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REVIEWS

Syphilis: Review with Emphasis on Clinical, Epidemiologic, and Some Biologic Features

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INTRODUCTION

"He who knows syphilis, knows medicine"
Sir William Osler

The origins of syphilis have been discussed for many centuries (68, 251, 266, 341). Two main theories have been proposed—the New World or Columbian theory and the Old World or pre-Columbian theory. The former holds that syphilis was endemic in the part of the world now known as Haiti and was then acquired and carried to Europe by Columbus in the 1400s. The pre-Columbian theory purports that syphilis originated in central Africa and was introduced to Europe prior to the voyage by Columbus. A third theory, the Unitarian theory, could be made to fit the pre-Columbian theory (251). This theory proposed that syphilis and the nonvenereal treponematoses were all manifestations of the same infection, with the observed clinical differences being due mainly to environmental factors, especially temperature. However, recent bacteriological work has demonstrated genetic differences between these organisms (44). Regardless of the origins, however, it remains clear that by 1495 a widespread syphilis epidemic had spread throughout Europe (251). From there the disease spread to India in 1498 and China in 1505 (251).

Early names for syphilis included the Great Pox, lues venereum (venereal disease), morbus gallicus (French disease), and the Italian, Spanish, German, or Polish disease, but the name that was to become part of the everyday language was syphilis (251). Hieronymus Fracastorius in 1530 is believed to be the first to coin the term "syphilis," derived from a mythical shepherd, Syphilus, described in his poem *Syphilis Sive Morbus Gallicus*, which means "Syphilis or the French Disease" (251).

Many early investigators contributed to our knowledge of syphilis, and the following highlights but a few. John Hunter (1728 to 1793) believed the Unity or Monist Theory, which holds that syphilis and gonorrhea were the same disease (68, 251). This theory was supported by his well-known experiment of 1767 in which he inoculated matter from a patient whom he believed to have gonorrhea onto the prepuce and glans of a recipient, who traditionally is believed to be himself. However, since the experiment was reported in the third person, it is now believed that the recipient was someone else (67). Ten days after the inoculation, a chancre appeared, followed by signs of secondary syphilis (251). It is now believed that the donor had both syphilis and gonorrhea, but Hunter was convinced that he had induced syphilis by inoculation of gonorrheal pus. It was not until 1838 that Philippe Ricord demonstrated conclusively that syphilis and gonorrhea were separate diseases based on over 2,500 human inoculations (251, 341). Ricord was also the first to propose a scheme for the categorization of syphilis into primary, secondary, and tertiary stages, which is still used today (251). Giovanni Lancisi (1654 to 1720) and Herman Boerhaave (1668 to 1738) implicated syphilis as a cause of cardiovascular disease. Alfred Fournier (1832 to 1914) confirmed the syphilitic origins of neurosyphilis (294). Paul Diday (1812 to 1894) and Jonathan Hutchinson (1828 to 1913) contributed greatly to our knowledge of congenital infections (251).

In 1905, the association of *Treponema pallidum* with syphilis was described by Schaudinn and Hoffman, who demonstrated spirochetes in Giemsa-stained smears of fluid from secondary syphilitic lesions (295). August von Wassermann devised a serum reaction test for syphilis in 1906, and serologic tests for syphilis were born (349).

Treatments for syphilis included mercury, organic arsenical compounds, and bismuth until the advent of penicillin (294). In 1943, Mahoney et al. successfully treated the first four cases of syphilis with penicillin, and more than half a century later penicillin remains the drug of choice (204).

ETIOLOGY

Although given various names following its discovery, the causative organism of syphilis was finally named *Treponema* because of its resemblance to a twisted thread and *pallidum* because of its pale color (266).

T. pallidum is a member of the order *Spirochaetales*, family *Spirochaetaceae*, and genus *Treponema*, which includes four human pathogens and at least six human nonpathogens (245). The pathogenic species are *T. pallidum* subsp. *pallidum* which causes venereal syphilis, *T. pallidum* subsp. *endemicum*, which causes endemic syphilis (bejel), *T. pallidum* subsp. *pertenue*, which causes yaws, and *T. carateum*, which is the etiologic agent of pinta. Initial studies indicated that these four agents were morphologically indistinguishable, with >95% DNA homology (223, 241). Recently, however, a genetic signature was defined in the 5′-flanking region of the 15-kDa lipoprotein gene (*tpp15*) that distinguishes *T. pallidum* subsp. *pallidum* from *T. pallidum* subsp. *pertenue* and *endemicum* (44).

Most of our knowledge of the physiology, metabolism, and antigenic structure of *T. pallidum* is derived from the Nichols strain, which has been maintained in rabbits since 1912 (240). *T. pallidum* is a spirochete varying from 0.10 to 0.18 μm in diameter and from 6 to 20 μm in length, making it invisible by light microscopy (245, 360). Dark-field microscopy is generally used in clinical practice for visualization (60). The average number of windings is 6 to 14, and the organism has pointed ends and lacks the hook shape seen in some commensal human spirochetes (245). The bacterium exhibits characteristic corkscrew motility due to endoflagella, with rapid rotation about the longitudinal axis and flexing, bending, and snapping about the full length (245).

The genome of *T. pallidum* subsp. *pallidum* has recently been sequenced by the whole pulse genome random sequencing method (106). The genome is a circular chromosome of 1,138,006 bp and contains 1,041 open reading frames (ORFs). Predicted biological roles were assigned to 55% of ORFs, while 17% match those encoding hypothetical proteins from other species and 28% represent novel genes. Physiologic studies have previously shown that the organism has limited biosynthetic capabilities, requiring multiple nutrients from the host (106). The *T. pallidum* genome confirms this by demonstrating the inability of the organism to synthesize enzyme cofactors, fatty acids, and nucleotides de novo and by encoding for a pathway for the conversion of phosphoenolpyruvate or pyruvate to aspartate. Given its limited biosynthetic properties, it is assumed that *T. pallidum* must have good transport proteins, and, indeed, the *T. pallidum* genome contains 57 ORFs (5% of the total) that encode 18 distinct transporters specific for amino acids, carbohydrates, and cations. Metabolio-pathway analysis shows that genes encoding all of the enzymes of the glycolytic pathway are present in *T. pallidum*, suggesting that it uses several carbohydrates as energy sources. The or-

ganism has previously been demonstrated to survive better in very low concentrations of oxygen and is therefore considered microaerophilic (89). This is confirmed by the lack of genes encoding superoxide dismutase, catalase, or peroxidase, which protect against oxygen toxicity. Motility-associated genes are highly conserved in *T. pallidum*, consistent with the importance of this activity; 36 genes encode proteins in the flagellar structure. Freeze fracture studies of the outer membrane of *T. pallidum* show that it contains a small number of integral membrane proteins which may allow it to evade the host immune response (59, 271, 348); genomic analysis indicates 22 putative lipoproteins consistent with these studies. Potential virulence factors are hinted at by the presence of a large number of duplicated genes (*tprA* through *tprL*) that encode putative membrane proteins that may function as porins and adhesins. Multiple copies of the *tpr* genes may represent a mechanism for antigenic variation in *T. pallidum* and in addition may provide new targets for vaccine development. Previous studies have indicated that *T. pallidum* does not produce lipopolysaccharide or potent exotoxins, although cytotoxic activity against neuroblasts and other cell types has been observed (94, 363). Genome analysis shows five genes encoding proteins similar to bacterial hemolysins. Comparison of the *T. pallidum* genome with that of another spirochete, *Borrelia burgdorferi*, showed that 46% of the *T. pallidum* ORFs have orthologs in *B. burgdorferi*, of which 76% have predicted biological function. A total of 115 ORFs shared by *T. pallidum* and *B. burgdorferi* encode proteins of unknown biological function, of which 50% appear unique to the spirochete group.

EPIDEMIOLOGY

Transmission of Disease

The primary mode of transmission is by sexual contact, and the next most common is transfer across the placenta (324). Kissing, blood transfusion, and accidental inoculation have also been reported as routes of transmission but are of minor importance today (324). Partner notification studies have estimated a transmission rate of primary, secondary, and early latent syphilis of 18 to 80% (54, 187, 299, 302, 312, 347), while prospective trials of prophylactic treatment have estimated a transmission rate of 9 to 63% (3, 228, 304). The limitations of these studies have recently been discussed, and the authors conclude that the transmission probability per partner is around 60% (108).

The majority of infants with congenital syphilis are infected in utero, but the newborn can also be infected by contact with an active genital lesion at the time of delivery (95, 140). Presumed nonsexual transmission resulting in lesions of the finger and hand has been described in health care workers before the routine use of gloves and in young children sharing a bed with an infected person (324, 340).

The risk of transmission through blood is negligible due to improved donor selection, uniform serologic testing of all blood donors, and a shift from transfusion of fresh blood to transfusion of refrigerated blood components (9, 360). Transmission via blood products is nonetheless theoretically possible since organisms may survive for up to 5 days in refrigerated blood (342, 343). Needle sharing probably does not play a significant role in syphilis transmission, but this remains unclear (175).

Occurrence of Disease

Developed countries. (i) United States. *(a) Primary and secondary syphilis.* In 1947, prior to the penicillin era, the incidence of primary and secondary syphilis was reported at 66.4 cases per 100,000 persons (236). Rates declined to 3.9 cases per 100,000 persons by 1956 due to the availability of penicillin, changes in sexual behavior, and public health measures (236). Studies published by the U.S. Public Health Service suggest that antibiotic therapy, whether intentional or not, contributed to this decline. Since the nadir in 1956, syphilis rates have peaked and troughed in approximately 10-year cycles, with the overall trend being toward increasing rates. The most recent epidemic was noted in 1990, with reported rates for primary and secondary syphilis at 20 per 100,000 persons, a 59% increase since 1985 (41, 111, 351). Although no single factor can explain this trend, an important contributing factor is crack cocaine use and the exchange of illegal drugs for sex (7, 37, 39, 212, 225, 281). In 1991, there was a reversal of the 5-year increasing trend (72). The reasons for the decline are unclear but may be related to renewed priority and increased resources given to syphilis control programs (350). By 1997, a rate of 3.2 cases per 100,000 persons was reported, the lowest incidence ever reported (320).

(b) Race and sex. There are reported differences across race and sex (41). African American and Hispanic race are strong markers for syphilis seroreactivity (128, 307). Between 1985 and 1990, rates in African Americans increased from 51.1 to 142.6 cases per 100,000 persons, with African Americans accounting for 80% of all cases in 1990 (236). Approximately 10 to 12% of these patients were adolescents (42). Despite a decline by 1996 to 30.2 cases per 100,000 in African Americans, this rate was still nearly 50 times that for non-Hispanic whites (72). Although some of these differences may be due to differential reporting of syphilis in African Americans to public health agencies, identified risk factors for this group include younger age, geographic instability, and poverty (10, 211, 323). Poor access to health care has probably also played a role (11, 41, 211, 225, 323). The rate of syphilis in Native Americans also remains higher than for the general population (109).

In the past, men have had consistently higher rates of infection than women. The male-to-female ratio of primary and secondary syphilis peaked at 3.5:1 in 1980, largely due to an epidemic in white males who reported having at least one male sex partner (35, 88). Since then, the male-to-female ratio has fallen to approximately 1:1 (236). The relative increase in rates of syphilis among women has been attributed to prostitution related to crack cocaine. Some studies have demonstrated that men have higher rates of primary syphilis than women whereas the reverse is true for secondary syphilis (160, 211). Possible explanations for this finding include the facts that women may be less likely to see primary lesions than men because they are internal and that men may have lower rates of secondary syphilis due to higher rates of diagnosis and treatment of primary cases (211).

(c) Regional differences. Regional differences have also been noted, with the highest rates in the southern United States followed by the Northeast, the West, and the Midwest (351). The rate in the South peaked in 1990 at 33.7 cases per 100,000 persons (236). By 1996, the rate in the South had declined to 8.7 cases per 100,000 population (72). Generally, the highest rates occur in urban areas, with the overall rate of primary and secondary syphilis for 63 large cities (with >200,000 population) representing twice the total U.S. rate during the 1980s and 1990s (74). However, a study in North Carolina reported higher rural than urban rates (334). Between 1981 and 1993, the rates of syphilis for African Americans in various regions peaked at similar levels but in different years (236). Mathematical modeling suggests that syphilis epidemics may start by introducing infection into a core group of susceptible persons

with multiple sexual partners (254). This core group will then transmit infection to large numbers of partners. The epidemic would be limited by the fact that the core group would then either be treated or progress to later, less infectious stages of syphilis. The temporal differences in the peaking of the regional epidemics may then be explained by the differential development of susceptible populations (236).

(d) Congenital syphilis. Reported cases of congenital syphilis in New York City increased from 57 to 357 per 100,000 persons from 1986 to 1988 (39, 236). This increase paralleled a 240% rise in early syphilis in women. Similar increases have been reported elsewhere and are associated with maternal crack cocaine use as well as underutilization and inadequacy of antenatal care (33, 37–39, 212, 310).

In 1993, African Americans accounted for 72% of cases of congenital syphilis, with reported rates of 344.9 cases per 100,000 live births (74). This is in contrast to rates of 96.3 cases per 100,000 live births in Hispanics and 6.1 cases per 100,000 live births in non-Hispanic whites (74). Between 1994 and 1996, overall rates of congenital syphilis decreased from 55.6 to 30.4 cases per 100,000 live births, but compared with 1995, increases were observed for four states in 1996 (72).

(ii) Other developed countries. The rate of primary and secondary syphilis in Canada peaked at a rate of 5.5 per 100,000 population in 1984 and then declined (73). Except for a small rise in 1992, the rate has remained low, with a reported rate of 0.4 per 100,000 in 1995 (73). Overall rates of latent and congenital syphilis have also fallen in the last decade, and it is noteworthy that only five cases of congenital syphilis have been reported in Canada since 1990 (73). The decline in latent syphilis may be related to improved screening and treatment of early symptomatic disease.

In the United Kingdom, rates of infectious syphilis fell in the early 1980s, with a greater percentage fall in men, and they have remained stable since 1988 (8). Data from Australia show a different trend by geographic area, with rates falling from 201 per 100,000 in 1980 to 4 per 100,000 in 1993 in South Australia and increasing from 513 per 100,000 in 1980 to 721 per 100,000 in the Northern Territory (71, 139). Ninety percent of syphilis infections in Australia occur in aboriginals, who account for less than 2% of the population (139).

Developing countries. Although accurate figures on the incidence of syphilis are not available for most developing countries, population-based studies have shown the seroprevalence to vary widely, from 0.9 to 94% depending on the group tested (12, 355). The World Health Organization estimated that there were approximately 12 million new cases of syphilis in adults worldwide in 1995 (355). The greatest number of cases was estimated to have occurred in South and Southeast Asia, with 5.8 million cases, while a further 3.5 million cases occurred in sub-Saharan Africa (355). Factors associated with a high prevalence of syphilis include certain occupations such as long-distance truck driving and commercial sex work, presence of other sexually transmitted diseases (STDs), lack of male circumcision, and level of education (239, 355). African long-distance drivers have been reported to have rates of syphilis as high as 15%, while commercial sex workers have rates varying from 23 to 47% in North Africa and the Middle East (355).

Parallel with the rise of syphilis in western countries, countries such as Trinidad and Tobago, Singapore, and the former USSR have reported a rise in the number of cases of early and congenital syphilis since the mid-1980s (4, 194, 330, 337). In the Russian Federation, there were 2.5 cases per 100,000 in 1947, rising to a peak of 28 cases per 100,000 in 1978 and 1979 (337). The number of cases then fell once again to 4.2 per 100,000 in 1988, before rising to 263 per 100,000 in 1996, a 62-fold increase since 1988. The largest increases were for primary and secondary syphilis in those aged 15 to 19 years (337). The causes of this epidemic are probably multifactorial and include increasing poverty and unemployment, especially among women, a decline in government-funded public health services, and increased population movements occurring with the opening of borders (337).

Other countries such as Thailand and Zimbabwe have reported a declining prevalence of syphilis, although these still represent relatively high incidence rates (190, 262). In Thailand, the decline has been attributed to a government campaign promoting condom use among commercial sex workers and to the widespread antibiotic use (190). However, in 1992 in Zimbabwe, the introduction of user fees resulted in a sharp fall in attendance at outpatient clinics, which may explain the decline in reported cases (262).

The prevalence of syphilis in pregnant women attending antenatal clinics in major African cities ranges from 4 to 15% (123, 305). Similarly, the prevalence of syphilis in pregnant women in other countries also varies markedly from 1.3% in Honduras and 0.6% in Korea to 6.3% in Paraguay and 14.2% in Fiji (355). Although true estimates of the effect on pregnancy outcome are unknown for persons with untreated early maternal syphilis, it is postulated that 5 to 8% of all pregnancies surviving past 12 weeks will end in spontaneous abortion, perinatal or infant death, or a live infant with congenital syphilis (305). Untreated maternal infection is also associated with prematurity and low birth weight (76).

PATHOGENESIS AND PATHOLOGIC FINDINGS

Pathogenesis

Most of the information on the pathogenesis of syphilis is derived from animal models because of the limited information available from human studies (91, 233). *T. pallidum* is presumed to penetrate through small breaks in the skin (91, 205, 206). Magnuson et al. were able to demonstrate that two organisms inoculated intracutaneously in rabbits produced a dark-field positive lesion in 47% of cases (202). This increased to 71 and 100% when 20 and 200,000 organisms were inoculated, respectively. On intracutaneous inoculation, the incubation period varied with the size of the inoculum, so that with a large inoculum, e.g., 10^7 organisms, a chancre appeared in 5 to 7 days (202). An inoculation study in human volunteers, which would be considered unethical by today's standards, showed similar findings (203). Animal studies have shown that the organisms appear within minutes in lymph nodes and disseminate widely within hours (61, 272, 324). Although the exact mechanisms by which *T. pallidum* enters cells is not known, it has been shown to attach to mammalian cells in vitro (93, 143). Attachment may occur by specific attachment ligands (17, 331, 332). Invasion appears to be a critical virulence factor for *T. pallidum*, as demonstrated by its ability to penetrate endothelial cell monolayers and intact membranes (277, 333).

Pathologic Findings

The pathologic findings of all stages of syphilis are characterized by vascular involvement with endarteritis and periarteritis and in the gummatous stage by granulomatous inflammation. In most primary lesions, the epidermis demonstrates hyperplasia with widening and elongation of the rete ridges (81). The ulcer surface is covered with an exudate consisting of fibrin, necrotic tissue fragments, and polymorphonuclear leukocytes. A dense inflammatory infiltrate is seen in the adjacent

dermis, with predominantly lymphocytes and plasma cells, but histiocytes and polymorphonuclear cells are also seen. The perivascular area is particularly involved and associated with endothelial-cell swelling. Silver staining invariably demonstrates the presence of spirochetes, mainly in the dermal-epidermal junction in the perivascular area.

In secondary syphilis, a wide variety of histologic changes are seen, with lymphocytes and plasma cells present in the dermis in 75 to 100% of patients (1, 81). Silver staining reveals the presence of treponemes in around 70% of patients (81). Small blood vessels often show endothelial-cell swelling (1). The epidermis is frequently involved, with exocytosis, spongiosis, parakeratosis, and acanthosis being the most frequent changes (1). In late secondary lesions, the infiltrate may become granulomatous (1).

Histopathologic examination of syphilitic aneurysms demonstrates invasion of the aorta by spirochetes (156). An inflammatory exudate of lymphocytes and plasma cells forms about the vasa vasorum of the adventitia and is followed by obliterative endarteritis of nutrient vessels. In later cases, gumma and scar tissue develops.

In meningitis, the meninges are infiltrated by lymphocytes, plasma cells, and occasionally polymorphonuclear leukocytes with or without perivascular infiltration and vessel thrombosis due to endarteritis (222). In meningovascular syphilis, there is diffuse thickening and lymphocytic infiltration of the meninges and the perivascular spaces (148). The large and medium-sized vessels show fibroblastic and collagenous thickening of the intima, thinning of the media, and fibrous change of the adventitia, together with lymphocytic and plasma cell infiltration (148). Luminal narrowing leads to thrombosis and ischemic infarction of adjacent brain (148). Rarely, aneurysmal dilatation of the affected vessel may occur (148). When a gumma of the central nervous system forms, the histologic tests show a chronic inflammatory infiltrate with primarily lymphocytes, plasma cells, and multinucleate giant cells with or without necrosis (104, 179).

NATURAL HISTORY AND CLINICAL MANIFESTATIONS

The manifestations of syphilis have been recognized for centuries. Juan de Vigo described genital pustulae in his account of the "French sickness" in 1514 (266). Many others subsequently described the primary chancre followed by a reddish rash whose superficial resemblance to smallpox was responsible for the origin of the term "pox." Protean late manifestations involving all organ systems have been described, heralding syphilis as the "great imitator." The key to diagnosis remains a high index of suspicion.

Natural History

Descriptions of the natural history of untreated syphilis originate primarily from two large prospective studies and one retrospective study.

