and multinucleation. Application of dilute acetic acid to the cervix followed by colposcopy may show flat-topped papules or plaques representing inconspicuous disease. These lesions most commonly contain HPV-6 and HPV-11. Lesions

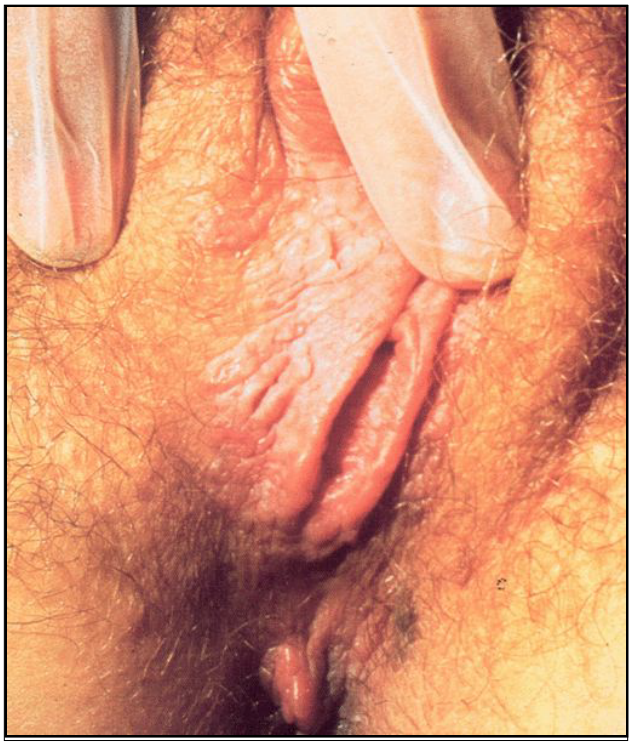

Fig. 19-33. Diffuse, confluent lesions of condyloma acuminata give this patient's vulva a distinctive "cobblestone" appearance.

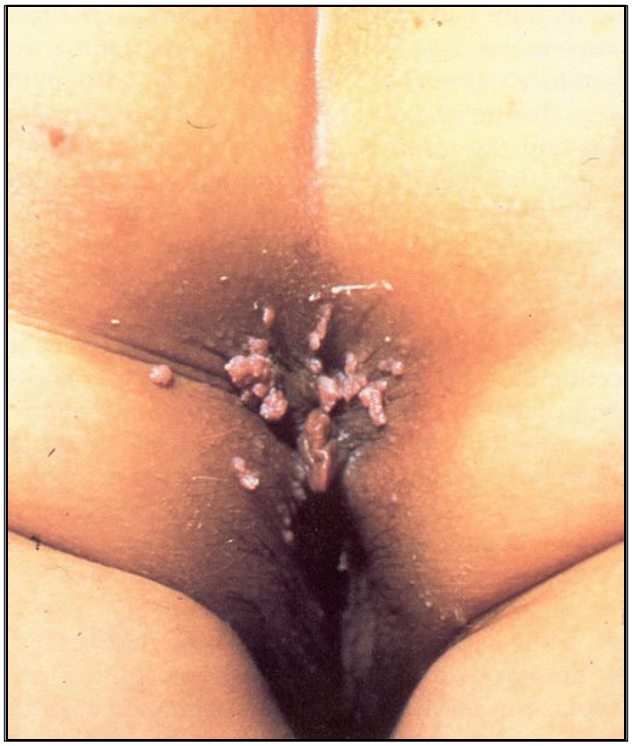

Fig. 19-35. Perianal condyloma acuminata. These lesions, which may involve the anal mucosa as well as the perianal skin, are difficult to eradicate and frequently recur.

