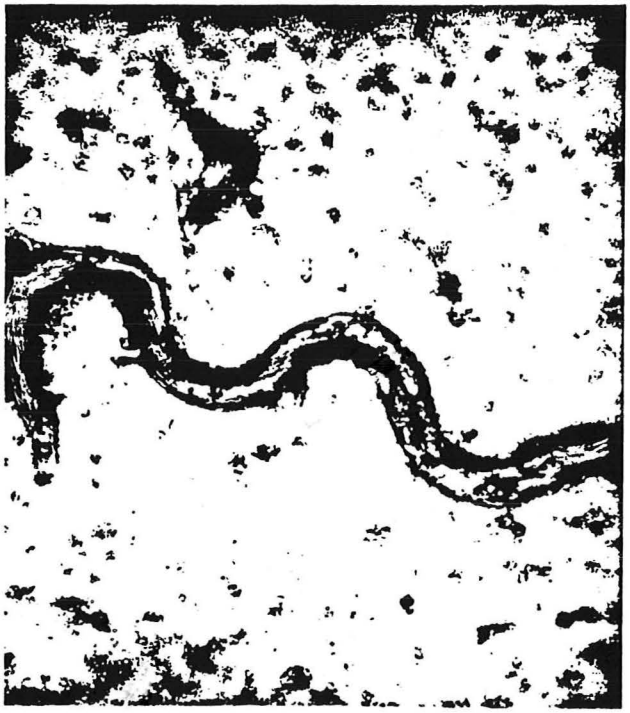
Syphilis 1988: Goodbye, Columbus



O Rose, thou art sick.
The invisible worm
That flies in the night
In the howling storm,

Has found out thy bed
Of crimson joy,
And his dark secret love
Does thy life destroy.

William Blake
The Sick Rose

Justin Radolf, M.D.

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I. The "Colombian" Theory

Medical historians and archaeologists have provided abundant evidence that many contemporary afflictions have existed since the the dawn of antiquity. Examples include the relapsing fevers, malaria, tuberculosis, and leprosy. The history of syphilis is entirely different. Syphilis appeared dramatically in Western Europe in the form of a highly virulent epidemic illness during the late fifteenth and early sixteenth centuries. The "Great Pox" devastated Western Europe for more than fifty years (1,2). Medical writings of the time leave little doubt that the mysterious plague was indeed syphilis. As early as 1502, Spanish physicians recognized that the infection was being transmitted venereally. Ulrich von Hutten, a German knight afflicted with the Pox, left a particularly colorful description 1519 "... in Women the disease resteth in their secret Places, wherein are pretty Sores, full of venemous Poison, being very dangerous for such as knowingly meddle with them.". Its skin lesions, he wrote, "...stood out like Acorns from whence issued such filty stinking Matter that whosoever came within the Scent, believed himself infected. " (2).

Where did this new affliction come from? Dias de Isla, a physician practicing in Barcelona in the early 1500's, leveled the charge that has stuck for more than five centuries. He laid the blame for the newly recognized "Disease of the Isle of Espanola" squarely on the shoulders of Christopher Columbus and his crew:

> at the time that the Admiral Xristoual Colon (Christopher Columbus) arrived in Spain, the Catholic sovereigns were in the city of Barcelona. And when they went to give them an account of their voyage and of what they had discovered immediately the city began to be infected and the aforesaid disease spread...(1)

De Isla claimed that Spanish mercenaries in the army of Charles VII of France spread the malady to Italy during the monarch's ill-fated conquest of Naples. From there, he wrote, it spread throughout the Continent (1,2).

From the late sixteenth century onwards, syphilis remained highly endemic in the Western world and, showing no respect for either privilege or rank, it exerted a tremendous influence on the course of Western civilization (3). At present, the correctness of the Colombian theory remains in doubt. For example, examination of skeletal remains has provided evidence that some form of treponemal infection existed in the Old World prior to Columbus. On the other hand, numerous pre-Colombians New World skeletons have been unearthed with evidence of gummatous diease (1,2). Interestingly, within a century after its appearance, its severity moderated into the occasionally severe, but rarely fatal, infection that clinicians usually encounter today. The abruptness of the disease's appearance has led others to speculate that a molecular event transformed a relatively low level pathogen into a highly virulent one.