Boeck performed a prospective natural history study of 1,978 patients with early syphilis in 1891 (56). His observations over 20 years were then continued by Brusgaard, and this information was later termed the Oslo Study (56). Between 1949 and 1951, Gjestland undertook a monumental follow up of 1,404 of the original 1,978 patients (115). The data were reviewed in 1955 and then reanalyzed in 1964 by Clark and Danbolt (55, 56). Although the study is important in terms of defining natural history because of its large sample size, long follow-up, and almost complete absence of treatment, it does have some major design flaws. Diagnoses were made clinically since neither serologic testing nor microscopy was available when the study began, more women than men were admitted because more female beds were available, there were no controls, and autopsies were carried out on only 24% of patients. The results indicate that approximately one-third of the patients developed tertiary manifestations of neurologic, cardiovascular, and gummatous (late benign) syphilis and that the probability of dying due to untreated syphilis was 17% in males and 8% in females (55). Late benign syphilis was the most frequent manifestation, occurring in 14% of males and 17% of females, 1 to 46 years after healing of the secondary lesions. The incidence of clinically apparent cardiovascular syphilis was 13.6% in males and 7.6% in females, but the true incidence may have been higher had more autopsies been carried out. Symptomatic neurosyphilis developed in approximately 9.4% of males and 5.0% of females.

In 1932, the U.S. Public Health Service initiated the Tuskegee study observing African American men with untreated syphilis for 40 years (279, 335). The study has been heavily criticized on ethical grounds, primarily because written informed consent was not obtained from patients and also because treatment was withheld (335). A total of 412 men with untreated latent syphilis and 204 uninfected matched controls were monitored prospectively. Vonderlehr reviewed autopsy material from the first years of the study and noted that only one-fourth of the untreated patients were without evidence of tertiary syphilis after 15 years of infection (346). Cardiovascular involvement was the most frequently detected abnormality, with 50% of the patients infected for 10 years demonstrating cardiovascular involvement (259). Of the 41% survivors at 30 years follow-up, 12% had evidence of late, predominantly cardiovascular syphilis (279).

Rosahn retrospectively reviewed all autopsies at the Yale University School of Medicine from 1917 to 1941 (289). Of 4,000 autopsies of persons aged over 20 years at death, 9.7% had clinical, laboratory, or autopsy evidence of syphilis. About half had received no therapy. Among clinically diagnosed patients, 39% had late anatomic lesions. Of 77 patients with untreated syphilis and late anatomic lesions at autopsy, 83% had cardiovascular complications, 9% had late benign lesions, and 8% had neurosyphilis (289).

In summary, the three studies demonstrate that 15 to 40% of untreated patients with syphilis develop recognizable late complications. A higher mortality rate was noted in populations with syphilis, men were twice as likely to develop late complications, and it was suggested that African Americans were more likely to develop cardiovascular syphilis whereas whites were more likely to develop neurosyphilis (56, 289).

Effects of untreated syphilis on pregnancy outcome in 1951 demonstrated marked differences in risk according to the stage of maternal infection (162). If maternal infection occurred early during pregnancy, the incidence of stillbirth was 25%, that of neonatal death was 14%, that of infected infants was 41%, and that of noninfected infants was 20%. This is in contrast to rates of 12% for stillbirth, 9% for neonatal death, 2% for infected infants, and 77% for noninfected infants when maternal infection occurred late during pregnancy.

Clinical Manifestations

The clinical manifestations of the various stages of syphilis are summarized in Table 1.

Primary syphilis. The classic lesion of primary syphilis, the chancre, is a single, painless, indurated ulcer with a clean base (324). However, there is significant variability in morphologic

TABLE 1. Common clinical manifestations of syphilis

Stage of syphilis	Clinical manifestations	Incubation period
Primary	Chancre, regional lymphadenopathy	3 wk (3–90 days)
Secondary	Rash, fever, malaise, lymphadenopathy, mucus lesions, condyloma lata, alopecia, meningitis, headaches	2–12 wk (2 wk–6 mos)
Latent	Asymptomatic	Early, <1 yr; late, >1 yr
Tertiary		
Cardiovascular syphilis	Aortic aneurysm, aortic regurgitation, coronary artery ostial stenosis	10–30 yr
Neurosyphilis		
Asymptomatic	None	
Acute syphilitic meningitis	Headache, meningeal irritation, confusion	<2 yr
Meningovascular	Cranial nerve palsies	
General paresis	Prodrome: headache, vertigo, personality disturbances, followed by acute vascular event with focal findings	5–7 yr
Tabes dorsalis	Insidious onset of dementia associated with delusional state, fatigue, intention tremors, loss of facial-muscle tone	10–20 yr
	Lightning pains, dysuria, ataxia, Argyll Robertson pupil, areflexia, loss of proprioception	15–20 yr
Gumma	Monocytic infiltrates with tissue destruction of any organ	1–46 yr (most cases 15 yr)
Congenital		
Early	Fulminant disseminated infection, mucocutaneous lesions, osteochondritis, anemia, hepatosplenomegaly, neurosyphilis	Onset <2 yr
Late	Interstitial keratitis, lymphadenopathy, hepatosplenomegaly, bone involvement, condylomata, anemia, Hutchinsonian teeth, eight-nerve deafness, recurrent arthropathy, neurosyphilis	Persistence >2 yr after birth

presentation, making clinical diagnosis unreliable (46, 48, 70). The classic combination of a painless, ulcerated lesion with a clean base has a sensitivity of only 31% but a specificity of 98% (70). Induration is the single most specific sign, occurring in 47 to 92% of patients (46, 70). Purulence involving less than 30% of the base has been reported to be the most sensitive finding (70). The size of the chancre varies from 0.3 to 3.0 cm, and occasionally there are multiple lesions (46, 70). There is usually a sharply marginated border, although lesions with undetermined edges have been described (46, 70). Painless regional lymphadenopathy occurs in up to 80% of patients and is more often associated with genital lesions (46, 70, 224). Although pain is uncommon, as many as 36% of patients experience tenderness on palpation (70). The incubation period varies from 3 to 90 days.

Chancres occur at the site of inoculation. In men, the commonest site affected is the penis, more specifically the coronal sulcus and glans (224). Anorectal chancres are common in homosexual men (218, 224, 268). In women, the commonest locations of the lesions, in order of decreasing frequency, are the labia majora, labia minora, fourchette, and perineum (46, 324).

Extragenital chancres occur infrequently; in recent series they have been reported in less than 2% of patients (224). Unlike genital lesions, extragenital chancres have little or no basal induration with edges rising above the surrounding surface (340). Pain is a prominent symptom in extragenital lesions involving the fingers, border of the tongue, and anus (224, 340). Between 40 and 70% of extragenital chancres occur on the mouth, with approximately one-fifth of these being located on the lip (224, 340).

Secondary syphilis. There may be no sharp demarcation between primary and secondary syphilis. A primary chancre is still present in as many as one-third of patients with secondary syphilis (47, 224). Alternatively, the primary lesion may have healed for, typically, 8 weeks before any cutaneous or constitutional signs appear. As many as 60% of patients found to have syphilis do not recall lesions of any sort. Secondary syphilis is often a subtle disease; the skin lesions may be easily overlooked and may mimic other dermatologic diseases (47, 324). The appearance of the skin rash ranges from macular to maculopapular, follicular, and occasionally pustular (47, 324). Classically, the lesions are described as "raw ham" or copper colored. They tend to be universally distributed, and the palms and soles are commonly involved (47, 324). Although the lesions are generally described as nonpruritic, patients may experience various degrees of pruritus (47). In untreated patients, the lesions resolve over several weeks and may heal with scarring or hyper- or hypopigmentation, although the majority heal without any scarring. The classic alopecia of secondary syphilis is patchy with a "moth-eaten appearance" and has been reported in up to 7% of patients (47, 224, 324).

Skin lesions may be associated with diffuse inflammatory involvement of the pharynx and tonsils, which may cause a symptomatic sore throat (47, 324). The typical lesion of the mucus membranes is the mucus patch, occurring in 5 to 22% of patients and involving the tongue, buccal mucosa, and lips (47, 224, 324). The lesions range in size from 5 to 10 mm and are

usually slightly raised and painless with a central erosion covered with a thin membrane.

Genital mucus lesions are more common in women and range from macules to papules, ulcerations, and condylomata (324). Although the lesions may be evanescent and disappear within hours to days, they typically last 2 to 3 weeks.

Systemic symptoms associated with secondary syphilis range from slight malaise to prostration and cachexia (324). Usually, the symptoms are mild. They may begin as early as a week after the primary chancre. Headache is present in up to one-third of patients, and fever is usually low-grade, seldom exceeding 100°F. Asymptomatic meningitis occurs in 8 to 40% of patients, while cranial nerve palsies (of nerves II to VIII) occur infrequently (220). Gastrointestinal symptoms include anorexia, nausea, and occasionally vomiting. Painless adenopathy is present in 70 to 85% of patients and most commonly involves the suboccipital, cervical (especially posterior cervical), posterior auricular, and epitrochlear nodes (324).

Although vague bone and joint pain has been reported in approximately 12% of patients with secondary syphilis, osteitis and arthritis are rarely described (274).

Jaundice has been reported to occur in as many as 12% of patients with early syphilis, but syphilitic hepatitis has been only rarely described (32, 260, 297). Syphilis of the kidneys is an extremely rare but well-described complication of secondary syphilis (336). Proteinuria is still the most common manifestation, but clinical findings range from nephrotic syndrome to acute nephritic syndrome, rapidly progressive glomerulonephritis, and renal failure (157). Syphilis of the stomach is usually manifested by mucosal erosions, rugal hypertrophy, or shallow ulcers involving the antral and pyloric areas (122, 362).

Ocular complications of syphilis can involve almost any inflammatory process including episcleritis, scleritis, interstitial keratitis, iridocyclitis, vitritis, posterior uveitis, optic nerve involvement, and pupillary abnormalities (69, 208, 227, 296, 318). Together with the other symptoms of secondary syphilis, a patient may present with bilateral tinnitus and deafness (230). Sensorineural deafness is found in as many as 17% of cases of early syphilis.

Ulceronodular or malignant syphilis is a rare manifestation with a typical prodrome of fever, headache, and myalgia followed by papular eruptions that progress to pustules with ulcerated necrotic centers (90, 237). An association with human immunodeficiency virus (HIV) has been suggested, with 11 of 12 cases reported since 1989 occurring in either HIV-infected patients or those at high risk for HIV (293).

Latent (early and late) syphilis. The latent or asymptomatic stage of syphilis is defined as the period from disappearance of the secondary manifestations until therapeutic cure occurs or tertiary manifestations develop (156). Latent disease is arbitrarily divided into early and late syphilis based on the time to spontaneous mucocutaneous (infectious) relapse of untreated patients. About 90% of first relapses occur within 1 year, 94% occur within 2 years, and the rest occur over 4 years (115). Early latent syphilis is therefore defined as occurring within 1 year of infection, and late latent syphilis is defined as occurring after 1 year. A patient with early latent syphilis is considered to be infectious due to the 25% risk of relapse to secondary syphilis (115).

Tertiary syphilis. (i) Cardiovascular syphilis. Although in the prepenicillin era, it was estimated that cardiovascular syphilis accounted for 10 to 15% of all clinical cardiovascular disease (324) and was demonstrable in 55 to 86% of all patients with syphilis at autopsy (156), it is now considered rare (144, 166). Concomitant involvement of the nervous system has been reported in up to 43% of patients (57). Cardiovascular involvement usually occurs between 10 and 30 years after the initial infection (57).

Syphilitic aortitis is the most common manifestation and typically involves the ascending aorta (57, 156, 177). Uncomplicated aortitis is usually asymptomatic, but symptoms include substernal dull, aching pain in about 20% of patients with aortitis and heart failure in 25% (178, 324). The most common complication of untreated syphilitic aortitis is aortic regurgitation (156, 178). Clinical presentation usually occurs in the second or third decade of infection. Coronary ostial stenosis occurs in 20% of patients with syphilitic aortic insufficiency (144). Angina is the most frequent symptom but is rarely associated with myocardial infarction (29). Aneurysm formation is the least common complication of aortitis (178) and is symptomatic in 5 to 10% of patients (176). The majority are single aneurysms, usually saccular rather than fusiform and with involvement of the ascending aorta in 50% of patients (144, 156, 176).

(ii) Neurosyphilis (asymptomatic, meningeal, meningovascular, parenchymatous, and gumma). Although many patients with syphilis undergo cerebrospinalfluid (CSF) invasion by spirochetes, not all will develop CSF abnormalities or neurosyphilis (51, 200, 358). After initial invasion of the CSF by spirochetes, untreated or inadequately treated infection may follow one of several courses: spontaneous resolution, asymptomatic meningitis, or acute syphilitic meningitis (221). After this, the disease may either remain asymptomatic or progress to meningovascular syphilis, tabes dorsalis, or paresis (221). Although neurosyphilis has been divided into five major categories, i.e., asymptomatic, meningeal, meningovascular, parenchymatous, and gummatous, these entities represent a continuum and frequently overlap (221). More recently, reports of unusual presentations and rapid progression of syphilis in patients with concurrent HIV infection has led to the hypothesis that infection with HIV may alter the natural history of syphilis (21, 172, 182, 200, 235).

Asymptomatic neurosyphilis is defined as the presence of CSF abnormalities in the absence of neurologic symptoms or signs (129). Asymptomatic or more subtle, ill-defined syndromes have become more common in the antibiotic era and comprises one-third of clinically diagnosed cases of neurosyphilis (154, 155, 200, 308). The incidence of CSF abnormalities, including an elevated leukocyte count and protein or reactive CSF VDRL test, peaks 12 to 18 months following infection (249).

Early in the disease, symptoms of aseptic meningitis are common, usually occurring within the first 6 months of infection or at the time of the secondary rash (220, 222, 308). Clinical findings include severe headache, confusion, nausea, vomiting, and stiff neck without fever. The cranial nerves most commonly involved are the facial and auditory nerves, with sensorineural deafness occurring in up to 20% of patients (222). Ocular abnormalities including optic neuritis and iritis may also occur (222, 227).

Meningovascular syphilis represents about 10% of all cases of neurosyphilis, with peak occurrence at 4 to 7 years after primary infection (154, 155, 308). The typical syndrome is one of a diffuse encephalitic presentation with superimposed focal features (148). Since meningitis is usually a concomitant factor, many patients complain of headaches for several days or weeks before the onset of the vascular insult (220). The prodrome may also include personality changes, emotional lability, vertigo, and insomnia (148). The presence of seizures, altered level of consciousness, and focal findings depends on the involved site (220).

Unlike meningovascular syphilis, classic late parenchyma-

tous neurosyphilis has become relatively rare since the advent of modern antimicrobial therapy (155). This syndrome may present as paresis or tabes dorsalis (155).

The symptoms and signs of paresis may be varied and are more common in men than in women (155, 221). The incubation period is usually 5 to 25 years (221). Early in the disease, the symptoms are similar to those of other forms of dementia, with gradual impairment of memory and cognitive functions, the appearance of irritability, and a decline in personal appearance (308). As the disease continues, progressive dementia develops, with psychotic symptoms mimicking nearly every psychiatric illness (221).

Tabes dorsalis also affects males more frequently (221). The incubation period is usually 5 to 25 years, with involvement of pupillomotor structures and the spinal cord dorsal roots and columns (155, 221). Early manifestations are lightning pains (occurring in 75 to 90% of patients), paresthesias, pupillary changes, and areflexia (221, 308). The lightning pains most commonly affect the lower extremities. With disease progression, sensory ataxia affecting mainly the lower extremities becomes a prominent feature. There is impairment of position and vibration sense, resulting in a widebased gait and positive Romberg's sign. Gastric crises have been reported in 10 to 20% of patients and consist of sudden onset of vomiting or abdominal pain or both (221, 324). Although pupillary abnormalities are reported in 70 to 94% of patients, the classic Argyll Robertson pupil is reported in only 48 to 64% (195, 221). The pupil is small and irregular and accommodates but does not react to light. The change is usually bilateral (195). Damage to the optic nerves results in optic atrophy in 20% of patients (221, 308). Trophic lesions such as Charcot's joints (hips, knees, ankles) and distal-extremity neuropathic perforating ulcers (mal perforans) are found in 2 to 10% of patients (221, 308).

(iii) Late benign syphilis. The essential lesion of late benign syphilis is the gumma (246). The term "benign" implies that these lesions rarely cause total physical incapacity or death, but when the lesions occur in organs such as the brain or heart, serious complications may occur (156, 178, 220, 314, 324). The most common sites of involvement are the skin, bone, and liver (177). The gumma develops from 1 to 46 years after healing of secondary lesions, with the majority developing by the end of the 15th year (56). Skin lesions may appear as nodular, noduloulcerative, or ulcerative lesions (53, 246). Bone lesions are marked by periostitis involving the cranial bones, tibia, and clavicle, with the cardinal features of nocturnal pain and local swelling (177).

Congenital syphilis. Untreated syphilis can profoundly affect pregnancy outcome, resulting in spontaneous abortion, stillbirth, premature delivery, or perinatal death (103, 162, 352, 353). Prematurity and low birth weight have been reported for 10 to 40% of infants born to untreated mothers (184, 213). Congenital syphilis is also a potentially treatable cause of nonimmune hydrops fetalis (16, 79).

The rate of vertical transmission in untreated women is 70 to 100% for primary syphilis, 40% for early latent syphilis, and 10% for late latent disease (95). Thus, the longer the interval between infection and pregnancy, the more benign is the outcome in the infant (Kassowitz's law) (84).

The infected neonate may be asymptomatic or may have subtle findings or multiple-organ system involvement (22, 324). Postnatal manifestations are divided into early and late stages; early manifestations occur in the first 2 years of life, and late manifestations occur after 2 years of age.

Early clinical signs are variable (22, 49, 50, 95, 324). Most manifestations are not present at birth but develop within the first 3 months of life (49). "Snuffles" or persistent rhinitis is one of the earliest clinical manifestations, occurring in 4 to 22% of infants. The nasal discharge may be profuse and purulent or blood tinged and is highly infectious. Hepatomegaly with or without splenomegaly occurs in 33 to 100% of patients. Glomerulonephritis resulting in nephrotic syndrome may also occur. The infant may have generalized lymphadenopathy with discrete, hard, nontender nodes. Vesiculobullous lesions and an erythematous maculopapular rash occur in one-third to one-half of patients and frequently involves the palms or soles. Desquamation is not uncommon. Asymptomatic central nervous system involvement manifesting as CSF abnormalities of lymphocytosis, elevated protein levels, and positive serologic test occur in up to 80% of infected infants (263, 357). In the prepenicillin era, acute syphilitic meningitis occurring between 3 and 6 months of age was seen in 5 to 15% of infected patients, but such cases are now rare (357).

Bone lesions develop within 8 months of birth in early congenital syphilis (112, 273, 274). Osteochondritis (Parrot's pseudoparalysis) is the most common and earliest lesion, affecting mainly the upper limbs and knees. It can result in an asymmetric, painful, flaccid pseudoparalysis. The radiographic appearance demonstrates irregular epiphyseal lines, decalcification of subchondral bone, cupping of the diaphysis, irregularity of the cartilage adjacent to the epiphysis, and periosteal thickening (273, 274). Diaphyseal periostitis is asymptomatic and does not produce radiologic signs until after 3 months of age. The bones most often affected are the tibias, followed by the tubular bones of the hands and feet and, less frequently, the clavicles and skull. Osteomyelitis due to gummatous involvement of the diaphyseal-metaphyseal junction of long limb bones occurs rarely.

Late manifestations of congenital syphilis include Hutchinson's triad of interstitial keratitis, peg-shaped upper incisors, and eighth-cranial-nerve deafness (22, 84, 324). The hearing loss is sudden and usually occurs at 8 to 10 years of age. Other characteristic findings include frontal bossing, short maxillae, saddle nose, protruding mandible, high arched palate, mulberry molars, perioral fissures (rhagades), bilateral knee effusions, sternoclavicular thickening, saber shins, flaring scapulas, mental retardation, and hydrocephalus. Bilateral hydrarthrosis, or Clutton's joints, involving knees and elbows typically occurs between 8 and 15 years of age (274). As many as one-fourth to one-third of patients older than 2 years have asymptomatic neurosyphilis (357). Symptomatic neurosyphilis develops rarely, with juvenile paresis developing in 1 to 5% of patients with congenital syphilis (278, 357). The symptoms of juvenile paresis are usually more severe than those of acquired paresis, and the typical onset occurs in puberty.

Necrotizing funisitis, a rare deep-seated inflammatory process of the umbilical cord, was noted to be virtually diagnostic of congenital syphilis and occurs almost exclusively in preterm infants with an average gestational age of 32 weeks (105, 167). The majority of infants with necrotizing funisitis are stillborn, and the remainder die within a few weeks of birth.

DIAGNOSIS

The diagnosis of syphilis depends on clinical findings, examination of lesion material for treponemes, and/or serologic tests for syphilis (366). The laboratory diagnosis of syphilis has been extensively reviewed in a previous issue of this journal (192).