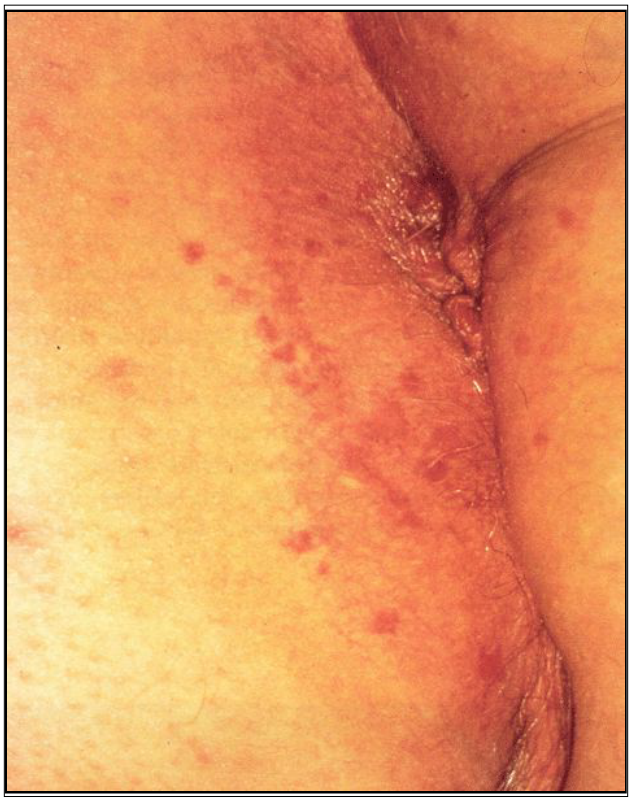

Fig. 19-34. These are the reddish brown lesions of Bowenoid papulosis, which were confirmed by shave biopsy.

that histologically show atypia are more often associated with HPV-16.[121]

Bowenoid papulosis refers to human papillomavirus infection that is characterized by small, pigmented, smooth-to-verrucous papules that show histological changes suggestive of carcinoma in situ (Figure 19-34). Although previously thought to be benign, recent studies have shown that female partners of men with Bowenoid papulosis have a higher incidence of cervical neoplasia, supporting a causative role of HPV and the subtypes, especially HPV-16, in these conditions.[124]

Anal warts may be found in heterosexual, homosexual, and bisexual men, with HPV-6 and HPV-11 found in the majority of cases (Figure 19-35). In renal transplant recipients and men who are infected with HIV, anal condylomata may become large, exophytic growths. These may be difficult to eradicate with any modality, and invasive squamous cell carcinomas may develop from these lesions.[121]

Giant condyloma of Buschke and Löwenstein is classified by some[54] as a low-grade verrucous carcinoma, although others[125] consider it a benign lesion.