With all due apologies to Phillip Roth, this brief historical overview should provide at least a partial explanation for the title of my Grand Rounds. The title is meant to epitomize the current status of syphilis in 1988. In one respect, it denotes the fact that the clinical and research tools are finally available to amass a frontal assault on a disease whose pathogenesis is extraordinarily complex. The advent of molecular biology has created the opportunity to examine years of accumulated dogma. The title is also meant to convey the impact of AIDS (and AIDS hysteria) upo syphilis. For now that syphilis has entered the AIDS era, its natura story and the course of syphilology have changed accordingly.

Much attention has been generated in the lay press about the possibility that *Treponema pallidum*, the bacterium which causes syphilis, may actually be the etiologic agent of AIDS (4). Suffice it to say that this is a ridiculous notion. However, many historical and clinical similarities exist between the two diseases (5,6), and it is easy to see how confusion between them might arise both within the academic world and on its periphery. It is ironic that, at a time so ripe for progress in syphilis, the AIDS hysteria threatens to replace old dogma with new. One of the major purposes of this Grand Rounds will be to analyze carefully the burgeoning literature on these two infections to determine how much we really know about the relationships between these two infections. While it seems to be true that "something is out there", only tentative conclusions can be offered pending more comprehensive clinical studies.

II. Contempary Epidemiology of Syphilis

Prior to World War II, syphilis was so prevalent in our society that Vonderlehr and Usilton (7) estimated that a person in the United States stood a one in ten chance of acquiring it during his lifetime. The demonstration in 1943 of the efficacy of penicillin for treatment of syphilis and its widespread application after the War led to a precipitous decline in the number of reported new cases; the annual incidence rate reached an all time low in 1954. From that nadir, the incidence has risen more or less in a steady fashion.

The early increases of the late 1950's and 1960's occurred among heterosexuals probably as a result of the changing societal mores now recognized as the Sexual Revolution. In the mid to late 1970's, a major epidemiological shift occurred. Practitioners in a number of urban centers noted that homosexual males represented a large proportion of the new cases of syphilis (8). This fact has important implications. Researchers have pointed out that these epidemiological trends support the possibility that widespread dissemination of syphilis facilitated transmission of HIV infection among the gay population. In fact, it is probably true that peak HIV transmission rates occurred about the same time as those for syphilis (9). At the very least it created a population of individuals many of whom are co-infected with syphilis and HIV. Therefore, we are faced with the problem of relating the incompletely understood natural histories of two very complex infectious diseases.

Syphilis rates declined in the mid 1980's, probably reflecting the adoption of safe sexual practices among heterosexual males in response to the AIDS epidemic. Surprisingly, they climbed sharply since 1986, and a major epidemiological trend has once again occurred (10,11). The increases are localized primarily to three major urban areas--New York City, Miami, and Los Angeles and are occurring almost entirely among non-Caucasion, heterosexuals. Concomitant with the increases in early syphilis among non-white females, is an increasing number of cases of congenitally acquired infection among their offspring (11).

In March of this year, a panel of experts at the CDC concluded that much of the increase in syphilis among blacks and Hispanics represents an offshoot of drug-related activitites (12). "Sex for drugs" is a common occurrence in crack-houses, the 1988 equivalent of the gay bath houses of the 1970's and early 1980's. Other factors such as limited public health resources, inadequate reporting, surveillance and contact tracing; and transmission of syphilis by contaminated needles were listed as possible contributory factors (12). Why are these trends so alarming? The answer relates back to the potential role of syphilis as a co-factor for transmission of HIV infection. Urban blacks and Hispanics, which already are disproportionately represented among ethnic groups with HIV infection (13), may be repeating the AIDS/syphilis experience of homosexuals in the 1970's.