Dark-field microscopy is the main diagnostic method for primary syphilis (324). Direct fluorescent-antibody testing for *T. pallidum* (DFA-TP) has also been described (163, 164, 283). However, neither dark-field microscopy nor the DFA-TP can

distinguish *T. pallidum* from the other pathogenic species of *Treponema* (192).

Efforts to cultivate the organism in vitro have been largely unsuccessful, but there has been one report in the literature of successful culture of *T. pallidum* on artificial medium (58). *T. pallidum* is readily cultivated by animal inoculation (313, 360). However, rabbit infectivity tests (RIT) are expensive and require 3 to 6 months to complete (192). This method is impractical for routine clinical use but is very sensitive, with the theoretical ability to identify one viable organism (192).

Serologic testing remains the mainstay of laboratory diagnosis for secondary, latent, and tertiary syphilis (192). Serologic tests are divided into nontreponemal and treponemal, tests and neither alone is sufficient for diagnosis. Nontreponemal tests are useful for screening, while treponemal tests are used to confirm the diagnosis.

Nontreponemal tests include the Venereal Disease Research Laboratory (VDRL) and the Rapid Plasma Reagin (RPR) card test, both modifications of the original Wasserman reaction (134, 265). Nontreponemal tests use an antigen comprising lecithin, cholesterol, and purified cardiolipin (a component of mammalian cell membranes) to detect an antibody against cardiolipin that is present in the sera of many patients with syphilis. Although these tests are widely available and relatively inexpensive, they are limited by their lack of sensitivity in early and late syphilis and by false-positive reactions. False-positive reactions are associated with increased age, pregnancy, drug addition, malignancy, and autoimmune diseases, such as systemic lupus erythematosus, as well as with viral (particularly Epstein-Barr virus and hepatitis virus), protozoal, or mycoplasmal infection (152, 192).

Treponemal tests include the serum fluorescent treponemal antibody absorption test (FTA-ABS) and the microhemagglutination test for *T. pallidum* (MHA-TP), which use lyophilized *T. pallidum* or a lysate of pathogenic *T. pallidum*, respectively (66, 133, 158, 291). These tests have higher sensitivity and specificity than the nontreponemal tests and are used as confirmatory tests for syphilis after a reactive nontreponemal test has been reported. False-positive results are rare but have been found in association with mixed connective tissue and autoimmune disease, viral infections, and pregnancy (316).

DNA PCR has been used to identify *T. pallidum* in clinical specimens but is not readily available for routine clinical use (31, 124, 142, 242). While DNA PCR methods have not been shown to be as sensitive as RIT, a highly sensitive reverse transcriptase PCR, which is able to detect a single treponeme, has been described (45). In addition, multiplex PCRs have been described for the simultaneous detection of the three major causes of genital ulcer disease: herpes simplex virus types 1 and 2, *Haemophilus ducreyi*, and *T. pallidum* (252).

There is no "gold" standard for the diagnosis of neurosyphilis, and it is usually based on a combination of reactive serologic tests, abnormalities of CSF cell count and protein levels, or a reactive CSF VDRL (43). Two or more CSF abnormalities are generally considered to be compatible with a diagnosis of neurosyphilis. The CSF VDRL has high diagnostic specificity but low diagnostic sensitivity (30 to 78%) in neurosyphilis (30, 154, 169, 316). A false-positive VDRL titer should occur only if the CSF is contaminated with blood (65, 165). The presence of treponemal antibody in the CSF is not diagnostic for neurosyphilis since it may represent passive diffusion of treponemal antibody from the blood into the CSF rather than active central nervous system infection (169). A negative CSF FTA-ABS however, may be useful to rule out neurosyphilis (170, 192, 209, 316). Some investigators have suggested that the CSF FTA-ABS, *T. pallidum* hemagglutination test, and MHA-TP are more sensitive than the VDRL in the diagnosis of neurosyphilis, but this is not uniformly accepted (64, 138, 170). Other CSF abnormalities include an elevated leukocyte count with predominantly lymphocytes and elevated protein levels (30). The indications for performing a lumbar puncture in patients with syphilis include neurologic or ophthalmologic symptoms or signs, tertiary syphilis (e.g., aortitis, gumma, and iritis), treatment failure, HIV infection if the RPR is >1:32 or if there are neurologic symptoms or signs, and congenital syphilis (43). Some experts recommend that all patients with HIV infection undergo lumbar puncture, but this recommendation is not strongly supported by available evidence.

The diagnosis of syphilis in pregnancy is most often made by serologic screening done at the first antenatal visit. In the United States, it is currently recommended that all pregnant women be screened by a nontreponemal test early in pregnancy (43). In areas of high prevalence and in patients considered to be at high risk, testing should also be done twice during the third trimester (43). If the nontreponemal test is positive, confirmatory testing by treponemal tests should be carried out. In pregnant women with a history of previous syphilis, nontreponemal titers may increase nonspecifically; this increase may be confused with reinfection or relapse (36, 192). The increase in titer may be attributed to pregnancy if there is clear documentation of previous treatment in the absence of lesions suggestive of syphilis, a fourfold increase in titer, or history of sexual contact with a person with infectious syphilis (192).

All infants born to mothers with positive serologic tests for syphilis should be evaluated by a quantitative nontreponemal serologic test within the first month of life (43). Serum from the neonate is the preferred specimen, since cord blood may produce false-positive results (52). The diagnosis of congenital syphilis is complicated by passive transfer of antibodies from mother to infant, but most of these antibodies should be catabolized and undetectable in noninfected infants by age 6 to 12 months (36, 43, 325). In addition, during the first month of life, infants born to mothers with positive serologic tests should be examined thoroughly for physical signs of congenital syphilis (43, 325). Maternal serologic test results and records should also be reviewed (43). Pathologic examination of the placenta or umbilical cord by using DFA-TP testing is also suggested (43). Dark-field microscopy with DFA-TP testing should be carried out on any suspicious lesions or body fluids, e.g., nasal discharge (43). Additional investigations, such as long-bone radiographs or chest X ray, are dependent on abnormalities found on physical examination. CSF analysis for cell count, protein, and VDRL is indicated if the infant has an abnormal physical examination consistent with congenital syphilis, a quantitative nontreponemal serologic titer in serum that is fourfold greater than the mother's titer, or a positive dark-field or DFA-TP result for tests of body fluids (43). Any prepubertal child with a reactive syphilis serologic test should undergo a full evaluation, and maternal serologic test results and records should also be reviewed (43).

The diagnosis of congenital syphilis depends on a combination of physical, radiographic, serologic, and direct microscopic criteria (36, 325, 369). A confirmed case is defined as occurring in an infant in whom *T. pallidum* is identified in specimens from lesions, placenta, umbilical cord, or autopsy material (36). A presumptive case is one in any infant or child whose mother was untreated or inadequately treated at delivery or who has a reactive treponemal test for syphilis and one of the following: evidence of congenital syphilis on physical examination or on long-bone X ray, elevated cell count or protein level (without other cause) in CSF, or reactive FTA-ABS immunoglobulin M antibody (36). A syphilitic stillbirth is defined as a

TABLE 2. Treatment of syphilis in non-HIV-infected persons[a]

Stage	Treatment[a] in:	
	Patients not allergic to penicillin	Patients allergic to penicillin[c]
Primary, secondary and early latent syphilis (<1 yr)	Benzathine penicillin G, 2.4 mU i.m. in a single dose Children: Benzathine penicillin, 50,000 U/kg i.m., to a maximum of 2.4 mU	Doxycycline,[d] 100 mg p.o. bid for 2 wk *or* Tetracycline, 500 mg p.o. qid for 2 wk *or* Erythromycin,[e] 40mg/kg/day (max 500 mg/dose) p.o. in divided doses for 14 days *or* Ceftriaxone, 1 g daily for 8–10 days
Late latent (> 1 yr) or latent syphilis of unknown duration[f]	Benzathine penicillin G, 7.2 mU i.m., given as three doses of 2.4 mU i.m. each at 1-wk intervals Children: Benzathine penicillin, 150,000 U/kg i.m., to a maximum of 7.2 mU, divided and given as three equal doses at 1-wk intervals	Doxycycline,[d] 100 mg p.o. bid for 4 wk *or* Tetracycline, 500 mg p.o. qid for 4 wk
Late syphilis[g] (gumma or cardiovascular syphilis, not neuro)	Benzathine penicillin G, 7.2 mU i.m., given as three doses of 2.4 mU i.m. each, at 1-wk intervals	Doxycycline,[d] 100 mg p.o. bid for 4 wk *or* Tetracycline, 500 mg p.o. qid for 4 wk
Neurosyphilis, including syphilitic eye disease[h]	Aqueous crystalline penicillin G, 18–24 mU daily, administered as 3–4 mU i.v. every 4 h for 10–14 days *or* Procaine penicillin, 2.4 mU i.m. daily, *plus* probenecid, 500 mg p.o. qid, both for 10–14 days	
Congenital syphilis[i]		
<1 mo old	Aqueous crystalline penicillin G, 100,000–150,000 U/kg/day, administered as 50,000 U/kg/dose i.v. every 12 h for the first 7 days of life and every 8 h thereafter for a total of 10 days *or* Procaine penicillin, 50,000 U/kg/dose i.m. daily in a single dose for 10 days	
>1 mo old	Aqueous crystalline penicillin G, 200,000–300,000 U/kg/day i.v., administered as 50,000 U/kg every 4-6 h for 10 days	

[a] Adapted from references 43 and 191 with permission of the publishers.
[b] i.m., intramuscular; mU, million units; p.o., orally; bid, twice daily; tid, thrice daily; qid, four times daily; i.v., intravenous.
[c] Penicillin-allergic pregnant patients and those with neurosyphilis should be treated with penicillin, after desensitization if necessary.
[d] There is less clinical experience with doxycycline than tetracycline, but compliance is likely to be better with doxycycline.
[e] If adequate compliance and follow-up can be assured. Note that this is less effective than other regimens.
[f] Tertiary disease should be excluded before treatment for latent syphilis is started.
[g] Patients with symptomatic late syphilis should undergo CSF examination before therapy. There is very little evidence to support the use of nonpenicillin regimens, and if these are to be used, a lumbar puncture should be carried out before therapy is begun.
[h] Many experts recommend treating patients with auditory syphilitic disease with the same regimens as for neurosyphilis, regardless of the findings on the CSF examination. Many experts recommend following intravenous therapy for neurosyphilis with i.m. benzathine penicillin, 2.4 mU weekly for 3 weeks.
[i] Asymptomatic infants with negative laboratory findings born to women treated with nonpenicillin regimens should receive benzathine penicillin, 50,000 U/kg i.m., as a single dose if follow-up is assured.

fetal death occurring after 20 weeks gestation or weighing more than 500 g in which the mother had untreated or inadequate treatment for syphilis at delivery (36).

TREATMENT

History

Mercury was one of the first treatments used for syphilis, coming into use in 1497 (294, 341). In 1909, Ehrlich introduced arsphenamine (Salvarsan), which was quickly shown to be superior to mercury and became the drug of choice (294). Clinical cure, however, required repeated injections over 18 months. Other preparations of heavy metals, including bismuth compounds, were found to be efficacious and less toxic. In 1917, Wagner von Jauregg introduced the technique of malaria inoculation for the treatment of paretic cases (294). The real breakthrough in the treatment of syphilis occurred in 1943, when Mahoney et al. successfully used penicillin to treat four patients with primary syphilis (204).

Overview

Current recommendations for the treatment of syphilis are summarized in Table 2. Although many guidelines have been published for the treatment of syphilis, no prospective controlled studies have addressed the optimum dosage or duration of therapy for any stage of syphilis (43, 191). Since the introduction of penicillin, its use in the treatment of syphilis has

been based on clinical experience and on observational uncontrolled studies.

Although *T. pallidum* has not developed any measurable penicillin resistance, there have been anecdotal reports of persistence of the organism in aqueous humor, CSF, and inner ear despite treatment with recommended regimens (183, 200, 201, 339). In vitro resistance to erythromycin has been described in a single clinical isolate of *T. pallidum* from a penicillin-allergic patient who failed treatment with erythromycin (319). Norgard and Miller (244) have reported the identification of a plasmid in *T. pallidum*, which also suggests that the organism has the genetic potential to develop antibiotic resistance, but these findings have not been confirmed or reproduced.

The antibiotics used, as well as the dosage and length of treatment, are dependent on the stage of syphilis (43). Oral penicillin is not used due to inadequate levels in blood. Although other antibiotics have been used, they are alternate choices because of less spirocheticidal action, variable absorption, concerns with patient compliance, and diminished efficacy, especially in pregnant women (341).

The cure of syphilis depends not only on the antibiotic effect but also on the integrity of the immune capacity of the host. Although this has been recognized for many years, HIV infection has made it a very important and controversial issue.

Early Syphilis (Primary, Secondary, and Early Latent)

Penicillins and cephalosporins. Benzathine penicillin remains the recommended first-line therapy for early syphilis (43). A retreatment rate of approximately 10% is reported for treatment failures (303). It is worth noting, however, that the retreatment rates in this and many of the treatment studies that follow did not differentiate between treatment failure and reinfection. Some reports of penicillin failure have been attributed to poor penetration of benzathine penicillin into the CSF and persistence of *T. pallidum* in CSF in early syphilis (21, 172, 200, 339).

Most treatment studies of early syphilis have used aqueous or procaine penicillin, but because of dosing issues, benzathine penicillin has been substituted (232). Probenecid has been used to increase penicillin levels in serum and CSF (85, 264).

Ceftriaxone, a broad-spectrum cephalosporin with a long half-life in serum (7 h), has demonstrated activity against *T. pallidum* in a rabbit model (174, 189). The long half-life in serum allows for single daily dosing (321). After preliminary studies indicated efficacy, Hook et al. described its successful use in 27 patients exposed to infectious syphilis (151, 153, 229). All were treated with ceftriaxone, 125 mg intramuscularly (i.m.), and 25 of 27 (93%) had no serologic or clinical evidence of progression at 3 months follow-up (153). A further 16 patients with primary or secondary syphilis were treated with either 250 mg of ceftriaxone once daily for 10 days or 500 mg every 48 h for five doses; all patients were considered cured (153). Ceftriaxone has the advantage of good CSF penetration, which may reduce the likelihood of treatment failures and/or subsequent neurosyphilis (321). However, a 23% treatment failure rate has been reported in HIV-infected individuals with latent syphilis or asymptomatic neurosyphilis (77). This limited data suggests that ceftriaxone may be an alternative treatment, but additional studies are required before this agent can be recommended for routine use.

Erythromycin. Current guidelines recommend erythromycin base in the treatment of penicillin-allergic patients with early syphilis, at doses of 40 mg/kg/day orally (p.o.) (maximum 500 mg per dose) for 14 days (43, 191). The initial studies with erythromycin estolate in syphilis recommended total doses of 15 to 20 g over 10 days (27). However, other forms of erythromycin were often substituted due to the complications of cholestatic jaundice (24, 303). Schroeter et al. recommended a minimum total dose of 30 g of erythromycin base after their study demonstrated a 25% retreatment rate with lower dosages (303). However, failure of erythromycin therapy, even with the recommended total dosage, has been reported in the treatment of primary syphilis (141).

Tetracycline. Tetracycline, 3 g per day p.o. for 10 days, results in 9.2% retreatment rates at 12 months compared to 3 to 5% with penicillin regimens (303). Only very limited studies of doxycycline have been done, but it has been added to treatment guidelines due to improved compliance and presumed efficacy equal to tetracycline (135, 250).

Chloramphenicol. The early literature concluded that chloramphenicol was as effective as tetracycline in all stages of syphilis, with the advantage of few or no gastrointestinal side effects (247). However, the blood dyscrasias later reported led to its removal as an alternate therapy for syphilis (247).

Late Latent Syphilis

A longer duration of therapy has been suggested for late latent syphilis because treponemes divide more slowly in late infection and presumably require longer exposure to penicillin (275). Reviews of the limited studies in the treatment of late latent syphilis have deemed them inadequate to determine an optimal treatment regimen (168, 370). The main concern at this stage is to prevent the development of late complications of syphilis (280). The available data assessing the use of penicillin in preventing progression to late disease was accumulated in studies of patients with asymptomatic neurosyphilis rather than latent syphilis. However, it is likely that the findings from these studies can be extrapolated to include latent syphilis (280). In 1956 Smith et al. reported a cumulative relapse rate of 21% at 18 months in 47 patients treated with 2.4 to 2.5 mU of benzathine penicillin G (311). They also reported a 10% relapse rate in 53 patients treated with 4 to 5.9 mU of other penicillin preparations. Even given the obvious concerns about the nonrandomization of patients in this study and the use of different penicillin preparations, the data suggests that 2.4 mU of benzathine penicillin G is inadequate for the treatment of asymptomatic neurosyphilis. The currently recommended three-dose regimen for late latent syphilis is largely empirical but is likely to be effective (280).

Tertiary Syphilis

Cardiovascular syphilis. The effect of treatment on cardiovascular syphilis remains unclear (177). It is known that the acute aortitis heals with scar formation and that treatment may hasten this healing, leading to the development of rapidly progressing aortic regurgitation during treatment (177). The currently recommended regimen is three doses of benzathine penicillin, 2.4 mU, at weekly intervals (43).

Neurosyphilis. The first question in addressing the treatment of neurosyphilis is whether the disease is present (63). The presence of a reactive VDRL in CSF associated with increased cell counts and increased total protein levels in the CSF is strong evidence of active infection (63). A decision analysis study by Wiesel et al. has suggested that CSF examination offers little additional benefit to empirical treatment with benzathine penicillin for most patients with late latent syphilis (356). In this study of asymptomatic patients with untreated syphilis for more than 1 year, they compared treatment involving 7.2 mU of benzathine penicillin G with performing a

lumbar puncture to test for asymptomatic neurosyphilis and management based on CSF analysis. Both strategies resulted in a cure rate of at least 99.7%, and although using lumbar puncture resulted in a 0.2% higher cure rate, a 0.3% complication rate was also reported.

The goal of therapy for neurosyphilis, especially general paresis and tabes dorsalis, is to halt the progression of the disease. The symptoms of meningitis and to some extent of meningovascular syphilis should resolve with therapy. Failure of symptoms to improve does not necessarily indicate ongoing infection or treatment failure, since preexisting damage does not reverse with treatment (63). On the other hand, inadequate treatment with persistent CSF pleocytosis may be the cause of progressive neurologic signs (226).

Most of the early trials in neurosyphilis used repeated i.m. injections of different dosages, intervals, and duration of penicillin (248). Failure rates of 3.3% were reported by the Cooperative Clinical Group in 1956, and a further 9.5% of patients had to be treated for persistent or increased CSF pleocytosis (130, 131).

The currently recommended therapy for neurosyphilis is aqueous crystalline penicillin G, 12 to 24 mU daily for 10 to 14 days, or procaine penicillin, 2.4 mU daily plus probenecid, 500 mg p.o. four times a day, both for 10 to 14 days (43). These regimens result in penicillin levels in CSF severalfold above the minimal treponemicidal concentration of 0.018 μg/ml during treatment (300). Benzathine penicillin is not recommended, since it does not achieve detectable levels in the CSF (226, 264). However, due to concerns regarding the persistence of slowly dividing organisms after therapy, some experts do recommend benzathine penicillin G (2.4 mU i.m.) weekly for 3 weeks following the completion of intravenous (i.v.) or i.m. therapy (43).

There is even less data on penicillin alternatives. Tetracycline or doxycycline has been used in penicillin-allergic, nonpregnant patients, and pharmacologic studies demonstrated treponemicidal levels of doxycycline in CSF at 400 mg daily (367). Chloramphenicol has also been shown to produce adequate levels in CSF as well as satisfactory clinical responses in penicillin-allergic patients (284, 286). Due to the small numbers of patients evaluated, however, none of these agents can be recommended as alternatives, and penicillin desensitization should be carried out in penicillin-allergic patients.

Pregnancy and Congenital Syphilis

The aim of treatment in pregnancy is to cure the mother and to prevent fetal infection (280). Even before the penicillin era, it was clear that maternal treatment early in pregnancy resulted in a reduction of the number of infected fetuses (255).

All pregnant women with syphilis who have not been previously treated should receive penicillin appropriate to their stage of disease. Unless there is clinical or serologic evidence of new infection or a history of recent sexual contact with a person with early syphilis, retreatment during pregnancy is not necessary. If penicillin allergy is reported, desensitization is strongly recommended. If this is not possible (for example, if the patient refuses to undergo penicillin desensitization), erythromycin may be used, but the infant should then be managed as if born to an untreated mother. Erythromycin does not readily cross the placenta, and the fetus may still develop congenital infection (87, 315). Unpredictable maternal levels of erythromycin in serum are also a concern (261). Tetracycline should not be used because it may cause yellow-brown discoloration of the teeth and have adverse effects on long-bone growth in the newborn (78).