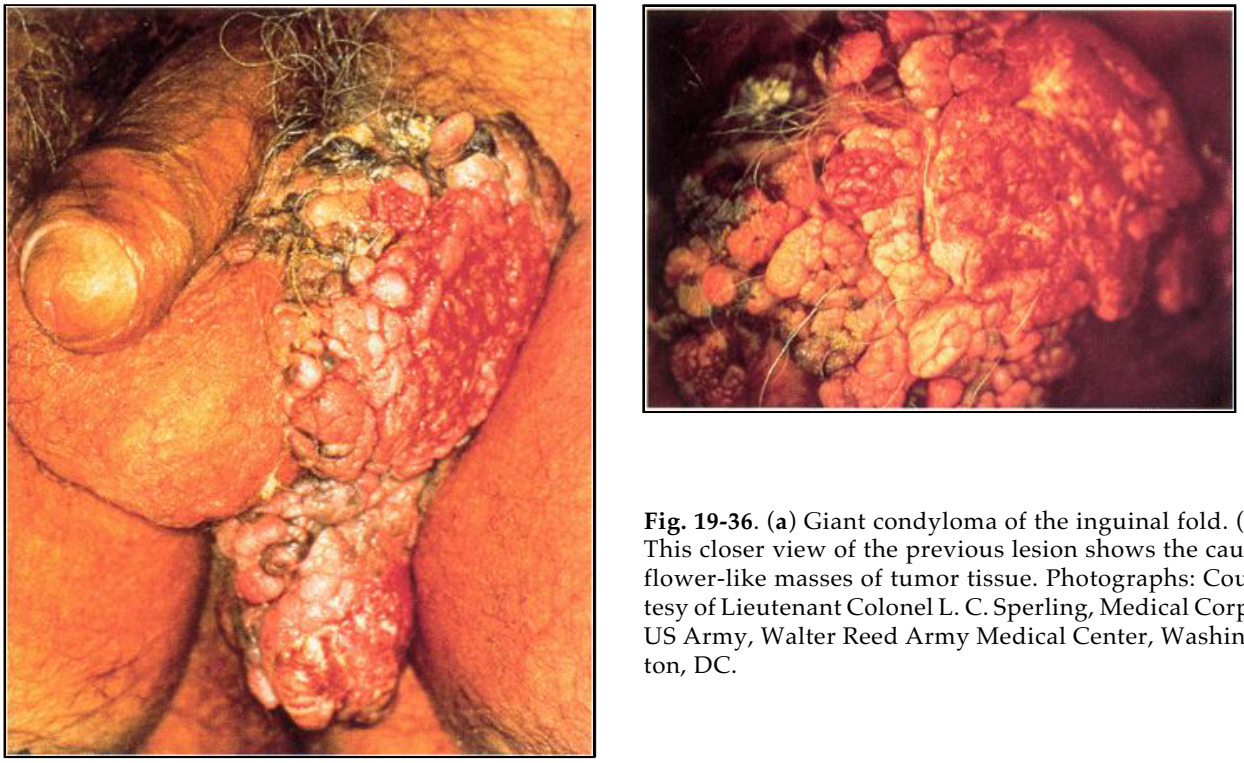

Fig. 19-36. (**a**) Giant condyloma of the inguinal fold. (**b**) This closer view of the previous lesion shows the cauliflower-like masses of tumor tissue. Photographs: Courtesy of Lieutenant Colonel L. C. Sperling, Medical Corps, US Army, Walter Reed Army Medical Center, Washington, DC.

It most commonly occurs on the glans penis and foreskin of uncircumcised men. Less often, these lesions occur on the vulva or in the perianal area.[54] Patients with giant condyloma present with large cauliflower-like growths (Figures 19-36 and 19-37), which may penetrate into underlying structures such as the urethra or corpora cavernosa. Local compression and destruction of normal structures result. The lack of nerve, blood vessel, and lymphatic invasion probably accounts for the rarity of metastases. DNA sequences of HPV-6 and HPV-11 have been isolated from giant condyloma, supporting the contention that HPV is involved in the genesis, and possible malignant transformation, of these lesions.[123,126,127]

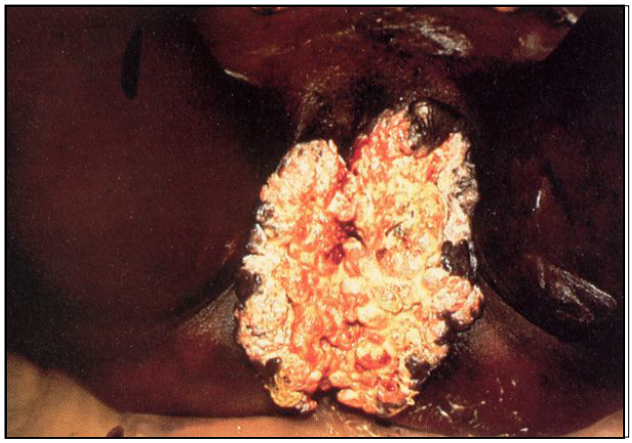

Fig. 19-37. Massive Buschke-Loewenstein tumor of the vulva. Photograph: Courtesy of Walter Reed Army Medical Center Dermatology Service slide file, Washington, DC.

When seen in children, condyloma acuminata is considered a risk factor for sexual abuse, with estimates varying from 30% to 80% of cases (Figure 19-38).[128] Pregnancy has a profound influence on the condylomata, with lesions increasing dramatically in size and number. There is a concomitant increase in the amount of viral DNA material from pregnant women compared to nonpregnant women. There is a risk of laryngeal papillomatosis and anogenital condyloma in infants born to mothers with cervical or vulvar condylomata.[122] Condyloma acuminata in children and during pregnancy will not be discussed further in this chapter.