III. Epidemiology of AIDS and Syphilis--Syphilis as a Co-Factor

A strong epidemiological association between syphilis and HIV infection has been apparent since the beginning of the AIDS epidemic. Surveys of both homosexual and heterosexual individuals with HIV infection consistently demonstrated a statistically significant association between the two diseases (15,16). Initially, serological evidence for syphilis was interpreted as being merely an epidemiological marker for the risk factors associated with HIV infection. However, the observation that transmissibility of HIV appears to vary under different circumstances raised the possibility that co-factors may facilitate HIV transmission. Co-existent sexually transmitted diseases seemed like good candidates for such co-factors.

Recently, investigators have begun to look carefully at the possible role of syphilis as a co-factor of HIV transmission. The most obvious connection seemed to be the possibility that genital ulcerations, of which syphilitic chancres are an important cause, may provide portals of entry for HIV. In the case of syphilis, this conjecture has particular appeal because of the unique histopathology of the chancre. Syphilitic ulcers typically contain intense lymphocytic infiltrates. In experimentally induced lesions in rabbits, the infiltrate is T cells (16). However, the relative proportions of lymphocyte subsets (especially CD4-bearing cells) within syphilitic lesions of humans have not been determined. In humans and rabbits, macrophages, also HIV-susceptible cells, also are commonly seen in syphilitic infiltrates (16).

Several recent studies have refined the epidemiological association between syphilis and HIV infection by demonstrating that genital ulcer disease may be related to both heterosexual transmission of HIV infection

in Africa (17,18) and homosexual transmission in the United States (19). Among patients attending the Baltimore City Health Department clinics, Quinn et al.(17) found that a reactve serological test for syphilis or a history of syphilis correlated more strongly than any other sexually transmitted disease with HIV seropositivity. Simonsen et al. (18) found that 63% of HIV seropositive men in Nairobi, Kenya had a history of genital-ulcer disease, compared with only 19% of seronegative men. Sexual contact with prostitutes seems to be the common denominator in many of the studies of heterosexual transmission. Similar data were reported from Seattle by Stamm and co-workers (19). Those investigators found that histories or reactive serologies for either syphilis or herpes genitalis were significantly associated with HIV seropositivity. No association was found for non-ulcerative sexually transmitted diseases. However, because none of these studies were prospective, a direct relationship between genital ulcers and HIV transmission remains to be proven. Granted such studies would be difficult to accomplish. It is also possible that the association is still largely coincidental. For instance, if the genital ulcer is not present at the time of HIV inoculation, how can it have contributed to HIV infection? Perhaps the microscopic abrasions necessary for HIV infection also facilitated simultaneous acquisition of syphilis.

IV. Clinical Manifestations of Syphilis in HIV Infection

A number of reports have appeared in the last several years suggesting that the suppression of cellular immunity induced by HIV infection can accelerate the natural history of syphilis (20-26). The largest series, that of Johns et. al. (23), reported four patients. All four of their cases were HIV seropositive gay males; two of them developed neurological complications of syphilis during or shortly after the onset of secondary manifestations (syphilitic meningitis). The third presented with meningovascular syphilis after an unspecified incubation period, and a fourth patient (the only one with frank AIDS) presented with asymptomatic neurosyphilis. Two of the four patients, including the patient with asymptomatic neurosyphilis, had been "adequately" treated for neurosyphilis with benzathine penicillin. The crux of their argument is that these are highly unusual presentations for neurosyphilis; the fact that they tended to occur in early in the course of infection suggested that HIV had accelerated their course. The recent PMH experience with neurosyphilis seems to agree with their findings. Other "unusual" forms of syphilis besides neurosyphilis have been reported in HIV-infected patients. These have included posterior uveitis (chorioretinitis) and several rare types of skin lesions (20,22,26). Recently at Parkland we saw an HIV positive patient with lues maligna and an HIV positive woman with a huge cervical chancre, syphilitic endometritis and enlarged pelvic lymph nodes. Despite these reports and anecdotes, the hypothesis that HIV has altered the natural history of syphilis remains far from proven. To see why, we must examine in deal what we know about the pathogenesis, immunology, and natural history of syphilis.