Infants should be treated for congenital syphilis if they were born to mothers with (i) untreated syphilis at delivery, (ii) serologic evidence of relapse or reinfection, (iii) treatment with nonpenicillin regimens for syphilis during pregnancy, (iv) treatment for syphilis within 1 month of delivery, (v) poor documentation of treatment for syphilis, or (vi) insufficient serologic follow-up during pregnancy (43). In addition, any infant with physical or laboratory findings consistent with the diagnosis of congenital syphilis should receive treatment (22, 43).

Single-dose benzathine penicillin has not been evaluated in prospective, randomized controlled trials but was used for many years to treat congenital syphilis. However, limited use of this regimen is currently recommended because benzathine penicillin may not achieve or maintain treponemicidal levels in the CSF of neonates (180, 317). In addition, a small number of treatment failures have been reported with single-dose benzathine penicillin therapy (18, 132, 364).

Both crystalline penicillin G and procaine penicillin have been studied in patients with congenital syphilis (216, 263). The regimens described in Table 2 are those currently recommended for congenital syphilis (43, 191).

Some experts believe that therapy with other penicillins may suffice in the treatment of congenital syphilis (234). Small case series have shown that oral amoxicillin, 6 g daily, plus probenecid twice daily achieved treponemicidal levels in CSF (85, 231). However, these limited data should be interpreted with caution until further studies are done.

Newer and Experimental Agents

Given the reported failures of penicillin therapy in some patients and the limited treatment options in penicillin-allergic patients, there is a need for newer agents. Limited animal studies have shown the newer macrolides clarithromycin, roxithromycin (RU965), and azithromycin to be effective treatments for experimental syphilis (2, 198, 199). A pilot study of azithromycin documented cure in 11 of 13 patients with primary or secondary syphilis (345). A nonrandomized study of azithromycin, 500 mg daily for 10 days or 500 mg on alternate days for 11 days, in 100 patients with early syphilis reported complete resolution of clinical signs and 90% reversion to a negative serum Wasserman reaction (214). *T. pallidum* immobilization (TPI) and FTA-ABS became negative 12 months after treatment in 40% of patients. Time to resolution of clinical signs was also shorter in the azithromycin group than in the penicillin and erythromycin groups. The newer cephalosporins, i.e., cefmetazole, ceftizoxime, and cefetamet (Ro 15-8074), also show promise in animal models (14, 92, 188). Although useful in the treatment of other sexually transmitted diseases, quinolones have shown poor efficacy in animal models of syphilis (6, 327, 344).

Jarisch-Herxheimer Reaction

The Jarisch-Herxheimer (J-H) reaction was first observed by Jarisch in 1895 and Herxheimer in 1902 after the use of mercury but has since been described with other treatments (25, 156, 324, 341). One large study showed that the J-H reaction occurred more often after treatment with penicillin than with erythromycin or tetracycline (5). It has been reported to occur in 30 to 70% of patients with early syphilis, 43 to 55% of infants with congenital syphilis, 45% of pregnant patients with syphilis, and 2% of patients with neurosyphilis (25, 86, 186). The cause is not completely understood, but the release of *T. pallidum* lipoproteins with inflammatory activities from dead or dying organisms is the likely inducer of this clinical phenomenon

TABLE 3. Expected serologic response to treatment[a]

Disease stage	Decrease in nontreponemal titer at:		
	6 mo posttreatment	12 mo posttreatment	24 mo posttreatment
Primary	4-fold[b]	6-fold	8-fold
Secondary	6-fold	8-fold	
Early latent		4-fold	

[a] Adapted from reference 191 with permission of the publisher.
[b] For example, a fourfold decrease in titer is 1:32 to 1:8.

(243, 270, 276). Also described as "therapeutic shock," the reaction is a local and systemic exacerbation of whatever stage of syphilis is being treated (324). For example, a primary chancre may become edematous, lymphadenopathy may increase, or a secondary rash may become more prominent. There is usually a rise in temperature to 101 to 102°F, with reactions occurring within 12 h of initiation of treatment and terminating within 24 h. Associated headache, pharyngitis, malaise, myalgias, and leukocytosis with lymphopenia have also been reported (25). Symptomatic antipyretic and analgesic treatment is useful in reducing any discomfort. Reactions do not appear to be modified by pretreatment with antihistamines or initial use of small doses of penicillin (25). Steroid therapy reduces the incidence of febrile reactions associated with the J-H reaction, but since the febrile reaction does not often produce significant morbidity, the routine use of steroids in this setting is not warranted (25, 119, 125).

In pregnant women, the reaction is similar in frequency, character, and intensity, but increased uterine activity and transient reduction in fetal movements and fetal heart rate abnormalities have been described (186). If the fetus is severely infected prior to treatment, the woman may experience preterm labor or delivery or fetal death (186).

SEROLOGIC RESPONSE TO TREATMENT

In the absence of a microbiologic "test for cure," patients treated for syphilis are monitored by quantitative nontreponemal tests (126, 196). As a general guide, patients with early and congenital syphilis should have repeat serologic testing (nontreponemal and treponemal tests) 1, 3, 6, 12, and 24 months after treatment and patients with late disease (excluding neurosyphilis) should be seen 12 and 24 months after treatment (191). Patients with neurosyphilis should be reviewed clinically, and follow-up CSF examinations should be done at 6-month intervals over the first 2 years or until the CSF becomes normal (43). Resolving pleocytosis should occur over the first 6 months, while the CSF VDRL titer (if initially high) should decline fourfold within 1 year (63). It is noteworthy that the CSF VDRL titer may take years to revert to negative (63). In addition to follow-up at 1, 3, 6, 12, and 24 months after treatment, HIV-infected patients should continue to be monitored at yearly intervals thereafter. When the quantitative dilutions of the nontreponemal test decrease adequately, the patient is considered cured (Table 3) (191). A sustained fourfold or greater rise in the quantitative nontreponemal titer without reinfection suggests treatment failure and the need for reevaluation.

Individuals with their first infection are more likely to serorevert than those with reinfections, regardless of the disease stage (26, 285). After treatment, seroreversal is more rapid if the duration of infection or clinical lesions is shorter and if the initial titer is lower (26, 97, 285). It has also been noted that the decline of initially high titers is more rapid after treatment than the decline of lower titer seroreactivity (75).

Schroeter et al. reported that 97% of patients treated for primary syphilis with benzathine penicillin, 2.4 mU i.m., developed a negative VDRL titer within 2 years whereas 77% with secondary syphilis became nonreactive (303). Using data acquired from an early syphilis study, Brown et al. demonstrated that after treatment, the VDRL titer declined approximately fourfold at 3 months and eightfold at 6 months in patients with primary or secondary syphilis (26). The serologic response of patients treated with erythromycin was inferior to that achieved with either penicillin or tetracycline.

A series of studies by Fiumara involving a total of 588 patients with primary syphilis and 623 with secondary syphilis demonstrated that all patients with primary syphilis seroreverted their nontreponemal tests within 1 year while all with secondary syphilis seroreverted within 2 years (96, 97, 100, 102). However, the dose of penicillin used was twice that currently recommended by the Centers for Disease Control and Prevention (CDC) (43). In two studies of early latent syphilis, Fiumara demonstrated a serologic response (defined as a fourfold decline in the RPR titer at 1 year and a nonreactive RPR in 4 years) to treatment in 368 patients (98, 101). More than 95% became seronegative within 2 years, and all did so within 4 years. Again, however, twice the CDC-recommended dose of benzathine penicillin was used.

In a retrospective study of 1,532 patients with early syphilis, the VDRL was nonreactive 6 months after treatment in 84% of patients with primary syphilis, 72% of patients with secondary syphilis, and 81% of patients with early latent syphilis (326). The percentages were 93, 92, and 88%, respectively at the end of the 30-month study period. Approximately 86% of patients were treated with benzathine penicillin, 2.4 mU. Although the numbers of treated patients were too small to draw firm conclusions, it appeared that treatment with higher doses of benzathine penicillin (4.8 mU) and procaine penicillin resulted in a better serologic response.

In contrast to the above studies, Romanowski et al. found that 72 and 56% of 882 patients with primary and secondary syphilis, respectively, had seroreverted their RPR by 36 months (285). The patients were treated with the currently recommended benzathine penicillin regimens. A fourfold decrease (for example, a change in titer from 1:32 to 1:8 is a fourfold drop) and a sixfold decrease were seen in patients with primary and secondary syphilis by 6 and 12 months, respectively, while only a fourfold decline was seen in patients with early latent syphilis by 12 months. RPR seroreversion at 1 year was seen in 44% of patients with their first episode of primary syphilis, and the proportion increased to 60 and 72% at 2 and 3 years, respectively. The 1-, 2-, and 3-year RPR seroreversion rates for secondary syphilis were 22, 42, and 56%, respectively, while for early latent disease the corresponding rates were 13, 13, and 26%. Serologic response was not affected by sex, age, race, or sexual orientation. Although the classic teaching is that the treponemal tests do not serorevert with treatment, this study demonstrated that in immunocompetent patients with first-episode syphilis, 24% had a nonreactive FTA-ABS and 13% had a nonreactive MHA-TP at 36 months. The differences between this study and those reported by other investigators are probably related to a number of factors. Different antibiotic regimens were used, and the definition of reinfection in previous studies was defined as a fourfold or higher rise in titer without consideration of treatment failure.

It remains unclear whether the serologic criteria for adequate treatment of early syphilis are too stringent (126). Until further studies are carried out, all patients with early syphilis

should be monitored until they are free of clinical disease and nontreponemal tests are either seronegative or at a stable low titer (for example, 1:4 dilution) (196).

Mathematical modeling suggests that an individual's serologic response to treatment appears to be a linear function of time when both axes are logarithmic (290). RPR titers plotted in the first few months after treatment will determine the slope of the line, and this slope, when used in conjunction with the pretreatment RPR titer, is suggested as an important predictor of the time of seroreversion (290). This is useful clinically, since it may indicate the need for retreatment if the patient's first-year response is not below the line (290).

Few studies have been done on the serologic response to treatment in late latent disease. A study by Fiumara suggests that the decline in titer may be more gradual and that low titers persist in approximately 50% of patients after 2 years of observation (99). The majority of patients had nonreactive nontreponemal tests 5 years after treatment.

A slow decline in the titer of nontreponemal serologic tests may also be seen in other late stages of syphilis. The persistence of a reactive CSF VDRL following therapy is not necessarily indicative of ongoing central nervous system infection (63). With successful therapy, the cell count should return to normal within 6 months and should be followed by a decrease in the protein level and finally a decline in the quantitative CSF VDRL, which can remain reactive for more than 1 year after treatment (63, 131, 341).

SYPHILIS AND HIV INFECTION

Shortfalls in the current knowledge of syphilis are increasingly obvious as investigators consider the interrelationships between syphilis and HIV. Several questions need to be answered: (i) whether syphilis modifies the risk for HIV acquisition or transmission; (ii) whether the presence of coexistent HIV infection modifies the natural history, clinical, or laboratory manifestations of syphilis; and (iii) whether currently recommended therapy for syphilis is adequate for patients with coexistent HIV.

Cross-sectional epidemiologic studies have demonstrated strong associations between evidence of past syphilis and HIV risk (149). Studies from Africa have repeatedly demonstrated associations between reactive syphilis serologic test results or a history of genital ulceration and the likelihood of HIV (62, 113, 121, 269, 309, 320). There is further evidence that the presence of other sexually transmitted infections are also risk factors for HIV acquisition. In light of these epidemiologic links between HIV and syphilis, all patients with syphilis should be encouraged to undergo testing for HIV and vice versa.

The majority of patients with coincident HIV present with typical manifestations of syphilis. However, a number of reports suggest that the clinical spectrum of syphilis and the rapidity of disease progression may be modified by the presence of HIV (118, 159, 301, 368). Theoretically, depressed cellular immune function might result in accelerated progression of syphilis or an increased frequency of complicated syphilis.

Hutchinson et al. performed a case-controlled trial comparing the clinical presentation of syphilis in HIV-positive and -negative patients (159). They examined 309 patients with primary, secondary, and early latent syphilis; 70 of the group were HIV reactive. The HIV-infected patients were more likely to present with secondary disease ($P < 0.001$), but this significance did not hold for women. Although there was a trend for those with a CD4 count of <500 to present with secondary syphilis, this finding did not reach significance. The characteristics of the rash were identical in both groups. In contrast, other authors did not observe any unusual clinical manifestations or any differences in the stage of presentation (118, 368).

Alteration of B-cell function may result in an increased likelihood of biological false-positive reactions or rising RPR titers. The literature reports false-positive rates from 1 to 5.8% (13, 207, 287, 292) in HIV-infected patients compared to 0.2 to 0.8% in those not infected. Injected-drug use is a consistent contributing factor, but the level of immunosuppression does not appear to influence the rate of this occurrence. False-negative serologic tests are extremely rare in HIV-infected patients.

Two studies examining the loss of treponemal reactivity by using stored sera from patients previously treated for syphilis have been reported (127, 173). Haas analyzed sera from 90 HIV-positive and 19 HIV-negative men observed for a mean follow-up of 4 years (127). All HIV-negative men had persistent treponemal reactivity, while 13 (14.4%) HIV-positive men lost reactivity. The highest loss of reactivity was seen in individuals with symptomatic HIV infection, those with a single episode of syphilis, or an initial VDRL titer of ≤1:32. Interestingly, loss of reactivity did not increase with the time since the last episode of syphilis. Johnson found that 3 of 29 patients with AIDS (10%) seroreverted both the *T. pallidum* hemagglutination (TPHA) and FTA-ABS over a period of 3 years; this was not observed in any of the 29 controls (173).

There continues to be lack of agreement on the treatment of patients with both syphilis and HIV. Much of the confusion arises from the lack of prospective trials. Gourevitch et al. shed some light on this topic by providing results of a longitudinal study of injected-drug users with syphilis, 31 of whom were HIV positive and 19 of whom were HIV negative (118). Nontreponemal titers were higher in HIV-infected individuals than in non-HIV-infected individuals with their first episode of syphilis (median of 1:128 and 1:32, respectively); these results were not affected by the CD4 count. Over a follow-up of 11 months, there was no difference in the rate of decrease of nontreponemal titers in response to standard penicillin treatment by HIV status, CD4 count, or stage of disease. Seroreversion of the treponemal tests occurred with equal frequency in both HIV-positive (17.6%) and HIV-negative (15.4%) individuals.

Telzak et al. offered a retrospective review of response to standard therapy in HIV-infected individuals with primary or secondary syphilis (328). They reported that HIV-negative patients with primary syphilis were more likely to have a decrease in RPR titer of greater than fourfold or seroconversion within 6 months compared to HIV-positive individuals ($P = 0.03$). There was no statistically significant difference in response by HIV status for patients with secondary syphilis. In another series of 56 HIV-positive patients monitored for a mean of 28 months, Malone et al. reported a relapse or failure rate of 18% (207). Treatment outcome was not related to CD4 count or to a specific antimicrobial regimen. However, this retrospective study suggests that clinical evidence of secondary syphilis and/or asymptomatic neurosyphilis correlates with a high rate of relapse compared to that in patients with latent syphilis.

Goeman et al. reported on a group of HIV-positive and -negative commercial sex workers in Zaire who were all treated with benzathine penicillin, 7.2 mU (116). The authors assumed that most cases were late latent syphilis. The geometric mean RPR titer at presentation was significantly lower for the HIV-positive patients than for the HIV-negative ones (2.6 and 3.8, respectively; $P = 0.01$), and no difference in response to treatment was found after 2 years of follow-up. Another series of 64 HIV-infected patients and matched controls also found no

significant difference in response to treatment at 12 months (368).

Rolfs et al. randomized 541 patients, including 101 who were HIV infected, with early (primary, secondary, and early latent) syphilis to receive 2.4 mU of i.m. benzathine penicillin G with or without enhanced therapy consisting of 2 g of amoxicillin and 500 mg of probenecid p.o. three times daily for 10 days (282). By the end of the follow-up period of 1 year, 14% of patients were serologically defined as treatment failures. Failure rates did not differ according to the treatment group. HIV-infected patients were more likely than non-HIV-infected patients to have serologic treatment failure, regardless of the CD4 counts. The RPR titer also declined more slowly in HIV-infected patients. CSF abnormalities of >5 leukocytes/mm^3, reactive VDRL, and increased protein levels were more common in HIV-infected patients. However, detection of *T. pallidum* in CSF by PCR, RIT, or both did not differ according to HIV status or treatment group, either pre- or posttherapy. The authors concluded that the CDC treatment recommendations for treatment of early syphilis are appropriate for most patients, whether or not they have HIV infection.

In the past decade, a multitude of case reports have suggested that neurosyphilis may occur more frequently, progress more rapidly, and present with atypical signs in the presence of HIV infection (19–21, 117, 172, 182, 210, 215, 217, 235, 257, 338). However, it is difficult to draw conclusions because denominator data are not available. The diagnosis of neurosyphilis is more difficult in HIV-infected patients since 40 to 60% of this population may demonstrate CSF abnormalities including pleocytosis and elevated protein levels even without coexistent syphilis.

There has been a continuing and unresolved discussion about the place of lumbar punctures in the investigation of HIV patients with reactive syphilis serologic test results. The RPR titer is reported to be higher in patients with neurosyphilis (210, 338). Tomberlin et al. found titers of 1:128 in individuals with neurosyphilis compared to 1:8 in those with latent syphilis (338). Marra et al. found that those with both neurosyphilis and HIV had significantly higher RPR titers than did HIV-negative individuals with neurosyphilis (1:64 and 1:16, respectively; $P = 0.03$) (210). These results suggest that lumbar punctures may not be required in all HIV-infected individuals with syphilis but, rather, only in those with high nontreponemal titers (for example, RPR titer of >1:32). The CDC currently recommends lumbar puncture in all patients with HIV infection who have late latent syphilis or syphilis of unknown duration (43).

In 1987, Johns et al. reported the first series of four patients who progressed to neurosyphilis despite treatment with benzathine penicillin (172). Musher et al. compiled a series of 42 patients, 16 of whom had been treated for syphilis prior to the diagnosis of neurosyphilis; 5 of these developed neurosyphilis within 6 months of having received a recommended course of therapy (235). Similarly, three of the nine patients described by McLeish et al. received benzathine penicillin prior to development of neurologic or ocular syphilis, as did 3 of the 12 patients described by Katz and Berger (181, 217). These case reports support the contention that HIV-infected patients are more likely to develop syphilitic meningitis and meningovasculitis, often with concomitant ocular disease, after receiving standard therapy for syphilis.

Lukehart et al. reported a prospective series of 58 untreated patients with syphilis who had a lumbar puncture (200). Rabbit inoculation was used to test CSF for viable *T. pallidum*. *T. pallidum* was isolated from 30% of patients with untreated primary or secondary syphilis; significant associations were the presence of two or more CSF abnormalities (leukocyte counts, protein levels, VDRL titer). Concurrent infection with HIV was not associated with the isolation of *T. pallidum* or with an increased number of CSF abnormalities, although HIV-infected individuals were more likely to have >5 leukocytes. There were three treatment failures; all had received a single dose of benzathine penicillin for secondary syphilis and all were HIV-positive patients from whom *T. pallidum* had been isolated pretreatment.

There is little consensus in the literature on the treatment of neurosyphilis in individuals infected with HIV. Dowell et al. reported success rates of 77% when patients with latent syphilis or neurosyphilis were treated with ceftriaxone, 1 to 2 g/day (77). However, there was no correlation between treatment outcome, CD4 count, or CDC HIV staging. In another series of 11 patients with neurosyphilis who received 10 days of high-dose intravenous penicillin, there were three treatment failures (117). Again, there were no predictors of failure.

PREVENTION AND CONTROL

Surgeon General Thomas Parran in 1937 defined a five-point syphilis control plan including public education, screening, clinical treatment, partner notification, and prophylactic treatment (256). This framework still forms the basis of syphilis control today. However, given the changes in the epidemiology of syphilis, additional strategies are called for to improve syphilis control (322). The sequencing of the *T. pallidum* genome has also led to renewed hope for the elimination of syphilis in the United States (323).

Public Education

Educating the general public about the consequences and prevention of syphilis and other STDs is paramount in the primary prevention of these diseases (34, 319). Effective education could result in earlier recognition and therefore presentation for medical care with symptoms and signs of disease or in behavior modification strategies, such as safer sex practices. Safer sex practices among homosexual men to reduce the risk of HIV may have reduced the number of cases of syphilis and other STDs in this population (354). Condoms, although clearly effective in preventing the transmission of HIV and other STDs, are not used regularly by persons at risk (288). More innovative ways of promoting condom use and provision of condoms at low cost are necessary. Targeted media campaigns, especially in areas or communities with high syphilis rates, are important (34). Important strategies include school education, telephone hotlines to answer questions about STD, and other innovative means whereby the educational message can be sustained (33).