Clinical Diagnosis

Clinical examination remains the principal means of diagnosing genital warts. In a sexually active patient with typical condylomata, biopsy with histological examination offers little except reassurance to the patient that the diagnosis is correct. In the following instances though, additional studies

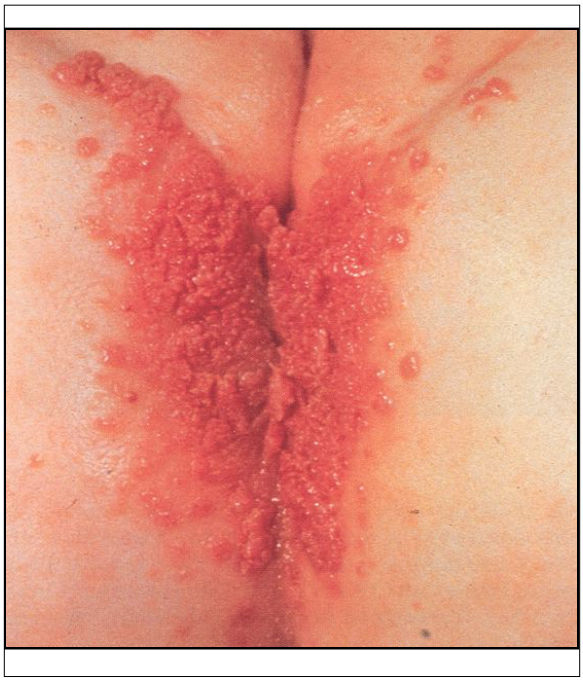

Fig. 19-38. Extensive condyloma acuminata in a prepubertal female child. This patient was also evaluated for sexual abuse. Photograph: Courtesy of Major J. Rowe, Medical Corps, US Army, Fort Bragg, N.C.

or histological confirmation should be considered:

- Atypical lesions. The condylomata lata of secondary syphilis may clinically resemble genital warts. Condylomata lata (*lata* means "broad" or "flat") tend to be broad, flat, and more rounded lesions that are covered with a mucoid exudate. Dark-field microscopy, serologic tests, and the presence of other findings of secondary syphilis are helpful in making the proper diagnosis. In some atypical lesions, biopsy may be necessary for confirmation.[123]
- Lesions that may actually be Bowenoid papulosis. Because of the risk of cervical neoplasia in female sexual partners, histological findings consistent with Bowenoid papulosis mandates careful follow-up in this population.
- Unresponsive lesions. Lesions that are unresponsive to treatment may not be condyloma acuminata. For example, melanocytic nevi, seborrheic keratoses, and epidermal nevi have all been mistaken for condylomata. A scissor biopsy performed under local anesthesia quickly resolves the issue.
- Pediatric presentation. When lesions are present in pediatric patients, and when abuse or other medicolegal issues are at issue, tissue can be submitted for histology and, if available, HPV typing.

Immunoperoxidase staining, using antibody against disrupted bovine papillomavirus as the antigen, has been useful for detecting HPV in tissue sections. Methods of DNA hybridization or ribonucleic acid (RNA) hybridization permit typing of HPV samples; utilizing the polymerase chain reaction to amplify the DNA of the HPV that is present greatly improves the sensitivity of the tests.[120]

The virus cannot be cultivated in vitro, and type-specific viral antigens are currently unavailable for the development of serologic tests.[122]

Treatment

Locally destructive methods (eg, cryosurgery, electrodesiccation, curettage, carbon dioxide–laser vaporization) and application of chemical agents (eg, podophyllin, 5-fluorouracil) are reasonably effective and convenient methods to treat condyloma acuminata. Unfortunately, all suffer from the same shortcomings: frequent recurrence of the lesions and persistence of the virus in otherwise normal-appearing tissue.

Cryosurgery with liquid nitrogen remains a time-honored and effective treatment for smaller lesions. Liquid nitrogen is applied to the wart until the ice ball extends 1 to 2 mm beyond the visible edge of the lesion. The procedure is somewhat uncomfortable for the patient, and blistering and erosions may result. Local anesthesia during the procedure and oral analgesics following cryosurgery may be necessary if extensive treatment is performed. Retreatment may be necessary every week or two until the lesions have completely resolved.[119] Care should be taken not to treat large areas of the glans penis or foreskin at one visit: the resulting edema may cause the patient to be unable to retract the foreskin, which can lead to acute urinary retention.