A. Immunopathogenesis of Syphilis

Treponema pallidum is a member of the family of helically shaped bacteria called spirochetes. Like conventional gram-negative bacteria, the organism possesses both outer and inner membranes. It is unlike regular gram-negative bacteria in several respects. First, the outer membrane is relatively fragile and does not contain lipopolysaccharide. Second, the organelles of motility, the endoflagella, are located in the periplasmic space between the two membranes (27). We believe that the motility of the organism is an important virulence factor.

The cellular events that accompany syphilitic infection are not well defined. What is known, however, provides great insight into occurrences within the infected host. As with most other bacterial pathogens, cellular attachment appears to be the initial event in syphilis pathogenesis. Rapid attachment to and (in the hands of some investigators), invasion of cell monolayers by pathogenic treponemes can be readily demonstrated. As one would expect, nonpathogenic treponemes neither attach to or invade cells (28,29). In humans, similar events are initiated following inoculation of intact mucosa or epithelial cells exposed by minor abrasions. Some investigators have provided evidence that attachment is mediated through specific fibronectin receptors (29). The invasiveness of these organisms *in vivo* can be appreciated by the fact that *T. pallidum* can be recovered from the bloodstream of rabbits within minutes following intratesticular inoculation (30). At the other end of their travels through the bloodstream, the organisms pass through the endothelial cells in the small blood vessels of the different organs they invade. This appears to be accomplished through their unique ability to pass between vascular endothelialial cells (31).

Rapid invasion and dissemination is characteristic of syphilis in humans as well as in rabbits. For example, the blood of persons with incubating syphilis (i.e. the stage prior to appearance of a chancre) can transmit the disease. Also invasion of numerous organ systems, including the central nervous system occurs extremely early in the course of infection. Early investigators demonstrated quite convincingly by means of rabbit inoculations that virulent treponemes are present in the central nervous systems of many patients with early syphilis, often times before the development of CSF abnormalities (32). Therefore, unlike the majority of pathogens of AIDS patients, which are mainly opportunists, *T. pallidum* is probably highly invasive in every patient it infects. One does not need a defect in immune defenses to acquire multi-system involvement.

The extremely slow rate of development of cellular and humoral immunity contrasts sharply with the extraordinarily rapid rate of dissemination (33,34). Recognition of this phenomenon led investigators in the 1980's to conjecture that *T. pallidum* itself has immunosuppressive properties (34). Now it is realized that rather than suppressing the immune system, the organism appears to have developed extraordinarily successful strategies for evading it. The appearance of clinical manifestations (e.g. skin lesions) weeks to months after dissemination and the clearance of organisms from a particular site correlates with the mobilization of host immune defenses. This has been

well demonstrated in the rabbit model where development of orchitis after intratesticular inoculation correlates with the influx of immune cells. Cortisone treatment abrogates both the inflammatory response and the development of the orchitis (35). Tertiary syphilis (especially cardiovascular and gummatous syphilis) in humans is also excellent example of this. Lesions in these patients typically have few detectable treponemes and can be induced in patients with latent syphilis by intradermal inoculation with small numbers of organisms (36). To state the corollary, the mere occurrence of clinical manifestations indicates that the host has mounted some form of immune response against the organism. The conclusion from this work, which has important bearings on the HIV question, is that <u>even in normal hosts</u> the immune system appears to be a rather inefficient barrier to systemic invasion. Once mustered, the immune response of normal individuals is capable of eliminating the majority, but not all, of the infecting organisms. The fact that one third of untreated patients develop tertiary syphilis after a variable period of latency provides clear evidence for the persistence of treponemes in sights unknown. Seen from this perspective a defect in host immunity might be responsible for failure to clear organisms from a particular site, but this might not necessarily be accompanied by clinical symptoms.