Screening

Screening for syphilis is carried out for several reasons, including prevention of the complications of syphilis, prevention of congenital syphilis, and reduction of the transmission of syphilis, which in turn will reduce the transmission of HIV through genital ulcers (298, 322). Screening generally detects patients with noninfectious latent disease and only occasionally detects those with symptoms or signs (298). Mass screening has not been shown to be cost-effective in terms of the benefits of case finding and interruption of transmission (137). For example, due to the low prevalence of syphilis in the United States, routine premarital serologic screening is no longer recommended since it is not believed to be cost-effective (185). The efficiency of case finding can be significantly improved by using

epidemiologic features to focus screening efforts; that is, screening of high-risk groups will identify more infectious cases (primary, secondary, and early latent) than will screening of the general population, which will identify more noninfectious (late latent) cases (40, 219). Not only should populations known to be at high risk be targeted for intervention, but also specific strategies should be developed for each group (366).

The concept that a "core" or small subset of persons contributes to a disproportionately large number of transmission events and eventually leads to persistence of syphilis is important (28, 254). It has been suggested that the syphilis epidemics of the 1980s and 1990s are the result of core transmission (254). Therefore, targeting of such core populations for prevention of transmission should, in theory, prevent community transmission and therefore lead to lower syphilis prevalence rates.

Targeting the screening and empirical treatment of persons at sites where sex and drugs are sold has been useful in the control of cocaine-related outbreaks (146). Other high-risk groups in which routine screening is justifiable and may be central to syphilis control efforts include populations in correctional facilities (23, 145), drug users in emergency rooms (82), and patients suspected of having STDs other than syphilis (83, 306).

To prevent congenital syphilis, the CDC currently recommends that all pregnant women be screened for syphilis (43). This approach, even in low-prevalence situations, has been shown to be cost-effective (107, 361). However, despite the serious consequences of syphilis in pregnancy, syphilis screening in all antenatal clinics is seldom practiced effectively (147, 329).

Similarly, continued screening of blood for antibodies to syphilis is also important. Although relative prevalence rates and the risk of transmission are low, syphilis acts a surrogate marker for other STDs, especially HIV (160, 238, 267).

Clinical Diagnosis and Treatment

Diagnosis and treatment of cases are essential components of syphilis control (34). Few studies have examined how many patients with syphilis recognize their symptoms or, if they do, how many present for medical attention. One study reported that 45% of partners of identified syphilis patients stated that they had not sought medical care despite recognizing symptoms of syphilis (365). In 1990, an estimated 62% of patients with a diagnosis of early syphilis sought clinical services of their own accord (34).

Early detection of disease and prompt treatment will reduce the complications and minimize further disease transmission (34, 137). Treatment should be inexpensive, safe, simple, and effective (33). The production, widespread distribution, and compliance with national treatment guidelines will aid in these objectives (366).

Partner Notification

Historically, partner notification with evaluation, treatment, and follow-up has been essential to limit the spread of disease (183). However, this method, in which health department personnel visit, inform, and interview all named sexual partners, is expensive, and recent studies have suggested that the yield may be very low (7, 253). Due to the high cost, this approach will probably have to be used more selectively in the future (322). Advising the individual patients to refer their sexual partners has the advantage of reduced cost but is likely to be unreliable and certainly is difficult to evaluate and monitor (33).

A recent randomized trial compared three approaches to partner notification for 1,966 patients with infectious syphilis (258). Patients were randomized to one of three groups: (i) partner notification by themselves within 2 days or by disease intervention specialists (DIS) if the patient failed to do so; (ii) immediate partner notification by DIS; or (iii) immediate partner notification by DIS, who also had the option to draw blood in the field if they believed that the contact would not attend the clinic. The cost and effectiveness of all three approaches were similar, but this was probably because most partners in the patient referral arm were notified by the DIS anyway. More importantly, it was also calculated that each method located an average of only 1.1 of 5.7 potentially exposed partners, emphasizing the need for alternative methods of case finding.

Cluster interviewing of specific populations rather than individuals may be more useful than partner notification. Cluster interviewing is a technique in which patients and their contacts are asked to provide information not only on sexual partners but also on persons for whom they think an examination for syphilis is indicated (183). Although this method produces a lower yield of infected patients than simply notifying those named as partners, it still identifies a high percentage of patients who would not have been identified in any other way (183). In addition, partner notification in certain situations, for example, cocaine-related outbreaks, may not be effective, since cocaine users either do not provide enough information to enable the identification of their sexual partners or may have multiple anonymous partners (7, 37, 40, 120, 225, 281). Recent studies have confirmed the effectiveness of approaches involving cluster interviewing (40, 80, 109).

The time frames for partner notification for primary, secondary, and early latent syphilis are 3, 6, and 12 months, respectively, before the development of symptoms in the index case (191). For contacts of patients with late latent syphilis, long-term partners and children should be evaluated. The mother of a patient with congenital syphilis and her sexual partner(s) should also be assessed. If exposure to early syphilis occurred within the previous 90 days, contacts should be treated prophylactically. If the exposure occurred more than 90 days earlier, serologic testing should be done, with management being dependent on the results.

Prophylactic Treatment

Since it is not possible to predict which contacts of individuals with infectious syphilis will develop the disease, "epidemiologic" or prophylactic treatment is recommended for all contacts (136, 359). This approach, together with partner notification, has been effective in controlling epidemics of syphilis (15, 193). "Mass" treatment of populations with a high prevalence of infection has also been effective; for example, treatment of commercial sex workers in Fresno, Calif., in 1977 interrupted an epidemic of syphilis (171).

Additional Strategies

Although Parran emphasized the need for community education and participation, the lack of emphasis of public health measures in these areas may be one of the reasons why syphilis rates in United States are 50 to 100 times higher than in most other developed nations (150). Community participation was essential in the management of the HIV epidemic in the early 1980s, and lessons from this could be used in syphilis control (322).

The disproportionately high rates of syphilis in African Americans mean that intensive and focused public health measures should be aimed at this group to control syphilis (197). Acceptance of public health measures is further complicated

by the distrust generated by the Tuskegee study (335). It is important to work with leaders from African American communities to help coordinate strategies (322).

In the United States, inadequate access to care in STD clinics may limit the ability to control syphilis prevalence, especially in the South (11, 114). New approaches to syphilis control might include such strategies as community-based outreach, off-site screening for identifying cases, and mass treatment of patients with presumptive syphilis (110, 114).

Finally, research is essential to find and evaluate new methods of syphilis control and prevention. For example, an inexpensive single-dose effective oral medication, in addition to a rapid diagnostic test from a noninvasive sample such as saliva, would be extremely useful in identifying and treating patients (322). The sequencing of the *T. pallidum* genome is likely to lead to the development of techniques to differentiate strains or subtypes of the organism, which will allow better epidemiologic studies of syphilis (323). To aid in the elimination of syphilis, studies of how, why, and where syphilis transmission persists in periods of declining rates rather than simply in the setting of epidemics or outbreaks are important (322). Additional research is also required to find the best ways to target "core" populations to prevent transmission; these methods may include improved surveillance systems to identify the populations in which new syphilis cases are appearing, understanding of the behavioral and social dynamics in these groups, and subsequent redirection of resources (254, 322).

CONCLUSION

Although syphilis is one of the best-known STDs, much remains to be learned about this disease and its manifestations, especially its interaction with HIV. Although effective treatment has been available since the introduction of penicillin in the mid-20th century, syphilis remains an important global health problem. Many of the available diagnostic tests lack sensitivity in some stages of syphilis and lack specificity in some populations. Treatment guidelines are based on relatively poor scientific data, and there is a need for well-designed prospective studies examining all stages of the disease as well as its course in patients infected with HIV. The lack of a good measure of "cure" makes this issue even more challenging. Control measures including aggressive partner notification are effective but expensive. More emphasis must be placed on primary prevention, not specifically related to syphilis but addressing the entire problem of STD.

REFERENCES

1. **Abell, E., R. Marks, and E. W. Jones.** 1975. Secondary syphilis: a clinicopathological review. Br. J. Dermatol. **93:**53–61.
2. **Alder, J., K. Jarvis, M. Mitten, N. L. Shipkowitz, P. Gupta, and J. Clement.** 1993. Clarithromycin therapy of experimental *Treponema pallidum* infections in hamsters. Antimicrob. Agents. Chemother. **37:**864–867.
3. **Alexander, L. J., and A. G. Schoch.** 1949. Prevention of syphilis. Arch. Dermatol. Syphilol. **59:**1–10.
4. **Ali, Z.** 1990. Resurgence of congenital syphilis in Trinidad. J. Trop. Pediatr. **36:**104–108.
5. **Anderson, J., A. Mindel, S. J. Tovey, and P. Williams.** 1989. Primary and secondary syphilis, 20 years' experience. 3. Diagnosis, treatment, and follow up. Genitourin. Med. **65:**239–243.
6. **Andriole, V. T.** 1989. An update on the efficacy of ciprofloxacin in animal models of infection. Am. J. Med. **87**(Suppl. 5A)**:**32S–34S.
7. **Andrus, J. K., D. W. Fleming, D. R. Harger, Y. Chin, D. V. Bennett, J. M. Horan, G. Oxman, B. Olson, and L. R. Foster.** 1990. Partner notification: can it control epidemic syphilis? Ann. Intern. Med. **112:**539–543.
8. **Anonymous.** 1994. Infectious and congenital syphilis in England. Commun. Dis. Rep. CDR Weekly **4:**91,94.
9. **Anonymous.** 1995. Infectious disease testing for blood transfusions, p. 13–14. *In* NIH Consensus statement 13. National Institutes of Health, Bethesda, Md.
10. **Aral, S. O.** 1996. The social context of syphilis persistence in the southeastern United States. Sex. Transm. Dis. **23:**9–15.
11. **Aral, S. O., and K. K. Holmes.** 1991. Sexually transmitted diseases in the AIDS era. Sci. Am. **264:**18–25.
12. **Arya, O. P., A. O. Osoba, and F. J. Bennett.** 1988. Syphilis, p. 39–132. *In* O. P. Arya, A. O. Osoba, and F. J. Bennett (ed.), Tropical venereology. Churchill Livingstone, Edinburgh, Scotland.
13. **Augenbraun, M. H., J. A. DeHovitz, J. Feldman, L. Clarke, Landesman, and H. M. Minkoff.** 1994. Biological false positive syphilis test results for women infected with human immunodeficiency virus. Clin. Infect. Dis. **19:**1040–1044.
14. **Baker-Zander, S. A., and S. A. Lukehart.** 1989. Efficacy of cefmetazole in the treatment of active syphilis in the rabbit. Antimicrob. Agents. Chemother. **33:**1465–1469.
15. **Ball, R. W.** 1965. Outbreak of infectious syphilis in South Carolina. JAMA **193:**101–104.
16. **Barton, J. R., E. M. Thorpe, D. C. Shaver, W. D. Hager, and B. M. Sibai.** 1992. Non-immune hydrops fetalis associated with maternal infection with syphilis. Am. J. Obstet. Gynecol. **167:**56–58.
17. **Baseman, J. B., and E. C. Hayes.** 1980. Molecular characterization of receptor binding proteins and immunogens of virulent *Treponema pallidum*. J. Exp. Med. **151:**573–586.
18. **Beck-Sague, C. and E. R. Alexander.** 1987. Failure of benzathine penicillin G treatment in early congenital syphilis. Pediatr. Infect. Dis. J. **6:**1061–1064.
19. **Berger, J. R.** 1991. Neurosyphilis in human immunodeficiency virus type 1-seropositive individuals. Arch. Neurol. **48:**700–702.
20. **Berger, J. R.** 1992. Spinal cord syphilis associated with human immunodeficiency virus infection: a treatable myelopathy. Am. J. Med. **92:**101–103.
21. **Berry, C. D., T. M. Hooton, A. C. Collier, and S. A. Lukehart.** 1987. Neurologic relapse after benzathine penicillin therapy for secondary syphilis in a patient with HIV infection. N. Engl. J. Med. **316:**1587–1589.
22. **Berry, M. C., and A. S. Dajani.** 1992. Resurgence of congenital syphilis. Infect. Dis. Clin. North Am. **6:**19–29.
23. **Blank, S., D. D. McDonnell, S. R. Rubin, J. J. Neal, M. W. Brome, M. B. Masterson, and J. R. Greenspan.** 1997. New approaches to syphilis control: finding opportunities for syphilis treatment and congenital syphilis prevention in a women's correctional setting. Sex. Transm. Dis. **24:**218–226.
24. **Braun, P.** 1969. Hepatotoxicity of erythromycin. J. Infect. Dis. **119:**911–915.
25. **Brown, S. T.** 1976. Adverse reactions in syphilis therapy. J. Am. Vener. Dis. Assoc. **3:**172–176.
26. **Brown, S. T., A. Zaidi, S. A. Larsen, and G. H. Reynolds.** 1985. Serological response to syphilis treatment. A new analysis of old data. JAMA **253:**1296–1299.
27. **Brown, W. J., W. G. Simpson, M. B. Moore, E. V. Price, and S. Weinstein.** 1963. Oral propionyl erythromycin in treating early syphilis. Public Health Rep. **78:**911–917.
28. **Brunham, R. C.** 1991. The concept of core and its relevance to the epidemiology and control of sexually transmitted diseases. Sex. Transm. Dis. **18:**67–68.
29. **Burch, G. E., and T. Winsor.** 1942. Syphilitic coronary stenosis, with myocardial infarction. Am. Heart J. **24:**740–751.
30. **Burke, J. M., and D. R. Schaberg.** 1985. Neurosyphilis in the antibiotic era. Neurology **35:**1368–1371.
31. **Burstain, J. M., E. Grimprel, S. A. Lukehart, M. V. Norgard, and J. D. Radolf.** 1991. Sensitive detection of *Treponema pallidum* by using polymerase chain reaction. J. Clin. Microbiol. **29:**62–69.
32. **Campisi, D., and C. Whitcomb.** 1979. Liver disease in early syphilis. Arch. Intern. Med. **139:**365–366.
33. **Cates, W., Jr.** 1987. Epidemiology and control of sexually transmitted diseases: strategic evolution. Infect. Dis. Clin. North Am. **1:**1–23.
34. **Cates, W., Jr., R. B. Rothenberg, and J. H. Blount.** 1996. Syphilis control. The historic context and epidemiologic basis for interrupting sexual transmission of *Treponema pallidum*. Sex. Transm. Dis. **23:**68–75.
35. **Centers for Disease Control and Prevention.** 1984. Syphilis—United States, 1983. Morbid. Mortal. Weekly Rep. **33:**433–436.
36. **Centers for Disease Control and Prevention.** 1988. Guidelines for the prevention and control of congenital syphilis. Morbid. Mortal. Weekly Rep. **37:**S1–S13.
37. **Centers for Disease Control and Prevention.** 1988. Relationship of syphilis to drug use and prostitution—Connecticut. Morbid. Mortal. Weekly Rep. **37:**755–758.
38. **Centers for Disease Control and Prevention.** 1988. Syphilis and congenital syphilis—United States, 1985–1988. Morbid. Mortal. Weekly Rep. **37:**486–489.
39. **Centers for Disease Control and Prevention.** 1989. Congenital syphilis—New York City, 1986–1988. Morbid. Mortal. Weekly Rep. **38:**825–829.
40. **Centers for Disease Control and Prevention.** 1991. Alternative case-finding methods in a crack-related syphilis epidemic—Philadelphia. Morbid. Mortal. Weekly Rep. **40:**77–80.
41. **Centers for Disease Control and Prevention.** 1991. Primary and secondary syphilis—United States, 1981–1990. Morbid. Mortal. Weekly Rep. **40:**314–315.
42. **Centers for Disease Control and Prevention.** 1993. Surveillance for gonor-