Electrosurgery and carbon dioxide–laser vaporization are locally destructive procedures that usually require the administration of local anesthesia prior to performing them. Small localized warts (eg, on the penile shaft) are treatable with electrodesiccation. Undertreatment frequently results in recurrence and overtreatment may lead to scarring. Genital warts in other locations and large exophytic lesions are not generally suitable for treatment with this modality.[119] With the carbon dioxide

laser, low-wattage treatment in the vaporization mode is an excellent method of rapidly treating genital warts with minimal risk of scarring. The laser beam destroys infected tissue by evaporation of water. However, recent concerns regarding the presence of viable HPV and other viruses (ie, HIV) in the electrosurgical and laser smoke plumes have dampened enthusiasm for these two modalities.[129]

Isolated lesions can be removed with a sharp curette or by scissor excision under local anesthesia.[123]

Application of 20% podophyllin in benzoin to condylomata results in arrest of cell mitosis and subsequent cell death. Podophyllin is an unstable, crude, plant extract with significant local reactions including irritation, necrosis, scarring, anal fistulae, and phimosis among the reported complications.[121,123]

Early in treatment, the medication is washed off in 3 to 4 hours. With subsequent applications, the time may be extended up to 12 hours as tolerated by the patient.[121] Care should be taken to avoid adjacent normal skin. Severe inflammation and necrosis can occur when podophyllin is applied to condylomata on the coronal rim or sulcus, or on the periurethral area. Other modalities should be used when treating genital warts in these areas, especially in uncircumcised men.

Systemic reactions caused by overzealous or extensive application are rare but have been reported. Under no circumstances should podophyllin be used in pregnant women because of the potential for maternal and fetal toxicity.[121]

Podophyllotoxin 0.5% in ethanol has been approved for home use by patients. The compound is applied twice daily for 3 days each week for up to 6 weeks. A cure rate of 82% was achieved with this regimen. The advantage is that patients can apply the medication at home, reducing the need for frequent office visits and assuring prompt treatment of recurrent lesions.[130]

The drug 5-fluorouracil has been used as a 5% cream in the treatment of warts in the intrameatal portion of the urethra in men. The cream is applied four times daily using an applicator stick, after the bladder has been emptied. A severe inflammatory reaction may develop and this treatment should be undertaken only by medical officers who are experienced in this method. Follow-up urethroscopy is important.[10]

Interferons, both intralesional and parenteral, and systemic retinoids have been used for human papillomavirus infections that are resistant to other forms of therapy. The doses and indications for these drugs can be found elsewhere.[131,132]

MOLLUSCUM CONTAGIOSUM

Although molluscum contagiosum is not a reportable disease, there is epidemiological evidence that a substantial increase in the number of cases has occurred since the 1970s. The current estimate is that from 2% to 8% of the population is affected by this condition at any time. However, because it is not currently possible to cultivate the molluscum contagiosum virus (MCV) in vitro, estimates are based on examination of populations of affected individuals.[133–135] Because MCV is a poxvirus, some researchers[135] have speculated that the cessation of routine vaccinia virus vaccination in the general population in the 1970s may be responsible for the increasing incidence.

MCV is a brick-shaped, DNA-containing poxvirus that morphologically and biochemically resembles other members of the Poxviridae (eg, variola, vaccinia, and cowpox). By analysis of viral DNA sequences, two subtypes have been identified and are designated MCV-1 and MCV-2. However, clinical lesions caused by both subtypes are identical. Studies of virus–host interaction, development of serologic tests, and vaccine production are currently not possible because researchers have been unable to cultivate the virus in vitro.[135] There have been isolated reports of successful propagation of the virus in cell culture.[136,137]

The lesions of molluscum contagiosum occur in two, and perhaps in three, groups. In adults, molluscum contagiosum is usually an STD, with lesions occurring predominately in the genital area (Figure 19-39). In children, lesions are often on exposed surfaces and the face, consistent with transmission by person-to-person contact or possibly by fomites. Recently, a third group of individuals, those with progressive HIV-1 infection, have been described with extensive cutaneous involvement (Figure 19-40).[138] These lesions are particularly refractory to therapy. Additionally, the number of lesions of molluscum contagiosum increase dramatically in these patients with deterioration of their immune status.