It should also be pointed out that the critical arms of the immune system for protective immunity against syphilis have not been adequately defined. Different groups have provided evidence that humoral and cellular responses (including macrophages) all play some role in host defenses. The basic histopathology of syphilis supports this concept. However, studies demonstrating sensitization of *T. pallidum*-specific T- cells in rabbits (37) are often cited incorrectly to support statements to the effect that protective immunity in syphilis T-cell dependent. Furthermore, despite "atypical" gross appearances, the histopathology of syphilitic skin lesions in HIV positive patients appears indistinguishable from lesions from HIV seronegative patients (20,25,26).

The term "neurosyphilis" also requires definition. Neurosyphilis, generally speaking, refers to invasion of the central nervous system by *T. pallidum* <u>and</u> the inflammatory response by the host. By this definition, "neurosyphilis" occurs frequently in early syphilis (32). However, the term is usually reserved for either neurological complications of early syphilis or evidence that an active process exists in the CNS of patients with late syphilis. Furthermore, neurosyphilis is not one affliction but a collection of more or less distinct clinical syndromes with different natural histories. Two forms of neurosyphilis, syphilitic meningitis and meningovascular, have a relatively short incubation period (32).

B. Natural History of Syphilis and Neurosyphilis

What is the natural history of plain, old, garden variety syphilis? The best data on this subject was provided by the "Oslo study" (38). From 1891 until 1910 Professor Boeck of Oslo, Norway witheld treatment from nearly 2000 patients with <u>clinically diagnosed</u> primary and secondary syphilis. For the next thirty years he simply followed their clinical course. The final retrospective analysis of 953 patients, completed

between 1948 and 1951 (the final Oslo study) engendered the natural history data quoted in most textbooks of internal medicine (38). The Oslo study, important as it was, created the false impression that patients with syphilis go through a rather orderly progression of stages with the development of tertiary syphilis, including neurosyphilis, occurring years after the initial infection. Particularly important, all of the Oslo data on neurosyphilis were obtained from only 62 patients! Although the meningovascular syphilis patients did represent a significant proportion of the total with neurosyphilis, the average incubation period for this form of neurosyphilis was nearly fifteen years. Syphilitic meningitis was not described at all in the Oslo cohort (38).

A somewhat different picture emerges if one examines data obtained specifically on patients with neurosyphilis. These investigations clearly demonstrate that neurosyphilis is an uncommon but not rare complication of early syphilis. Merritt and colleagues (32) described 80 cases of syphilitic meningitis in their classic 1946 monograph (32). The clinical features--subacute meningitis, cranial nerve palsies (especial Cr. Ns. III, VII, and VIII)--were quite similar to the recent cases in HIV infected patients (23). Of greatest importance was the observation that in nearly half (37 patients), the incubation period was less than one year from the time of infection. Therefore, development of neurosyphilis relatively soon after infection is completely consistent with the known natural history of the disease. To further confuse the issue, several investigators have claimed that in the postantibiotic era (but prior to the advent of AIDS), the clinical spectrum of neurosyphilis has shifted from the "parenchymatous" syndromes (e.g. tabes dorsalis and paresis) to a predominance of meningeal and meningovascular forms (39,40). If this trend is real, then its independent impact on the syphilis-HIV question also will need to be evaluated.

If one accepts the fact that early development of neurosyphilis in a particular patient does not require immunosuppression per se, what about the possibility that HIV-infected patients as a group have a statistically greater likelihood of developing neurosyphilis. This point is either implied or stated directly in all of the case reports. Such a statement, based solely upon the available data is unfounded from an epidemiological standpoint. For before one can say that patients with concurrent HIV and syphilis have a higher incidence of neurosyphilis than their HIV-seronegative counterparts, it is necessary to know the DENOMINATOR, i.e. the number of HIV-seropositive patients with syphilis (actually early syphilis). It is possible that merely because of the large number of HIV infected patients with syphillis, more patients with neurosyphilis are being seen but the relative risk imposed by HIV infection is negligible. It is interesting to note that, although the HIV-infected patients appear to represent a large majority of patients with neurosyphilis currently being seen at PMH, the number and percentage of reactive CSF VDRLs has not changed since 1978 (unpublished data). Another possibility, which I believe has yet to be disproved, is that the putative increased incidence of neurosyphilis in HIV disease represents the superimposition of two concurrently acquired infections with very similar incubation periods (9,32).