rhea and primary and secondary syphilis among adolescents, United States—1981–1991. Morbid. Mortal. Weekly Rep. **42:**1–11.
43. **Centers for Disease Control and Prevention.** 1998. 1998 guidelines for treatment of sexually transmitted diseases. Morbid. Mortal. Weekly Rep. **47:**28–49.
44. **Centurion-Lara, A., C. Castro, R. Castillo, J. M. Shaffer, W. C. Van Voorhis, and S. A. Lukehart.** 1998. The flanking region sequences of the 15-kDa lipoprotein gene differentiate pathogenic treponemes. J. Infect. Dis. **177:** 1036–1040.
45. **Centurion-Lara, A., C. Castro, J. M. Shaffer, W. C. Van Voorhis, C. M. Marra, and S. A. Lukehart.** 1997. Detection of *Treponema pallidum* by a sensitive reverse transcriptase PCR. J. Clin. Microbiol. **35:**1348–1352.
46. **Chapel, T. A.** 1978. The variability of syphilitic chancres. Sex. Transm. Dis. **5:**68–70.
47. **Chapel, T. A.** 1980. The signs and symptoms of secondary syphilis. Sex. Transm. Dis. **7:**161–164.
48. **Chapel, T. A., W. J. Brown, C. Jeffres, and J. A. Stewart.** 1977. How reliable is the morphological diagnosis of penile ulcerations? Sex. Transm. Dis. **4:**150–155.
49. **Chawla, V., K. Gupta, and M. B. Raghu.** 1985. Congenital syphilis: a clinical profile. J. Trop. Pediatr. **31:**204–208.
50. **Chawla, V., P. B. Pandit, and F. K. Nkrumah.** 1988. Congenital syphilis in the newborn. Arch. Dis. Child. **63:**1393–1394.
51. **Chesney, A. M., and J. E. Kemp.** 1924. Incidence of *Spirochaeta pallida* in cerebrospinal fluid during early stage of syphilis. JAMA **83:**1725–1728.
52. **Chhabra, R. S., L. P. Brion, M. Castro, L. Freundlich, and J. H. Glaser.** 1993. Comparison of maternal sera, cord blood and neonatal sera for detection presumptive congenital syphilis: relationship with maternal treatment. Pediatrics **91:**88–91.
53. **Chung, G., G. R. Kantor, and S. Whipple.** 1991. Tertiary syphilis of the face. J. Am. Acad. Dermatol. **24:**832–835.
54. **Clark, E. G.** 1940. Studies in the epidemiology of syphilis: epidemiologic investigations in a series of 996 cases of acquired syphilis. Vener. Dis. Inform. **21:**349–369.
55. **Clark, E. G., and N. Danbolt.** 1955. The Oslo Study of the natural history of untreated syphilis. J. Chronic Dis. **2:**311–344.
56. **Clark, E. G., and N. Danbolt.** 1964. The Oslo Study of the natural course of untreated syphilis. An epidemiologic investigation based on a re-study of the Boeck-Bruusgaard material. Med. Clin. North Am. **48:**613–623.
57. **Cole, H. N.** 1937. Cooperative clinical studies in the treatment of syphilis. The effect of specific therapy on the prophylaxis and progress of cardiovascular syphilis. JAMA **108:**1861–1866.
58. **Cox, D. L.** 1994. Culture of *T. pallidum*. Methods Enzymol. **236:**390–405.
59. **Cox, D. L., P. Chang, A. McDowall, and J. D. Radolf.** 1992. The outer membrane not a coat of host proteins, limits the antigenicity of virulent *Treponema pallidum*. Infect. Immun. **60:**1076–1083.
60. **Creighton, E. T.** 1990. Darkfield microscopy for the detection and identification of *Treponema pallidum*, p. 49–62. *In* S. A. Larsen, E. F. Hunter and S. J. Kraus (ed.), A manual of tests for syphilis. American Public Health Association, Washington, D.C.
61. **Cumberland, M. C., and T. B. Turner.** 1949. Rate of Multiplication of *Treponema pallidum* in normal and immune rabbits. Am. J. Syphilis **33:**201–212.
62. **Darrow, W. W., D. F. Echenberg, H. W. Jaffe, P. M. O'Malley, R. H. Byers, J. P. Getchell, and J. W. Curran.** 1987. Risk factors for human immunodeficiency virus (HIV) infection in homosexual men. Am. J. Public Health **77:**479–483.
63. **Dattner, B., E. W. Thomas, and L. D. Mello.** 1951. Criteria for the management of neurosyphilis. Am. J. Med. **10:**463–467.
64. **David, L. E., and J. W. Schmitt.** 1989. Clinical significance of cerebrospinal fluid tests for neurosyphilis. Ann. Neurol. **25:**50–55.
65. **Davis, L. E., and S. Sperry.** 1979. The CSF-FTA test and the significance of blood contamination. Ann. Neurol. **6:**68–69.
66. **Deacon, W. E., J. B. Lucas, and E. V. Price.** 1966. Fluorescent treponemal antibody-absorption (FTA-ABS) for syphilis. JAMA **198:**156–160.
67. **Dempster, W. J.** 1978. Towards a new understanding of John Hunter. Lancet **i:**316–318.
68. **Dennie, C. C.** 1962. A history of syphilis. Charles C. Thomas, Publisher, Springfield, Ill.
69. **Deschenes, J., C. D. Seamone, and M. G. Baines.** 1992. Acquired ocular syphilis: diagnosis and treatment. Ann. Ophthalmol. **24:**134–138.
70. **DiCarlo, R. P., and D. H. Martin.** 1997. The clinical diagnosis of genital ulcer disease in men. Clin. Infect. Dis. **25:**292–298.
71. **Disease Control Centre.** 1994. Northern Territory Sexual Diseases Program. Darwin, NT, Canada.
72. **Division of STD Prevention.** 1997. Sexually transmitted disease surveillance, 1996. Centers for Disease Control and Prevention, Atlanta, Ga.
73. **Division of STD Prevention and Control.** 1997. Syphilis: epidemiology and control. Laboratory Centre for Disease Control, Bureau of HIV/AIDS and STD, Ottawa, Ontario, Canada.
74. **Division of STD/HIV Prevention.** 1993. Sexually transmitted diseases surveillance, 1993. Centers for Disease Control and Prevention, Atlanta, Ga.
75. **Division of Venereal Disease.** 1951. Evaluation of antisyphilitic therapy with intensive follow-up. J. Vener. Dis. **32:**355–379.
76. **Donders, G. G., J. Desmyter, D. H. De Wet, and F. A. Van Assche.** 1993. The association of gonorrhoea and syphilis with premature birth and low birthweight. Genitourin. Med. **69:**98–101.
77. **Dowell, M. E., P. G. Ross, D. M. Musher, T. R. Cate, and R. E. Baughn.** 1992. Response of latent syphilis or neurosyphilis to ceftriaxone therapy in persons infected with human immunodeficiency virus. Am. J. Med. **93:**481–488.
78. **Elder, H. A., B. A. G. Santamarina, S. Smith, and E. H. Kass.** 1971. The natural history of asymptomatic bacteriuria during pregnancy: the effect of tetracycline on the clinical course and outcome of pregnancy. Am. J. Obstet. Gynecol. **111:**441–462.
79. **El Tabbakh, G. H., B. R. Elejade, and F. F. Broekhuizen.** 1994. Primary syphilis and nonimmune hydrops in a penicillin-allergic woman. J. Reprod. Med. **39:**412–414.
80. **Engelgau, M. M., C. H. Woernle, R. T. Rolfs, J. R. Greenspan, M. O'Cain, and R. D. Gorsky.** 1995. Control of epidemic early syphilis: the results of an intervention campaign using social networks. Sex. Transm. Dis. **22:**203–209.
81. **Engelkens, H. J., F. J. ten Kate, V. D. Vuzevski, J. J. van der Sluis, and E. Stolz.** 1991. Primary and secondary syphilis: a histopathological study. Int. J. Sex. Transm. Dis. Acquired Immune Defic. Syndr. **2:**280–284.
82. **Ernst, A. A., T. A. Farley, and D. H. Martin.** 1995. Screening and empiric treatment for syphilis in an inner-city emergency department. Acad. Emerg. Med. **2:**765–772.
83. **Ernst, A. A., J. D. Samuels, and D. K. Winsemius.** 1991. Emergency department screening for syphilis in patients with other suspected sexually transmitted diseases. Ann. Emerg. Med. **20:**627–630.
84. **Evans, H. E., and L. D. Frenkel.** 1994. Congenital syphilis. Clin. Perinatol. **21:**149–162.
85. **Faber, W. R., J. D. Bos, P. J. G. M. Rietra, H. Fass, and R. V. W. Van Eijk.** 1983. Treponemicidal levels of amoxicillin in cerebrospinal fluid after oral administration. Sex. Transm. Dis. **10:**148–150.
86. **Farmer, T. W.** 1948. The Jarisch-Herxheimer reaction in early syphilis. JAMA **138:**480–485.
87. **Fenton, L. J., and I. J. Light.** 1976. Congenital syphilis after maternal treatment with erythromycin. Obstet. Gynecol. **47:**492–494.
88. **Fichtner, R. R., S. O. Aral, J. H. Blount, A. A. Zaidi, G. H. Reynolds, and W. W. Darrow.** 1983. Syphilis in the United States: 1967–1979. Sex. Transm. Dis. **10:**77–80.
89. **Fieldsteel, A. H., J. G. Stout, and F. A. Becker.** 1979. Comparative behaviour of virulent strains of *Treponema pallidum* and *Treponema pertenue* in gradient cultures of various mammalian cells. Infect. Immun. **24:**337–345.
90. **Fisher, D. A., L. W. Chang, and D. L. Tuffanelli.** 1969. Lues Maligna. Presentation of a case and a review of the literature. Arch. Dermatol. **99:**70–73.
91. **Fitzgerald, T. J.** 1981. Pathogenesis and Immunology of *Treponema pallidum*. Annu. Rev. Microbiol. **35:**29–54.
92. **Fitzgerald, T. J.** 1992. Effects of cefetamet (Ro 15-8074) on *Treponema pallidum* and experimental syphilis. Antimicrob. Agents Chemother. **36:** 598–602.
93. **Fitzgerald, T. J., J. N. Miller, and J. A. Sykes.** 1975. *Treponema pallidum* (Nichols strain) in tissue cultures: cellular attachment, entry, and survival. Infect. Immun. **11:**1133–1140.
94. **Fitzgerald, T. J., I. A. Repesh, and S. G. Oakes.** 1982. Morphological destruction of cultured cells by the attachment of *Treponema pallidum*. Br. J. Vener. Dis. **58:**1–11.
95. **Fiumara, N. J.** 1975. Syphilis in newborn children. Clin. Obstet. Gynecol. **18:**183–189.
96. **Fiumara, N. J.** 1977. Treatment of secondary syphilis: an evaluation of 204 patients. Sex. Transm. Dis. **4:**96–99.
97. **Fiumara, N. J.** 1977. Treatment of seropositive primary syphilis: an evaluation of 196 patients. Sex. Transm. Dis. **4:**92–95.
98. **Fiumara, N. J.** 1978. Treatment of early latent syphilis of less than a year's duration: an evaluation of 275 cases. Sex. Transm. Dis. **5:**85–88.
99. **Fiumara, N. J.** 1979. Serologic responses to treatment of 128 patients with late latent syphilis. Sex. Transm. Dis. **6:**243–246.
100. **Fiumara, N. J.** 1980. The treatment of primary and secondary syphilis: serologic response. JAMA **243:**2500–2502.
101. **Fiumara, N. J.** 1986. Treatment of early latent syphilis under 1 year's duration: serologic response to treatment of 368 patients. J. Am. Acad. Dermatol. **15:**1059–1061.
102. **Fiumara, N. J.** 1986. Treatment of primary and secondary syphilis: serologic response. J. Am. Acad. Dermatol. **14:**487–491.
103. **Fiumara, N. J., W. L. Fleming, J. G. Downing, and F. L. Good.** 1952. The incidence of prenatal syphilis at the Boston city Hospital. N. Engl. J. Med. **247:**48–52.
104. **Fleet, W. S., R. T. Watson, and W. E. Ballinger.** 1986. Resolution of a gumma with steroid therapy. Neurology **36:**1104–1107.
105. **Fojaco, R. M., G. T. Hensley, and L. Moskowitz.** 1989. Congenital syphilis and necrotizing funisitis. JAMA **261:**1788–1790.
106. **Fraser, C. M., S. J. Norris, G. M. Weinstock, O. White, G. G. Sutton, R.**

Dodson, M. Gwinn, E. K. Hickey, R. Clayton, K. A. Ketchum, E. Sodergren, J. M. Hardham, M. P. McLeod, S. Salzberg, J. Peterson, H. Khalak, D. Richardson, J. K. Howell, M. Chidambaram, T. Utterback, L. McDonald, P. Artiach, C. Bowman, M. D. Cotton, and J. C. Venter. 1998. Complete genome sequence of *Treponema pallidum*, the syphilis spirochete. Science **281:**375–388.

107. **Garland, S. M., and V. N. Kelly.** 1989. Is antenatal screening for syphilis worthwhile? Med. J. Aust. **151:**368–372.
108. **Garnett, G. P., S. O. Aral, D. V. Hoyle, W. Cates, Jr., and R. M. Anderson.** 1997. The natural history of syphilis. Implications for the transmission dynamics and control of infection. Sex. Transm. Dis. **24:**185–200.
109. **Gerber, A. R., L. C. King, G. J. Dunleavy, and L. F. Novick.** 1989. An outbreak of syphilis on an Indian reservation: descriptive epidemiology. Am. J. Public Health **79:**83–85.
110. **Geringer, W. M., and M. Hinton.** 1993. Three models to promote syphilis screening and treatment in a high risk population. J. Community Health. **18:**137–151.
111. **Gershman, K. A., and R. T. Rolfs.** 1991. Diverging gonorrhea and syphilis trends in the 1980s: are they real? Am. J. Public Health **81:**1263–1267.
112. **Ghadouane, M., B. S. Benjelloun, L. Elharim-Roudies, M. Jorio-Benkhraba, and A. el Malki-Tazi.** 1995. Skeletal lesions in early congenital syphilis (a review of 86 cases). Rev. Rhum. Engl. Ed. **62:**433–437.
113. **Ghys, P. D., M. O. Diallo, V. Ettiegne-Traor'e, K. M. Yebou'e, E. Gnaor'e, F. Lorougnon, K. Kal'e, E. Van Dyck, Brettegaard, and Y. M. Hoyi.** 1995. Genital ulcers associated with human immunodeficiency virus-related immunosuppression in female sex workers in Abidjan, Ivory Coast. J. Infect. Dis. **172:**1371–1374.
114. **Gibson, J. J., W. Leverette, and M. Arvelo.** 1996. Providers of syphilis care in the United States. Sex. Transm. Dis. **23:**40–44.
115. **Gjestland, T.** 1955. The Oslo Study of untreated syphilis: an epidemiologic investigation of the natural course of syphilis infection based upon a restudy of the Boeck-Bruusgaard material. Acta Derm. Venereol. **35**(Suppl. 34)**:**1–368.
116. **Goeman, J., M. Kivuvu, N. Nzila, F. Behets, B. Edidi, E. Gnaore, and D. Van.** 1995. Similar serological response to conventional therapy for syphilis among HIV-positive and HIV-negative women. Genitourin. Med. **71:**275–279.
117. **Gordon, S. M., M. E. Eaton, R. George, S. Larsen, S. A. Lukehart, J. Kuypers, C. M. Marra, and S. Thompson.** 1994. The response of symptomatic neurosyphilis to high-dose intravenous penicillin G in patients with human immunodeficiency virus infection. N. Engl. J. Med. **331:**1469–1473.
118. **Gourevitch, M. N., P. A. Selwyn, K. Davenny, D. Buono, E. E. Schoenbaum, R. S. Klein, and G. H. Friedland.** 1993. Effects of HIV infection on the serologic manifestations and response to treatment of syphilis in intravenous drug users. Ann. Intern. Med. **118:**350–355.
119. **Graciansky, P. and C. Grupper.** 1961. Cortisone in the prevention of the Herxheimer reaction in early syphilis. Br. J. Vener. Dis. **37:**247–251.
120. **Greenberg, M. S., T. Singh, M. Htoo, and S. Schultz.** 1991. The association between congenital syphilis and cocaine/crack use in New York City. Am. J. Public Health **81:**1316–1318.
121. **Greenblatt, R. M., S. A. Lukehart, F. A. Plummer, T. C. Quinn, C. W. Critchlow, R. L. Ashley, L. J. D'Costa, J. O. Ndinya-Achola, L. Corey, A. R. Ronald, and K. K. Holmes.** 1988. Genital ulceration as a risk factor for human immunodeficiency virus infection. AIDS **2:**47–50.
122. **Greenstein, D. B., C. M. Wilcox, and D. A. Schwartz.** 1994. Gastric syphilis: report of seven cases and review of the literature. J. Clin. Gastroenterol. **18:**4–9.
123. **Greenwood, A. M., U. D'Alessandro, F. Sisay, and B. M. Greenwood.** 1992. Treponemal infection and the outcome of pregnancy in a rural area of The Gambia, West Africa. J. Infect. Dis. **166:**842–846.
124. **Grimprel, E., P. J. Sanchez, G. D. Wendel, J. M. Burstain, G. H. McCracken, Jr., J. D. Radolf, and M. V. Norgard.** 1991. Use of polymerase chain reaction and rabbit infectivity testing to detect *Treponema pallidum* in amniotic fluid, fetal and neonatal sera, and cerebrospinal fluid. J. Clin. Microbiol. **29:**1711–1718.
125. **Gudjonsson, H., and E. Skog.** 1968. The effect of prednisolone on the Jarisch-Herxheimer reaction. Acta Dermatol. Venereol. **48:**15–18.
126. **Guinan, M. E.** 1987. Treatment of primary and secondary syphilis: defining failure at three- and six-month follow-up. JAMA **257:**359–360.
127. **Haas, J. S., G. Bolan, S. A. Larsen, M. J. Clement, P. Bacchetti, and A. R. Moss.** 1990. Sensitivity of treponemal tests for detecting prior treated syphilis during human immunodeficiency virus infection. J. Infect. Dis. **162:**862–866.
128. **Hahn, R. A., L. S. Magder, S. O. Aral, R. E. Johnson, and S. A. Larsen.** 1989. Race and the prevalence of syphilis seroreactivity in the United States. Am. J. Public Health **79:**467–470.
129. **Hahn, R. D., and E. G. Clark.** 1946. Asymptomatic neurosyphilis: a review of the literature. Am. J. Syphilis Gonorrhea Vener. Dis. **30:**305–316.
130. **Hahn, R. D., J. C. Cutler, A. C. Curtis, G. Gammon, A. Heyman, E. Johnwick, J. H. Stokes, H. Solomon, E. Thomas, W. Timberlake, B. Webster, and G. A. Gleeson.** 1956. Penicillin treatment of asymptomatic central nervous system syphilis. 1. Probability of progression to symptomatic neurosyphilis. Arch. Dermatol. **74:**355–366.
131. **Hahn, R. D., J. C. Cutler, A. C. Curtis, G. Gammon, A. Heyman, E. Johnwick, J. H. Stokes, H. Solomon, E. Thomas, W. Timberlake, B. Webster, and G. A. Gleeson.** 1956. Penicillin treatment of asymptomatic central nervous system syphilis. 2. Results of therapy as measured by laboratory findings. Arch. Dermatol. **74:**367–377.
132. **Hardy, J. B., P. H. Hardy, E. H. Oppenheimer, S. J. Ryan, Jr., and R. N. Sheff.** 1970. Failure of penicillin in a newborn with congenital syphilis. JAMA **212:**1345–1349.
133. **Harner, R. E., J. L. Smith, and C. W. Israel.** 1968. The FTA-ABS test in late syphilis. JAMA **203:**545–548.
134. **Harris, A., A. Rosenberg, and L. M. Riedel.** 1946. A microflocculation test for syphilis using cardiolipin antigen: preliminary report. J. Vener. Dis. Inform. **27:**159–172.
135. **Harshan, V., and W. Jayakumar.** 1982. Doxycycline in early syphilis: a long-term follow-up. Indian J. Dermatol. **27:**119–124.
136. **Hart, G.** 1980. Epidemiologic treatment for syphilis and gonorrhea. Sex. Transm. Dis. **7:**149–160.
137. **Hart, G.** 1980. Screening to control infectious diseases. Evaluation of control programs for gonorrhoea and syphilis. Rev. Infect. Dis. **2:**701–712.
138. **Hart, G.** 1986. Syphilis tests in diagnostic and therapeutic decision making. Ann. Intern. Med. **104:**368–376.
139. **Hart, G.** 1992. STD epidemiology in Australasia: syphilis and gonorrhoea. Venereology **5:**115–120.
140. **Harter, C. A., and K. Benirschke.** 1976. Fetal syphilis in the first trimester. Am. J. Obstet. Gynecol. **7:**705–711.
141. **Hashisaki, P., G. G. Wertzberger, G. L. Conrad, and C. R. Nichols.** 1983. Erythromycin failure in treatment of syphilis in a pregnant woman. Sex. Transm. Dis. **10:**36–38.
142. **Hay, P. E., J. R. Clarke, R. A. Strugnell, D. Taylor-Robinson, and D. Goldmeier.** 1990. Use of polymerase chain reaction to detect DNA sequences specific to pathogenic treponemes in cerebrospinal fluid. FEMS Microbiol. **68:**233–238.
143. **Hayes, N. S., K. E. Muse, A. M. Collier, and J. B. Baseman.** 1977. Parasitism by virulent *Treponema pallidum* of host cell surfaces. Infect. Immun. **17:**174–186.
144. **Heggtveit, H. A.** 1964. Syphilitic aortitis. A clinicopathologic autopsy study of 100 cases, 1950 to 1960. Circulation **29:**349–355.
145. **Heimberger, T. S., H. G. Chang, G. S. Birkhead, G. D. DiFerdinando, and A. J. Greenberg.** 1993. High prevalence of syphilis detected through a jail screening program. A potential public health measure to address the syphilis epidemic. Arch. Intern. Med. **153:**1799–1804.
146. **Hibbs, J. R., and R. A. Gunn.** 1991. Public health intervention in a cocaine-related syphilis outbreak. Am. J. Public Health. **81:**1259–1262.
147. **Hira, S. K., G. J. Bhat, D. M. Chikamata, B. Nkowane, G. Tembo, and P. L. Perine.** 1990. Syphilis intervention in pregnancy: Zambian demonstration project. Genitourin. Med. **66:**159–164.
148. **Holmes, M. D., M. M. Brant-Zawadzki, and R. P. Simon.** 1984. Clinical features of meningovascular syphilis. Neurology **34:**553–556.
149. **Hook, E. W., III.** 1989. Syphilis and HIV infection. J. Infect. Dis. **160:**530–534.
150. **Hook, E. W., III.** 1996. Biomedical issues in syphilis control. Sex. Transm. Dis. **23:**5–8.
151. **Hook, E. W., III, S. A. Baker-Zander, B. L. Moskowitz, S. A. Lukehart, and H. H. Handsfield.** 1986. Ceftriaxone therapy for asymptomatic neurosyphilis. A case report and Western blot analysis of serum and cerebrospinal fluid IgG response to therapy. Sex. Transm. Dis. **13:**185–188.
152. **Hook, E. W., III, and C. M. Marra.** 1992. Acquired syphilis in adults. N. Engl. J. Med. **326:**1060–1069.
153. **Hook, E. W., III, R. E. Roddy, and H. H. Handsfield.** 1988. Ceftriaxone therapy for incubating and early syphilis. J. Infect. Dis. **158:**881–884.
154. **Hooshmand, H., M. R. Escobar, and S. W. Kopf.** 1972. Neurosyphilis. A study of 241 patients. JAMA **219:**726–729.
155. **Hotson, J. R.** 1981. Modern neurosyphilis: a partially treated chronic meningitis. West. J. Med. **135:**191–200.
156. **Howles, J. K.** 1943. Synopsis of clinical syphilis. The C. V. Mosby Co., St. Louis, Mo.
157. **Hunte, W., F. al-Ghraoui, and R. J. Cohen.** 1993. Secondary syphilis and the nephrotic syndrome. J. Am. Soc. Nephrol. **3:**1351–1355.
158. **Hunter, E. F., W. E. Deacon, and P. E. Meyer.** 1964. An improved FTA test for syphilis, the absorption procedure (FTA-ABS). Public Health Rep. **79:**410–412.
159. **Hutchinson, C. M., E. W. Hook III, M. Shepherd, J. Verley, and A. M. Rompalo.** 1994. Altered clinical presentation of early syphilis in patients with human immunodeficiency virus infection. Ann. Intern. Med. **121:**94–100.
160. **Hutchinson, C. M., A. M. Rompalo, C. A. Reichart, and E. W. Hook III.** 1991. Characteristics of patients with syphilis attending Baltimore STD clinics. Arch. Intern. Med. **151:**511–516.
161. **Reference deleted.**
162. **Ingraham, N. R.** 1951. The value of penicillin alone in the prevention and