Clinical Manifestations

Adolescents and adults with molluscum contagi-

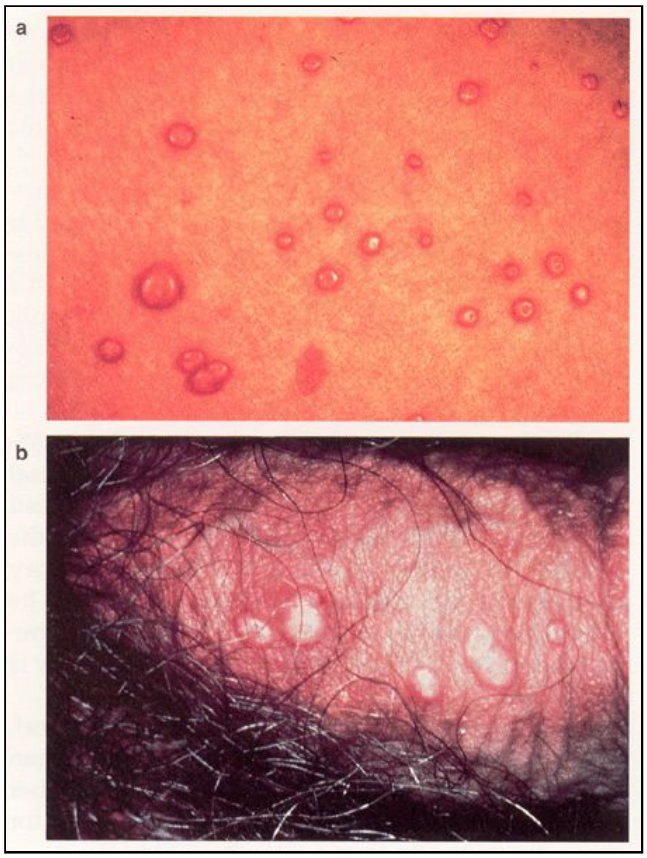

Fig. 19-39. (**a**) The umbilicated skin-colored-to-reddish papules of molluscum contagiosum. (**b**) Grouped umbilicated papules on the penile shaft. These papules are often confused with the lesions of genital herpes infection unless the contents of the lesions are expressed and examined.

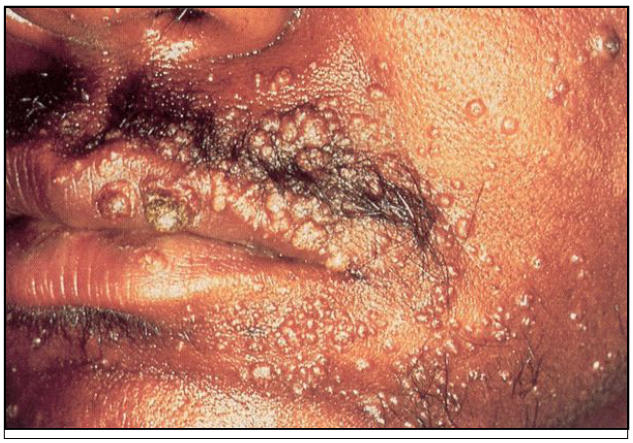

Fig. 19-40. This patient, who was infected with the human immunodeficiency virus, also had hundreds of papules of molluscum contagiosum on his face. Death occurred within months after the photograph was taken. Photograph: Courtesy of Colonel William D. James, Medical Corps, US Army, Walter Reed Army Medical Center, Washington, DC.

osum present with multiple, firm, 2- to 5-mm, dome-shaped, skin-colored papules that have a central umbilication or "dimple." Lesions occur most commonly in the inguinal area, buttocks, and inner thighs in both sexes (Figure 19-41).[139] Although most lesions are only a few millimeters in diameter, "giant" molluscum may develop, with lesions approaching 1 cm in diameter (Figure 19-42). In children, lesions are located on exposed surfaces subject to minor trauma—especially the face, trunk, and extremities. Lesions are often grouped, and a linear pattern may develop as a result of scratching. Most cases are asymptomatic; however, a few patients complain of mild pruritus. Lesions may rarely be found on the palms, soles and mucous membranes.[140]

Two groups of patients are at risk to develop extensive molluscum contagiosum: those with atopic dermatitis and those with HIV-1 infection. Patients