The same argument holds for some of the other "unusual" forms of syphilis being described in HIV infected patients. As one reviews these reports of uveitis, lues maligna, etc. (20,22) and compares them with the older literature, examples of each can be found in the pre-AIDS era (41-43). In fact, our unfamiliarity with these rarer manifestations of syphilis might be fostering the erroneous impression that their rareness might be related to HIV infection. that Therefore, on the basis of isolated case reports, it is simply impossibe to state that any of these represent an influence of HIV infection. Finally, we are reminded of the severity of syphilis in normal individuals during its early history.

C. Serological Tests for Syphilis (With and Without HIV Infection)

Many of the diagnostic dilemmas of syphilis arise from the fact that *T. pallidum* cannot be cultivated *in vitro*. Microbiological diagnosis of syphilis can be accomplished only by inoculating clinical material into rabbits (the Rabbit Infectivity Test). In the absence of lesions accessible to darkfield microscopy, diagnosis is almost always reliant upon serodiagnostic tests. Two types of serological tests are employed to diagnose syphilis. The first consists of the nontreponemal tests (e.g. VDRL, RPR). These are agglutination tests which measure antibodies to a mixture of lipids (with cardiolipin as the major component). The antigenic stimulus for production of these antibodies is unknown but is presumed to be of host origin (hence the term "nontreponemal"). The second type of serological test detects antibodies specifically directed against treponemal antigens (e.g. MHA-Tp, FTA-ABs); for this reason, they are designated the "treponemal" tests. Because diseases other than syphilis can give rise to reactive nontreponemal serologies, it is necessary that they be confirmed with a treponemal test. A reactive nontreponemal test with a nonreactive treponemal test, therefore, indicates that a condition other than syphilis is the source of the nontreponemal antibodies. Once past the primary stage of syphilis, treponemal tests are at least 98% sensitive. Therefore, a nonreactive treponemal test provides essential conclusive evidence that a patient never contracted syphilis. In addition to screening, nontreponemal antibody tests are essential for following the effects of antibiotic therapy. Treponemal tests, on the other hand, remain reactive for life regardless of a patient's treatment status (44,45).

Diagnosis of neurosyphilis represents one of the most controversial areas of clinical syphilology. The problem is that the most specific indicator of CNS involvement, the CSF VDRL, may be relatively insensitive. Estimates of the sensitivity of the CSF VDRL vary widely from as low as 50% to well over 90% (46); investigators in the pre-antibiotic era clearly recognized that neurosyphilis could be present in patients without CSF nontreponemal antibodies (32). While the CSF VDRL may be lacking in sensitivity, its specificity is nearly 100% (46). Other CSF parameters that are frequently abnormal in patients with neurosyphilis (e.g. protein and pleocytosis) are nonspecific (46). Relatively simple measurements of treponemal antibodies in CSF, such as the CSF-FTA, have not proven to be useful because the presence of such antibodies correlates poorly with a patient's clinical status (47).

Demonstration of intrathecal synthesis of specific anti-treponemal antibodies also has been reported in clinical neurosyphilis and in patients with early syphilis (48,49). One problem with the latter tests is that intrathecal antibody synthesis persists in some patients after therapy (47,48). Actual demonstration of *T. pallidum* within CSF by rabbit inoculation (46) is another potentially useful diagnostic test; however, few centers have the ability to perform this. For the meantime, diagnosis of neurosyphilis must be based upon routine CSF parameters.