treatment of congenital syphilis. Acta Dermato-Venereol. **31**(Suppl. 24)**:** 60–88.
163. **Ito, F., E. F. Hunter, R. W. George, V. Pope, and S. A. Larsen.** 1992. Specific immunofluorescent staining of pathogenic treponemes with a monoclonal antibody. J. Clin. Microbiol. **30:**831–838.
164. **Ito, F., E. F. Hunter, R. W. George, B. L. Swisher, and S. A. Larsen.** 1991. Specific immunofluorescence staining of *Treponema pallidum* in smears and tissues. J. Clin. Microbiol. **29:**444–448.
165. **Izzat, N. N., J. K. Bartruf, J. M. Glicksman, W. R. Holder, and J. M. Knox.** 1971. Validity of the VDRL test on cerebrospinal fluid contaminated by blood. Br. J. Vener. Dis. **47:**162–164.
166. **Jackman, J. D., Jr., and J. D. Radolf.** 1989. Cardiovascular syphilis. Am. J. Med. **87:**425–433.
167. **Jacques, S. M., and F. Qureshi.** 1992. Necrotizing funisitis: a study of 45 cases. Hum. Pathol. **23:**1278–1283.
168. **Jaffe, H. W.** 1976. Treatment of latent syphilis. J. Am. Vener. Dis. Assoc. **3:**143–145.
169. **Jaffe, H. W., and S. A. Kabins.** 1982. Examination of cerebrospinal fluid in patients with syphilis. Rev. Infect. Dis. **4:**S842–847.
170. **Jaffe, H. W., S. A. Larsen, M. Peters, D. F. Jove, B. Lopez, and A. L. Schroeter.** 1978. Tests for treponemal antibody in CSF. Arch. Intern. Med. **138:**252–255.
171. **Jaffe, H. W., D. T. Rice, R. Voigt, J. Fowler, and R. K. St John.** 1979. Selective mass treatment in a venereal disease control program. Am. J. Public Health **69:**1181–1182.
172. **Johns, D. R., M. Tierney, and D. Felsenstein.** 1987. Alteration in the natural history of neurosyphilis by concurrent infection with the human immunodeficiency virus. N. Engl. J. Med. **316:**1569–1572.
173. **Johnson, P. D., S. R. Graves, L. Stewart, R. Warren, B. Dwyer, and C. R. Lucas.** 1991. Specific syphilis serological tests may become negative in HIV infection. AIDS **5:**419–423.
174. **Johnson, R. C., R. F. Bey, and S. J. Wolgamot.** 1982. Comparison of the activities of ceftriaxone and penicillin G against experimentally induced syphilis in rabbits. Antimicrob. Agents. Chemother. **21:**984–989.
175. **Jose, B., S. R. Friedman, and A. Neaigus.** 1993. Possible parenteral transmission of syphilis among drug injectors, abstr. 3016. *In* Abstracts of the 121st Annual Meeting of the American Public Health Association.
176. **Kampmeier, R. H.** 1938. Saccular aneurysm of the thoracic aorta. A clinical study of 633 cases. Ann. Intern. Med. **12:**624–651.
177. **Kampmeier, R. H.** 1964. The late manifestations of syphilis: skeletal, visceral and cardiovascular. Med. Clin. North Am. **48:**667–697.
178. **Kampmeier, R. H., and H. J. Morgan.** 1952. The specific treatment of syphilitic aortitis. Circulation **5:**771–778.
179. **Kaplan, J. G., A. B. Sterman, D. Horoupian, N. E. Leeds, R. D. Zimmerman, and R. Gade.** 1981. Luetic meningitis with gumma: clinical, radiographic, and neuropathologic features. Neurology **31:**464–467.
180. **Kaplan, J. M., and G. H. McCracken, Jr.** 1973. Clinical pharmacology of benzathine penicillin G in neonates with regard to its recommended use in congenital syphilis. J. Pediatr. **82:**1069–1072.
181. **Katz, D. A., and J. R. Berger.** 1989. Neurosyphilis in acquired immunodeficiency syndrome. Arch. Neurol. **46:**895–898.
182. **Katz, D. A., J. R. Berger, and R. C. Duncan.** 1993. Neurosyphilis. A comparative study of the effects of infection with human immunodeficiency virus. Arch. Neurol. **50:**243–249.
183. **Kaufman, R. E., J. H. Blount, and O. G. Jones.** 1974. Current trends in syphilis. Public Health Rev. **3:**175–198.
184. **Kaufman, R. E., O. G. Jones, J. H. Blount, and P. J. Wiesner.** 1977. Questionnaire survey of reported early congenital syphilis. Problems in diagnosis, prevention, and treatment. Sex. Transm. Dis. **4:**135–139.
185. **Kingon, R. J., and P. J. Wiesner.** 1981. Premarital syphilis screening: weighing the benefits. Am. J. Public Health **71:**160–162.
186. **Klein, V. R., S. M. Cox, M. D. Mitchell, and G. D. Wendel, Jr.** 1990. The Jarisch-Herxheimer reaction complicating syphilotherapy in pregnancy. Obstet. Gynecol. **75:**375–380.
187. **Klingbeil, L. J., and E. G. Clark.** 1941. Studies in the epidemiology of syphilis. III. Conjugal syphilis: a statistical study of a series of 226 married patients whose spouses were examined. Vener. Dis. Inform. **22:**1–6.
188. **Korting, H. C., R. Haag, D. Walter, U. Riethmuller, and M. Meurer.** 1993. Efficacy of ceftizoxime in the treatment of incubating syphilis in. Chemotherapy **39:**331–335.
189. **Korting, H. C., D. Walther, U. Riethmuller, and M. Meurer.** 1987. Ceftriaxone given repeatedly cures manifest syphilis in the rabbit. Chemotherapy **33:**376–380.
190. **Kunawararak, P., C. Beyrer, C. Natpratan, W. Feng, D. D. Celentano, M. de Boer, K. E. Nelson, and C. Khamboonruang.** 1995. The epidemiology of HIV and syphilis among male commercial sex workers in northern Thailand. AIDS **9:**517–521.
191. **Laboratory Centre for Disease Control.** 1998. Canadian STD Guidelines 1998 Edition. Minister of Public Works and Government Services, Ottawa, Canada.
192. **Larsen, S. A., B. M. Steiner, and A. H. Rudolph.** 1995. Laboratory diagnosis and interpretation of tests for syphilis. Clin. Microbiol. Rev. **8:**1–21.
193. **Lee, C. B., R. C. Brunham, E. Sherman, and G. K. Harding.** 1987. Epidemiology of an outbreak of infectious syphilis in Manitoba. Am. J. Epidemiol. **125:**277–283.
194. **Linglof, T.** 1995. Rapid increase of syphilis and gonorrhea in parts of the former USSR. Sex. Transm. Dis. **22:**160–161.
195. **Loewenfeld, I. E.** 1969. The Argyll Robertson pupil 1869–1969. A critical survey of the literature. Surv. Ophthalmology **14:**199–299.
196. **Lukehart, S. A.** 1991. Serologic testing after therapy for syphilis: is there a test for cure? Ann. Intern. Med. **114:**1057–1058. (Editorial.)
197. **Lukehart, S. A.** 1995. Modern syphilis—still a shadow on the land. West. J. Med. **163:**587–588. (Editorial.)
198. **Lukehart, S. A., and S. A. Baker-Zander.** 1987. Roxithromycin (RU 965): effective therapy for experimental syphilis. Antimicrob. Agents Chemother. **31:**187–190.
199. **Lukehart, S. A., M. J. Fohn, and S. A. Baker-Zander.** 1990. Efficacy of azithromycin for therapy of active syphilis in the rabbit model. J. Antimicrob. Chemother. **25**(Suppl. A)**:**S91–S99.
200. **Lukehart, S. A., E. W. Hook, S. A. Baker-Zander, A. C. Collier, C. W. Critchlow, and H. H. Handsfield.** 1988. Invasion of the central nervous system by *Treponema pallidum*: implications for diagnosis and treatment. Ann. Intern. Med. **109:**855–862.
201. **Mack, L. W., J. L. Smith, E. K. Walter, E. N. Montenegro, and W. G. Nicol.** 1969. Temporal bone treponemes. Arch. Otolaryngol. **90:**11–14.
202. **Magnuson, H. J., H. Eagle, and R. Fleischman.** 1948. The minimal infectious inoculum of *Spirochaeta pallida* (Nichols Strain) and a consideration of its rate of multiplication in vivo. Am. J. Syphilis Gonorrhea Vener. Dis. **32:**1–18.
203. **Magnuson, H. J., E. W. Thomas, S. Olansky, B. I. Kaplan, L. de Mello, and J. C. Cutler.** 1956. Inoculation syphilis in human volunteers. Medicine **35:**33–82.
204. **Mahoney, J. F., R. C. Arnold, and A. D. Harris.** 1943. Penicillin treatment of early syphilis. Am. J. Public Health **33:**1387–1391.
205. **Mahoney, J. F., and K. K. Bryant.** 1933. Contact infection of rabbits in experimental syphilis. Am. J. Syphilis **17:**188–193.
206. **Mahoney, J. F., and K. K. Bryant.** 1934. Time element in penetration of genital mucosa by *Treponema pallidum*. J. Vener. Dis. Infect. **15:**1–5.
207. **Malone, J. L., M. R. Wallace, B. B. Hendrick, A. LaRocco, Jr., E. Tonon, S. K. Brodine, W. A. Bowler, B. S. Lavin, R. E. Hawkins, and E. C. Oldfield.** 1995. Syphilis and neurosyphilis in a human immunodeficiency virus type-1 seropositive population: evidence for frequent serologic relapse after therapy. Am. J. Med. **99:**55–63.
208. **Margo, C. E., and L. M. Hamed.** 1992. Ocular syphilis. Surv. Ophthalmol. **37:**203–220.
209. **Marra, C. M., C. W. Critchlow, E. W. Hook III, A. C. Collier, and S. A. Lukehart.** 1995. Cerebrospinal fluid treponemal antibodies in untreated early syphilis. Arch. Neurol. **52:**68–72.
210. **Marra, C. M., W. T. Longstreth, C. L. Maxwell, and S. A. Lukehart.** 1996. Resolution of serum and cerebrospinal fluid abnormalities after treatment of neurosyphilis. Sex. Transm. Dis. **23:**184–189.
211. **Maruti, S., L. Hwang, M. Ross, L. Leonard, J. Paffel, and L. Hollins.** 1997. The epidemiology of early syphilis in Houston, Texas, 1994–1995. Sex. Transm. Dis. **24:**475–480.
212. **Marx, R., S. O. Aral, R. T. Rolfs, C. E. Sterk, and J. G. Kahn.** 1991. Crack, sex, and STD. Sex. Transm. Dis. **18:**92–101.
213. **Mascola, L., R. Pelosi, J. H. Blount, C. E. Alexander, and W. Cates, Jr.** 1985. Congenital syphilis revisited. Am. J. Dis. Child. **139:**575–580.
214. **Mashkilleyson, A. L., M. A. Gomberg, N. Mashkilleyson, and S. A. Kutin.** 1996. Treatment of syphilis with azithromycin. Int. J. Sex. Transm. Dis. Acquired Immune Defic. Syndr. **7**(Suppl. 1)**:**13–15.
215. **Matlow, A. G., and A. R. Rachlis.** 1990. Syphilis serology in human immunodeficiency virus infected patients with symptomatic neurosyphilis: case report and review. Rev. Infect. Dis. **12:**703–707.
216. **McCracken, G. H., and J. M. Kaplan.** 1974. Penicillin treatment for congenital syphilis. JAMA **228:**855–858.
217. **McLeish, W. M., J. S. Pulido, S. Holland, W. W. Culbertson, and K. Winward.** 1990. The ocular manifestations of syphilis in the human immunodeficiency virus type 1 infected host. Ophthalmology **97:**196–203.
218. **McMillan, A., and I. W. Smith.** 1984. Painful anal ulceration in homosexual men. Br. J. Surg. **71:**215–216.
219. **Merino, H. I., F. N. Judson, D. Bennett, and T. R. Schaffnit.** 1979. Screening for gonorrhea and syphilis in gay bathhouses in Denver and Los Angeles. Public Health Rep. **94:**376–379.
220. **Merritt, H. H.** 1940. The early clinical and laboratory manifestations of syphilis of the central nervous system. N. Engl. J. Med. **223:**446–450.
221. **Merritt, H. H., R. D. Adams, and H. C. Solomon.** 1946. Neurosyphilis. Oxford University Press, New York, N.Y.
222. **Merritt, H. H., and M. Moore.** 1935. Acute syphilitic meningitis. Medicine **14:**119–183.
223. **Miao, R. M., and A. H. Fieldsteel.** 1980. Genetic relationship between *Treponema pallidum* and *Treponema pertenue*, two noncultivable human pathogens. J. Bacteriol. **141:**427–429.
224. **Mindel, A., S. J. Tovey, D. J. Timmins, and P. Williams.** 1989. Primary and

secondary syphilis, 20 years' experience. 2. Clinical features. Genitourin. Med. **65:**1–3.
225. **Minkoff, H. L., S. McCalla, I. Delke, R. Stevens, M. Salwen, and J. Feldman.** 1990. The relationship of cocaine use to syphilis and human immunodeficiency. Am. J. Obstet. Gynecol. **163:**521–526.
226. **Mohr, J. A., W. Griffiths, R. Jackson, H. Saadah, P. Bird, and J. Riddle.** 1976. Neurosyphilis and penicillin levels in cerebrospinal fluid. JAMA **236:** 2208–2209.
227. **Moore, J. E. and M. Gieske.** 1931. Syphilitic iritis. A study of 249 patients. Am. J. Ophthalmol. **14:**110–126.
228. **Moore, M. B., E. V. Price, J. M. Knox, and L. W. Elgin.** 1963. Epidemiologic treatment of contacts to infectious syphilis. Public Health Rep. **78:**966–970.
229. **Moorthy, T. T., C. Lee, K. Lim, and T. Tan.** 1987. Ceftriaxone for treatment of primary syphilis in men: a preliminary study. Sex. Transm. Dis. **14:**116–118.
230. **Morrison, A.** 1992. On syphilis and the ear—an otologist's view. Genitourin. Med. **68:**420–422.
231. **Morrison, R. E., S. M. Harrison, and E. C. Treatment.** 1985. Oral amoxicillin, an alternative treatment for neurosyphilis. Genitourin. Med. **61:**359–362.
232. **Musher, D. M.** 1988. How much penicillin cures early syphilis? Ann. Intern. Med. **109:**849–851.
233. **Musher, D. M.** 1990. Biology of *Treponema pallidum*, p. 205–211. *In* K. K. Holmes, P. Mardh, P. F. Sparling, P. J. Wiesner, W. Cates, Jr. and S. M. Lemon, (ed.), Sexually transmitted diseases. Mc-Graw-Hill Book Co., New York, N.Y.
234. **Musher, D. M.** 1992. Therapeutic considerations in congenital syphilis. Pediatr. Infect. Dis. J. **11:**505–506.
235. **Musher, D. M., R. J. Hamill, and R. E. Baughn.** 1990. Effect of human immunodeficiency virus (HIV) infection on the course of syphilis and on the response to treatment. Ann. Intern. Med. **113:**872–881.
236. **Nakashima, A. K., R. T. Rolfs, M. L. Flock, P. Kilmarx, and J. R. Greenspan.** 1996. Epidemiology of syphilis in the United States, 1941–1993. Sex. Transm. Dis. **23:**16–23.
237. **Neisser, A.** 1897. Malignant syphilis. Br. J. Dermatol. **9:**11–26.
238. **Nelson, K. E., D. Vlahov, S. Cohn, M. Odunmbaku, A. Lindsay, J. C. Antohony, and E. W. Hook III.** 1991. Sexually transmitted diseases in a population of intravenous drug users: association with seropositivity to the human immunodeficiency virus (HIV). J. Infect. Dis. **164:**457–463.
239. **Newell, J., K. Senkoro, F. Mosha, H. Grosskurth, A. Nicoll, and L. Barongo.** 1993. A population-based study of syphilis and sexually transmitted disease syndromes in north-western Tanzania. 2. Risk factors and health seeking behaviour. Genitourin. Med. **69:**421–426.
240. **Nichols, H. J., and W. H. Hough.** 1913. Demonstration of *Spirochaeta pallida* in the cerebrospinal fluid. JAMA **60:**108.
241. **Noordhoek, G. T., P. W. M. Hermans, A. N. Paul, L. M. Schouls, J. J. van der Sluis, and J. D. A. van Embden.** 1989. *Treponema pallidum* subspecies *pallidum* (Nichols) and *Treponema pallidum* subspecies *pertenue* (CDC 2575) differ in at least one nucleotide: comparison of two homologous antigens. Microb. Pathog. **6:**29–42.
242. **Noordhoek, G. T., E. C. Wolters, M. E. J. de Jonge, and J. D. A. van Embden.** 1991. Detection by polymerase chain reaction of *Treponema pallidum* in cerebrospinal fluid from neurosyphilis patients before and after antibiotic treatment. J. Clin. Microbiol. **29:**1976–1984.
243. **Norgard, M. V., L. L. Arndt, D. R. Akins, L. L. Curetty, D. A. Harrich, and J. D. Radolf.** 1996. Activation of human monocytic cells by *Treponema pallidum* and *Borrelia burgdorferi* lipoproteins and synthetic lipopeptides proceeds via a pathway distinct from that of lipopolysaccharide but involves the transcriptional activator NF-κB. Infect. Immun. **63:**3845–3852.
244. **Norgard, M. V., and J. N. Miller.** 1985. Plasmid DNA in *Treponema pallidum* (Nichols): Potential for antibiotic resistance in syphilis bacteria. Science **213:**553–555.
245. **Norris, S. J., and S. A. Larsen.** 1995. *Treponema* and other host-associated spirochetes, p. 636–651. *In* P. R. Murray, E. J. Baron, M. A. Pfaller, F. C. Tenover, and R. H. Yolken (ed.), Manual of clinical microbiology, 6th ed. ASM Press, Washington, D.C.
246. **Olansky, S.** 1964. Late benign syphilis. Med. Clin. North Am. **48:**653–665.
247. **Olansky, S. and W. Garson.** 1958. The treatment of syphilis with antibiotics other than penicillin. Arch. Dermatol. **77:**648–650.
248. **O'Leary, P. A., L. A. Brunsting, and O. Ockaly.** 1946. Penicillin in the treatment of neurosyphilis. JAMA **130:**698–700.
249. **O'Leary, P. A., H. N. Cole, J. E. Moore, J. H. Stokes, U. J. Wile, T. Parran, R. A. Vonderlehr, and L. J. Usilton.** 1937. Cooperative clinical studies in the treatment of syphilis: asymptomatic neurosyphilis. Vener. Dis. Infect. **18:** 45–65.
250. **Onoda, Y.** 1979. Therapeutic effect of oral doxycycline on syphilis. Br. J. Vener. Dis. **55:**110–115.
251. **Oriel, J. D.** 1994. The scars of venus. Springer-Verlag, London, England.
252. **Orle, K. A., C. A. Gates, D. H. Martin, B. A. Body, and J. B. Weiss.** 1996. Simultaneous PCR detection of *Haemophilus ducreyi*, *Treponema pallidum*, and herpes simplex virus types 1 and 2 from genital ulcers. J. Clin. Microbiol. **34:**49–54.
253. **Oxman, G.** 1996. A comparison of the case-finding effectiveness and average costs of screening and partner notification. Sex. Transm. Dis. **23:**51–57.
254. **Oxman, G. L., K. Smolkowski, and J. Noell.** 1996. Mathematical modelling of epidemic syphilis transmission. Implications for syphilis control programs. Sex. Transm. Dis. **23:**30–39.
255. **Paley, S. S.** 1937. Syphilis in pregnancy. N. Y. State J. Med. **37:**585–590.
256. **Parran, T.** 1937. Shadow on the land. Reynal and Hitchcock, New York, N.Y.
257. **Passo, M. S., and J. T. Rosenbaum.** 1988. Ocular syphilis in patients with human immunodeficiency virus infection. Am. J. Ophthalmol. **106:**1–6.
258. **Peterman, T. A., K. E. Toomey, L. W. Dicker, A. A. Zaidi, J. E. Wroten, and J. Carolina.** 1997. Partner notification for syphilis. A randomized controlled trial of three approaches. Sex. Transm. Dis. **24:**511–518.
259. **Peters, J. J., J. H. Peers, S. Olansky, J. C. Cutler, and G. A. G. Gleeson.** 1955. Untreated syphilis in the male Negro. Pathologic findings in syphilitic and nonsyphilitic patients. J. Chronic Dis. **1:**127–148.
260. **Petersen, L. R., R. H. Mead, and M. G. Perlroth.** 1983. Unusual manifestations of secondary syphilis occurring after orthotopic liver transplantation. Am. J. Med. **75:**166–170.
261. **Philipson, A., L. D. Sabath, and D. Charles.** 1973. Transplacental passage of erythromycin and clindamycin. N. Engl. J. Med. **288:**1219–1221.
262. **Piot, P., and M. Q. Islam.** 1994. Sexually transmitted diseases in the 1990s. Global epidemiology and challenges for control. Sex. Transm. Dis. **21**(Suppl. 2)**:**S7–S13.
263. **Platou, R. V.** 1949. Treatment of congenital syphilis with penicillin. Adv. Pediatr. **4:**39–86.
264. **Polnikorn, N., R. Witoonpanich, M. Vorachit, S. Vejjajiva, and A. Vejjajiva.** 1980. Penicillin concentrations in cerebrospinal fluid after different treatment regimens for syphilis. Br. J. Vener. Dis. **56:**363–367.
265. **Portnoy, J., J. H. Brewer, and A. Harris.** 1962. Rapid plasma reagin card test for syphilis and other treponematoses. Public Health Rep. **77:**645–652.
266. **Quetel, C.** 1990. History of syphilis. Blackwell Scientific Publications Ltd., Oxford, England.
267. **Quinn, T. C., R. O. Cannon, D. Glasser, S. L. Groseclose, W. S. Brathwaite, A. S. Fauci, and E. W. Hook III.** 1990. The association of syphilis with risk of human immunodeficiency virus infection in patients attending sexually transmitted disease clinics. Arch. Intern. Med. **150:**1297–1302.
268. **Quinn, T. C., L. Corey, R. G. Chaffee, M. D. Schuffler, F. P. Brancato, and K. K. Holmes.** 1981. The etiology of anorectal infections in homosexual men. Am. J. Med. **71:**395–406.
269. **Quinn, T. C., D. Glasser, R. O. Cannon, D. L. Matuszak, R. W. Dunning, R. L. Kline, C. H. Campbell, E. Israel, A. S. Fauci, and E. W. Hook III.** 1988. Human immunodeficiency virus among patients attending clinics for sexually transmitted diseases. N. Engl. J. Med. **318:**197–203.
270. **Radolf, J. D., M. V. Norgard, M. E. Brandt, R. D. Isaacs, P. A. Thompson, and B. Beutler.** 1991. Lipoproteins of *Borrelia burgdorferi* and *Treponema pallidum* activate cachectin/tumor necrosis factor synthesis: analysis using a CAT reporter construct. J. Immunol. **147:**1968–1974.
271. **Radolf, J. D., M. V. Norgard, and W. Shulz.** 1989. Outer membrane ultrastructure explains the limited antigenicity of virulent *Treponema pallidum*. Proc. Natl. Acad. Sci. USA **86:**2051–2055.
272. **Raiziss, G. W., and M. Severac.** 1937. Rapidity with which *Spirochaeta pallida* invades the bloodstream. Arch. Dermatol. Syphilol. **35:**1101–1109.
273. **Rasool, M. N., and S. Govender.** 1989. The skeletal manifestations of congenital syphilis. A review of 197 cases. J. Bone Joint Surg. Br. **71:**752–755.
274. **Reginato, A. J.** 1993. Syphilitic arthritis and osteitis. Rheum. Dis. Clin. North Am. **19:**379–398.
275. **Rein, M. F.** 1976. Biopharmacology of syphilotherapy. J. Am. Vener. Dis. Assoc. **3:**109–127.
276. **Riley, B. S., N. Oppenheimer-marks, E. J. Hansen, J. D. Radolf, and M. V. Norgard.** 1992. Virulent *Treponema pallidum* activates human vascular endothelial cells. J. Infect. Dis. **165:**484–493.
277. **Riviere, G. R., D. D. Thomas, and C. M. Cobb.** 1989. An in vitro model of *Treponema pallidum* invasiveness. Infect. Immun. **57:**2267–2271.
278. **Robinson, R. C. V.** 1969. Congenital syphilis. Arch. Dermatol. **99:**599–560.
279. **Rockwell, D. H., A. R. Yobs, and M. B. Moore.** 1964. The Tuskegee study of untreated syphilis. The 30th year of observation. Arch. Intern. Med. **114:** 792–798.
280. **Rolfs, R. T.** 1995. Treatment of syphilis, 1993. Clin. Infect. Dis. **20**(Suppl. 1)**:**S23–S38.
281. **Rolfs, R. T., M. Goldberg, and R. G. Sharrar.** 1990. Risk factors for syphilis: cocaine use and prostitution. Am. J. Public Health. **80:**853–857.
282. **Rolfs, R. T., R. Joessef, E. F. Hendershot, A. M. Rompalo, M. H. Augenbraun, M. Chiu, G. Bolan, S. C. Johnson, P. French, E. Steen, J. D. Radolf, and S. Larsen.** 1997. A randomized trial of enhanced therapy for early syphilis in patients with or without human immunodeficiency virus infection. The Syphilis and HIV Study Group. N. Engl. J. Med. **337:**307–314.
283. **Romanowski, B., E. Forsey, E. Prasad, S. Lukehart, and E. W. Hook III.** 1987. Detection of *Treponema pallidum* by a fluorescent monoclonal antibody test. Sex. Transm. Dis. **14:**156–159.
284. **Romanowski, B., E. Starreveld, and A. J. Jarema.** 1983. Treatment of