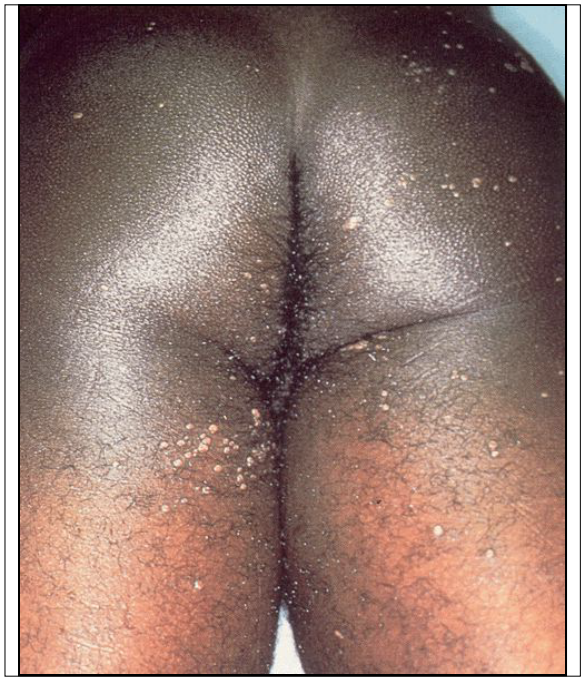

Fig. 19-41. Extensive involvement with molluscum contagiosum over the buttocks and thighs in an adult. Patients who present with molluscum in this distribution should be carefully examined for other sexually transmitted diseases.

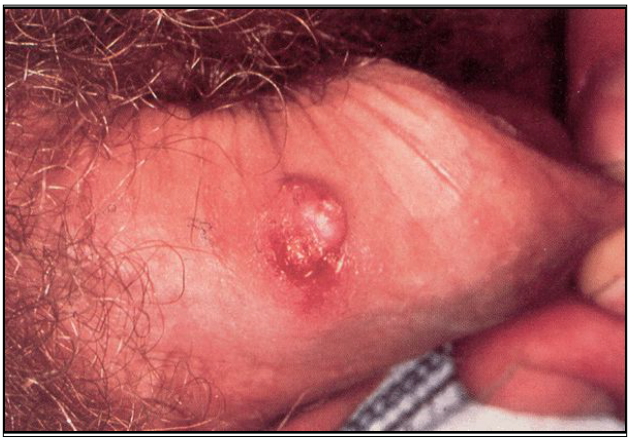

Fig. 19-42. Solitary "giant" molluscum on the penile shaft. Biopsy confirmed the diagnosis. Lesions of this size are often mistaken for cysts or tumors.

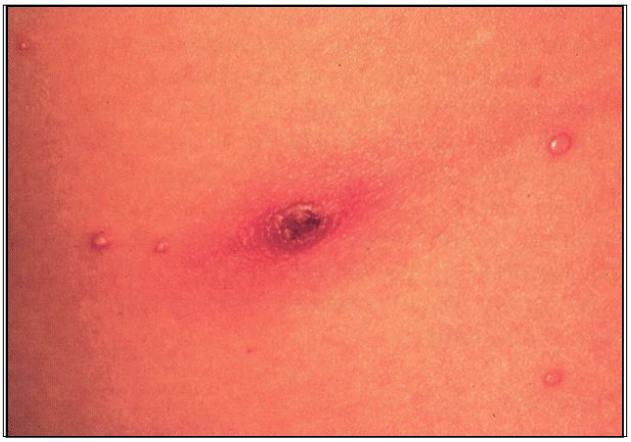

Fig. 19-43. This peripheral erythema and crusting is typical of a lesion of molluscum dermatitis.

with atopic dermatitis often develop numerous lesions in areas of active eczematous dermatitis, especially the flexural folds. The reasons given for the widespread lesions include autoinoculation from scratching, use of topical steroids, and impaired cellular immune response.[141,142] Patients with HIV-1 infection can have dozens or even hundreds of lesions, primarily on the face and trunk instead of the inguinal area. As noted previously, a dramatic increase in the number of lesions corresponds to the progressive deterioration of immune function.[143] Patients with sarcoidosis and those receiving chemotherapy or corticosteroids have also been reported to develop extensive molluscum contagiosum.[138]

Complications

Surprisingly few complications arise from infections with molluscum contagiosum. Two will be considered here—molluscum dermatitis and secondary bacterial infection—as well as the occurrence of molluscum lesions in the genital area of children, which raises the suspicion of child abuse. In about 10% of patients, a sharply demarcated, annular, eczematous dermatitis develops around individual lesions of molluscum contagiosum (Figure 19-43). A few, some, or all of the lesions may be involved, and the dermatitis resolves with disappearance of the molluscum contagiosum papule.[144] Lesions located on the eyelid or conjunctivae are also occasionally involved in molluscum dermatitis, and conjunctivitis or keratitis may develop.[145] Secondary bacterial infection with cellulitis may also occur.