neurosyphilis with chloramphenicol. A case report. Br. J. Vener. Dis. **59:** 225–227.
285. **Romanowski, B., R. Sutherland, G. H. Fick, D. Mooney, and E. J. Love.** 1991. Serologic response to treatment of infectious syphilis. Ann. Intern. Med. **114:**1005–1009.
286. **Romansky, M. J., S. Olansky, S. R. Taggart, G. C. Landman, and E. D. Robin.** 1951. Chloromycetin (chloramphenicol) in the treatment of various types of syphilis. Am. J. Syphilis Gonorrhea Vener. Dis. **35:**234–239.
287. **Rompalo, A. M., R. O. Cannon, T. C. Quinn, and E. W. Hook III.** 1992. Association of biologic false-positive reactions for syphilis with human immunodeficiency virus infection. J. Infect. Dis. **165:**1124–1126.
288. **Roper, W. L., H. B. Peterson, and J. W. Curran.** 1993. Condoms and HIV/STD prevention—clarifying the message. Am. J. Public Health **83:** 501–503.
289. **Rosahn, P. D.** 1947. Autopsy studies in syphilis. J. Vener. Dis. Infect. **21**(Suppl.).
290. **Rose, M. S., G. H. Fick, B. Romanowski, and E. J. Love.** 1997. First year serologic response to treatment for syphilis: a model for prediction of seroreversion. Stat. Med. **16:**2103–2115.
291. **Rudolph, A. H.** 1976. The microhemagglutination assay for *Treponema pallidum* antibodies (MHA-TP), a new treponemal test for syphilis: where does it fit? J. Am. Vener. Dis. Assoc. **3:**3–8.
292. **Rusnak, J. M., C. Butzin, D. McGlasson, and S. P. Blatt.** 1994. False positive rapid plasma reagin tests in human immunodeficiency virus infection and relationship to anti-cardiolipin antibody and serum immunoglobulin levels. J. Infect. Dis. **169:**1356–1359.
293. **Sands, M., and A. Markus.** 1995. Lues maligna, or ulceronodular syphilis, in a man infected with human immunodeficiency virus: case report and review. Clin. Infect. Dis. **20:**387–390.
294. **Sartin, J. S., and H. O. Perry.** 1995. From mercury to malaria to penicillin: the history of the treatment of syphilis at the Mayo Clinic. J. Am. Acad. Dermatol. **32:**255–261.
295. **Schaudinn, F. N., and E. Hoffman.** 1905. Vorlaufiger Bericht uber das Vorkommen von Spirochaeten in syphilitischen Krankheits produkten und bei Papillomen. Arbeiten K Gesundheits. **22:**527–534.
296. **Schlaegel, T. F., and S. F. Kao.** 1982. A review (1970–1980) of 28 presumptive cases of syphilitic uveitis. Am. J. Ophthalmol. **93:**412–414.
297. **Schlossberg, D.** 1987. Syphilitic hepatitis: a case report and review of the literature. Am. J. Gastroenterol. **82:**552–553.
298. **Schmid, G. P.** 1996. Serologic screening for syphilis. Rationale, cost and realpolitik. Sex. Transm. Dis. **23:**45–50.
299. **Schober, P. C., G. Gabriel, P. White, W. F. Felton, and R. N. Thin.** 1983. How infectious is syphilis? Br. J. Vener. Dis. **59:**217–219.
300. **Schoch, P. E., and E. C. Wolters.** 1987. Penicillin concentrations in serum and CSF during high-dose intravenous treatment for neurosyphilis. Neurology **37:**1214–1216.
301. **Schofer, H., M. Imhof, E. Thoma-Greber, N. H. Brockmeyer, M. Hartmann, G. Gerken, H. W. Pees, H. Rasokat, H. Hartmann, I. Sadri, C. Emminger, H. J. Stellbrink, R. Baumgarten, and A. Plettenberg.** 1996. Active syphilis in HIV infection: a multicentre retrospective study. Genitourin. Med. **72:** 176–181.
302. **Schrijvers, D., R. Josse, A. Trebucq, A. Dupont, H. Cheringou, and B. Larouze.** 1989. Transmission of syphilis between sexual partners in Gabon. Genitourin. Med. **65:**84–85.
303. **Schroeter, A. L., J. B. Lucas, E. V. Price, and V. H. Falcone.** 1972. Treatment for early syphilis and reactivity of serologic tests. JAMA **221:**471–476.
304. **Schroeter, A. L., R. H. Turner, J. B. Lucas, and W. Brown.** 1971. Therapy for incubating syphilis: effectiveness of gonorrhea treatment. JAMA **218:** 711–713.
305. **Schulz, K. F., W. Cates, Jr., and P. R. O'Mara.** 1987. Pregnancy loss, infant death, and suffering: legacy of syphilis and gonnorrhoea in Africa. Genitourin Med. **63:**320–325.
306. **Shew, M. L., and J. D. Fortenberry.** 1992. Syphilis screening in adolescents. J. Adolesc. Health **13:**303–305.
307. **Siegel, D., S. A. Larsen, E. Golden, S. Morse, M. T. Fullilove, and A. E. Washington.** 1994. Prevalence, incidence, and correlates of syphilis seroreactivity in multhiethnic San Francisco neighborhoods. Ann. Epidemiol. **4:**460–465.
308. **Simon, R. P.** 1985. Neurosyphilis. Arch. Neurol. **42:**606–613.
309. **Simonsen, J. N., D. W. Cameron, M. N. Gakinya, J. O. Ndinya-Achola, L. J. D'Costa, P. Karasira, M. Cheang, A. R. Ronald, P. Piot, and F. A. Plummer.** 1988. Human immunodeficiency virus infection among men with sexually transmitted diseases. Experience from a center in Africa. N. Engl. J. Med. **319:**274–278.
310. **Sison, C. G., E. M. J. Ostrea, M. P. Reyes, and V. Salari.** 1997. The resurgence of congenital syphilis: a cocaine-related problem. J. Pediatr. **130:**289–292.
311. **Smith, C. A., M. Kamp, S. Olansky, and E. V. Price.** 1956. Benzathine penicillin G in the treatment of syphilis. Bull. W. H. Or. **15:**1087–1096.
312. **Smith, D. C., and W. A. Brumfeld.** 1933. Tracing the transmission of syphilis. JAMA **101:**1955–1957.
313. **Smolin, G., R. A. Nozik, and M. Okumoto.** 1970. Growth of *Treponema pallidum* in rabbits. Am. J. Ophthalmol. **70:**273–276.
314. **Sohval, A. R.** 1935. Gumma of the heart. Arch. Pathol. **20:**429–444.
315. **South, M., D. H. Short, and J. M. Knox.** 1964. Failure of erythromycin estolate therapy in in utero syphilis. JAMA **190:**182–183.
316. **Sparling, P. F.** 1971. Diagnosis and treatment of syphilis. N. Engl. J. Med. **284:**642–653.
317. **Speer, M. E., L. H. Taber, D. B. Clark, and A. J. Rudolph.** 1977. Cerebrospinal fluid levels of benzathine penicillin G in the neonate. J. Pediatr. **91:**996–997.
318. **Spoor, T. C., P. Wynn, W. C. Hartel, and C. S. Bryan.** 1983. Ocular syphilis. Acute and chronic. J. Clin. Neuroophthalmol. **3:**197–203.
319. **Stamm, L. V., J. T. Stapleton, and P. J. Bassford.** 1988. In vitro assay to demonstrate high-level erythromycin resistance of a clinical isolate of *Treponema pallidum*. Antimicrob. Agents Chemother. **32:**164–169.
320. **Stamm, W. E., H. H. Handsfield, A. M. Rompalo, R. L. Ashley, P. L. Roberts, and L. Corey.** 1988. The association between genital ulcer disease and acquisition of HIV. JAMA **260:**1429–1433.
321. **Steele, R. W.** 1984. Ceftriaxone therapy of meningitis and serious infections. Am. J. Med. **77**(Suppl. 4C)**:**50–53.
322. **St. Louis, M. E.** 1996. Strategies for syphilis prevention in the 1990s. Sex. Transm. Dis. **23:**58–67.
323. **St. Louis, M. E., and J. N. Wasserheit.** 1998. Elimination of syphilis in the United States. Science **281:**353–354.
324. **Stokes, J. H., H. Beerman, and N. R. Ingraham.** 1944. Modern clinical syphilology. The W. B. Saunders Co., Philadelphia, Pa.
325. **Stoll, B. J.** 1994. Congenital syphilis: evaluation and management of neonates born to mothers. Pediatr. Infect. Dis. J. **13:**845–852.
326. **Talwar, S., M. A. Tutakne, and V. D. Tiwari.** 1992. VDRL titres in early syphilis before and after treatment. Genitourin. Med. **68:**120–122.
327. **Tartaglione, T. A., and T. M. Hooton.** 1993. The role of fluoroquinolones in sexually transmitted diseases. Pharmacotherapy **13:**189–201.
328. **Telzak, E. E., M. S. Greenberg, J. Harrison, R. L. Stoneburner, and S. Schultz.** 1991. Syphilis treatment response in HIV-infected individuals. AIDS **5:**591–595.
329. **Temmerman, M., F. Mohamed Ali, and L. Fransen.** 1993. Syphilis prevention in pregnancy: an opportunity to improve reproductive and child health in Kenya. Health Policy Plan **8:**122–127.
330. **Thirumoorthy, T., C. T. Lee, and K. B. Lim.** 1986. Epidemiology of infectious syphilis in Singapore. Genitourin. Med. **62:**75–77.
331. **Thomas, D. D., J. B. Baseman, and J. F. Alderete.** 1985. Fibronectin mediates *Treponema pallidum* cytadherence through recognition of fibronectin cell-binding domain. J. Exp. Med. **161:**514–525.
332. **Thomas, D. D., J. B. Baseman, and J. F. Alderete.** 1985. Putative *Treponema pallidum* cytadhesins share a common functional domain. Infect. Immun. **49:**833–835.
333. **Thomas, D. D., M. Navab, D. A. Haake, A. M. Fogelman, J. N. Miller, and M. A. Lovett.** 1988. *Treponema pallidum* invades intercellular junctions of endothelial cell monolayers. Proc. Natl. Acad. Sci. USA **85:**3608–3612.
334. **Thomas, J. C., A. L. Kulik, and V. J. Schoenbach.** 1995. Syphilis in the South: rural rates surpass urban rates in North Carolina. Am. J. Public Health **85:**1119–1122.
335. **Thomas, S. B., and S. C. Quinn.** 1991. The Tuskegee syphilis study, 1932 to 1972: implications for HIV education and AIDS risk education programs in the black community. Am. J. Public Health. **81:**1498–1505.
336. **Thompson, L.** 1920. Syphilis of the kidney. JAMA **75:**17–20.
337. **Tichonova, L., K. Borisenko, H. Ward, A. Meheus, A. Gromyko, and A. Renton.** 1997. Epidemics of syphilis in the Russian Federation: trends, origins, and priorities for control. Lancet **350:**210–213.
338. **Tomberlin, M. G., P. D. Holtom, J. L. Owens, and R. A. Larsen.** 1994. Evaluation of neurosyphilis in human immunodeficiency virus-infected individuals. Clin. Infect. Dis. **18:**288–294.
339. **Tramont, E. C.** 1976. Persistence of *Treponema pallidum* following penicillin G therapy. JAMA **236:**2206–2207.
340. **Tucker, H. A., and J. L. Mulherin.** 1948. Extragenital chancres. A survey of 219 cases. Am. J. Syphilis Gonorrhea Vener. Dis. **32:**345–364.
341. **U.S. Department of Health, Education and Welfare.** 1968. Syphilis, a synopsis. PHS publication 168. U. S. Government Printing Office, Washington, D. C.
342. **Van der Sluis, J. J., P. C. Onvlee, F. C. Kothe, V. D. Vuzevski, G. M. Aelbers, and H. E. Menke.** 1984. Transfusion syphilis, survival of treponema pallidum in donor blood. I. Report of an orientating study. Vox Sang. **47:**197–204.
343. **Van der Sluis, J. J., F. J. ten Kate, V. D. Vuzevski, F. C. Kothe, G. M. Aelbers, and R. V. van Eijk.** 1985. Transfusion syphilis, survival of treponema pallidum in donor blood. II. Dose dependence of experimentally determined survival times. Vox Sang. **49:**390–399.
344. **Veller-Fornasa, C., M. Tarantello, R. Cipriani, L. Guerra, and A. Peserico.** 1987. Effect of ofloxacin on *Treponema pallidum* in incubating experimental syphilis. Genitourin. Med. **63:**214.
345. **Verdon, M. S., H. H. Handsfield, and R. B. Johnson.** 1994. Pilot study of azithromycin for treatment of primary and secondary syphilis. Clin. Infect. Dis. **19:**486–488.

346. **Vondelehr, R. A., and T. Clark.** 1936. Untreated syphilis in the male Negro. A comparative study of treated and untreated cases. Vener. Dis. Infect. **17:**260–265.
347. **von Werssowetz, A. J.** 1948. The incidence of infection in contacts of early syphilis. J. Vener. Dis. Inform. **29:**132–137.
348. **Walker, E. M., L. A. Borenstein, D. R. Blanco, M. A. Miller, and M. A. Lovett.** 1991. Analysis of outer membrane ultrastructure of pathogenic *Treponema* and *Borrelia* species by freeze electron microscopy. J. Bacteriol. **173:**5585–5588.
349. **Wassermann, A., A. Neisser, and C. Bruck.** 1906. Eine serodiagnostische Reaktion bei Syphilis. Dtsch. Med. Wochenschr. **32:**745–746.
350. **Webster, L. A., and R. T. Rolfs.** 1993. Surveillance for primary and secondary syphilis—United States, 1991. CDC Surveillance Summaries. Morbid. Mortal. Weekly Rep. **42:**13–19.
351. **Webster, L. A., R. T. Rolfs, A. K. Nakashima, and J. R. Greenspan.** 1991. Regional and temporal trends in the surveillance of syphilis, United States, 1986–1990. CDC Surveillance Summaries. Morbid. Mortal. Weekly Rep. **40:**29–33.
352. **Wendel, G. D.** 1988. Gestational and congenital syphilis. Clin. Perinatol. **15:**287–303.
353. **Wendel, G. D., M. C. Maberry, J. T. Christmas, M. S. Goldberg, and M. V. Norgard.** 1989. Examination of amniotic fluid in diagnosing congenital syphilis with fetal death. Obstet. Gynecol. **74:**967–970.
354. **Werdegar, D., P. O'Malley, T. Bodecker, N. Hessol, and D. Echenberg.** 1987. Self-reported changes in sexual behaviors among homosexual and bisexual men from the San Francisco City Clinic cohort. Morbid. Mortal. Weekly Rep. **36:**188–189.
355. **WHO Office of HIV/AIDS and STDs.** 1995. An overview of selected curable STDs. Syphilis estimates, 1995. World Health Organization, Geneva, Switzerland.
356. **Wiesel, J., D. N. Rose, A. L. Silver, H. S. Sacks, and R. H. Bernstein.** 1985. Lumbar puncture in asymptomatic late syphilis. An analysis of the benefits and risks. Arch. Intern. Med. **145:**465–468.
357. **Wile, U., and L. K. Mundt.** 1942. Congenital syphilis: a statistical study with special regard to sex incidence. Am. J. Syphilis Gonorrhea Vener. Dis. **26:**70–83.
358. **Wile, U. J., and J. H. Stokes.** 1915. Involvement of the nervous system during the primary stage of syphilis. JAMA **64:**979–982.
359. **Willcox, R. R.** 1973. 'Epidemiologic treatment' in non-venereal and in treponemal diseases. Br. J. Vener. Dis. **49:**107–115.
360. **Willcox, R. R., and T. Guthe.** 1966. *Treponema pallidum*. A bibliographical review of the morphology, culture and survival of *T. pallidum* and associated organisms. Bull. W.H.O. **35:**1–169.
361. **Williams, K.** 1985. Screening for syphilis in pregnancy: an assessment of the costs and benefits. Community Med. 37–42.
362. **Winters, H. A., V. Notar-Francesco, K. Bromberg, S. A. Rawstrom, and J. Vetrano.** 1992. Gastric syphilis: five recent cases and a review of the literature. Ann. Intern. Med. **116:**314–319.
363. **Wong, G. H., B. M. Steiner, and S. Graves.** 1983. Inhibition of macromolecule synthesis in cultured rabbit cells by *Treponema pallidum* (Nichols). Infect. Immun. **41:**636–643.
364. **Woolf, A., C. Wilfert, D. Kelsey, and L. Gutman.** 1980. Childhood syphilis in North Carolina. N. C. Med. J. **41:**443–449.
365. **World Health Organization.** 1982. Treponemal infections. World Health Organization, Geneva, Switzerland.
366. **World Health Organization.** 1985. Control of sexually transmitted diseases. World Health Organization and Pan American Health Organization.
367. **Yim, C. W., N. M. Flynn, and F. T. Fitzgerald.** 1985. Penetration of oral doxycycline into the cerebrospinal fluid of patients with latent or neurosyphilis. Antimicrob. Agents Chemother. **28:**347–348.
368. **Yinnon, A. M., P. Coury-Doniger, R. Polito, and R. C. Reichman.** 1996. Serologic response to treatment of syphilis in patients with HIV. Arch. Intern. Med. **156:**321–325.
369. **Zenker, P.** 1991. New case definition for congenital syphilis reporting. Sex. Transm. Dis. **18:**44–45.
370. **Zenker, P. N., and R. T. Rolfs.** 1989. Treatment of syphilis, 1989. Rev. Infect. Dis. **12**(Suppl. 6)**:**S590–S609.