Regarding genital molluscum contagiosum in infants and children, there is considerable controversy over (*a*) how often the lesions are transmitted by sexual abuse and (*b*) when to refer families to social services for investigation. More than 90% of lesions of molluscum contagiosum in children are found on the trunk, axillae, and extremities. Therefore, lesions in the genital area are uncommon and should raise the suspicion of sexual abuse. On the other hand, the CDC opinion[25] is that molluscum contagiosum in infants and children is most frequently caused by nonsexual means of transmission. Several authorities recommend that a child who has genital molluscum alone should be viewed with increased suspicion of sexual abuse.[140,146]

Diagnosis

Diagnosis is principally on clinical grounds alone, as the appearance of the smooth, dome-shaped, umbilicated papules is characteristic. When doubt exists, a lesion may be curetted or incised and the whitish central core crushed between two glass microscope slides. It can then be stained with methylene blue or Wright-Giemsa stain and examined microscopically. The large, oval, dense, staining bodies known as molluscum bodies are keratinocytes filled with viral particles.[54] With atypical lesions, or in individuals who are infected with HIV, a shave or punch biopsy of a papule may be necessary to confirm the diagnosis. (Recent reports of the lesions of disseminated cryptococcal infection mimicking molluscum contagiosum in patients

infected with HIV lends support to the recommendation for biopsy confirmation in this population.[147]) Sections of hematoxylin-eosin–stained tissue show numerous intracytoplasmic inclusion bodies, which form in the lower epidermis; these large, basophilic molluscum bodies measure up to 35 μm in diameter (Figure 19-44). Disintegration of the stratum corneum in the center of the lesion leads to the development of the central crater.[54]

As noted above, serologic tests or viral cultures are not available.

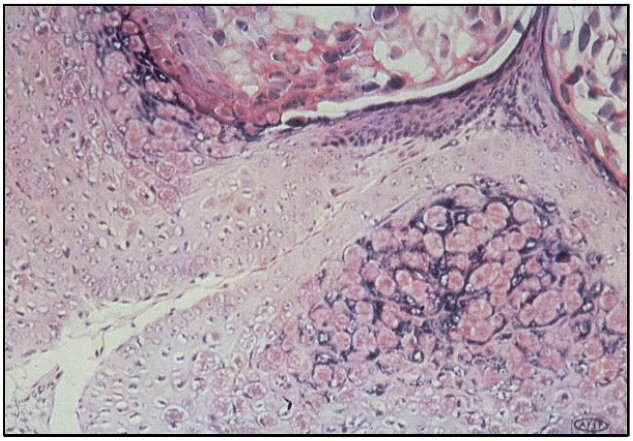

Fig. 19-44. This histological section (medium-power view) shows large keratinocytes filled with molluscum virus.

Treatment

Numerous modalities have been successful in the treatment of molluscum contagiosum. The disease is self-limited and asymptomatic, and in some instances, such as with very young children, it may be appropriate simply to observe the lesions. However, since autoinoculation and spread to other persons is frequent, it is advisable to initiate treatment. Curettage with a sharp curette, light electrodesiccation, light liquid nitrogen spray, or topical application of 50% trichloroacetic acid are all simple to perform and are nonscarring. Slight incision of the lesion with expression of the central core is also curative. Other suggested modalities have included topical retinoic acid or griseofulvin.[86] In the case of adolescents and adults with lesions in the genital area, it is important to look for other STDs, as they may also be present.

SUMMARY

STDs present formidable diagnostic and therapeutic challenges for the field medical officer. The classic STDs discussed in this chapter can, with reasonable care and a well-equipped laboratory and pharmacy, be properly diagnosed and treated. It is imperative, however, that the clinician be familiar with the subtle variations in clinical presentation, subclinical disease, and the ever-changing patterns of antibiotic sensitivity. Likewise, a particular STD is not acquired in a vacuum. The general medical officer evaluating a soldier with molluscum contagiosum or genital warts must remember that the patient may also be incubating syphilis or may be an asymptomatic carrier of gonorrhea, chlamydia, or HIV infection. A careful and thoughtful approach to the evaluation of the patient with an STD will ensure that both the patient and his or her sexual contacts will be well served.

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