Recently concerns have developed that syphilis serodiagnostic tests are unreliable in patients with HIV infection. In fact, there has been only one case report, that of Hicks et al. (25), of a patient with secondary syphilis and HIV infection who had negative syphilis serologies. The diagnosis in this patient was made by skin biopsy. The conjecture that HIV infected patients might not produce sufficient antibodies for syphilis serodiagnosis has some theoretical basis given the inadequate *de novo* antibody production characteristic of HIV infection (50). In reality, this does not appear to be a significant problem. Our experience at PMH is that such patients occasionally have extraordinarily high VDRL titers. One PMH patient had a titer of 1:32,000 and I have heard anecdotally about a titer of 1:128,000. CSF titers in both of these patients were also quite high, possibly as a result of passive transfer of antibody across the blood-brain barrier. In my experience, treponemal serologies are sensitive as well specific in HIV infected patients. When one tests HIV-infected patients sera by immunoblotting, one does occasionally find a relatively deficient antibody response (26). However, because the treponemal tests measure antibody to a number of antigens, even in these circumstances the amount of antibody present is sufficient to produce a reactive test. Thus, while syphilis serologies are not without their problems, there is presently no solid basis for questioning their utility in HIV-infected patients. Treatment of all AIDS patients with massive doses of penicillin regardless of their syphilis serology results is clearly not warranted.

V. Antibiotic Therapy of Syphilis (With and Without HIV Infection)

Two *in vitro* observations underlie antibiotic therapy of syphilis. First, extremely low concentrations of penicillin (.03 ug/ml) are capable of killing *T. pallidum*. Secondly, the treponemicidal effects of penicillin occur far more slowly than with other bacteria (51). This is presumed to reflect the extremely slow replication time (35 hours) of the organism, although recent data from our laboratory suggest that penetration of the outer membrane by the antibiotic also maybe a contributory factor. Studies in rabbits and in humans have demonstrated the relevance of these *in vitro* observations. Namely, successful therapy of syphilis appears to be more dependent upon prolonged maintenance of treponemicidal levels of penicillin than upon administration of massive doses of the antibiotic (52). In modern day practice, benzathine penicillin G has become the formulation of choice for achieving this. Current CDC recommendations for early syphilis (2.4 MU of benzathine penicillin G) are curative in greater than 95% of patients. (53).

The major controversy surrounding benzathine penicillin concerns its ability to eradicate treponemes in the central nervous system. As described above, CNS invasion by *T. pallidum*, both with and without CSF abnormalities, is common in early syphilis. Presumably, this event is the forerunner to late asymptomatic neurosyphilis and, eventually, symptomatic neurosyphilis (32,54). However, customary amounts of benzathine penicillin G rarely, if ever, achieve treponemicidal levels of penicillin in the CSF (55,56). The question then arises as to why benzathine penicillin G in the usual doses is so effective for early syphilis. Why don't patients frequently relapse with neurosyphilis? Two possible answers can be offered. First, it is possible that penicillin levels in CSF don't correlate well with cure and that adequate levels are achieved in the perivascular regions of the brain parenchyma. The second possibility is that clearance of treponemes from the CNS is largely immunologically mediated. However, this latter possibility assumes that CNS immune mechanisms are particularly effective when, in reality, the CNS is generally regarded as a site where the body's immune defenses function poorly.

Whatever the reason, in a small number of patients treated with benzathine penicillin, the mechanisms responsible for clearance of treponemes are inoperative. Over the years, scattered reports have appeared of neurological relapses in patients with early syphilis who were appropriately treated with benzathine penicillin (57,58). Tramont's report (54) is particularly notable because he documented treatment failures by the rabbit infectivity test of CSF. It is because of these occasional treatment failures that some authorities have never followed CDC treatment schedules for early syphilis and, instead, have given all patients with neurosyphilis more intensive antibiotic therapy (59).

Do treatment failures with benzathine penicillin G occur more frequently in HIV-infected patients and, if so, should all HIV-infected patients with early syphilis receive larger doses of penicillin? An important study which attempted to address this question was recently published by Lukehart and co-workers (60). These investigators used the rabbit infectivity test to analyze CSF from patients with syphilis and to follow the results of therapy. They confirmed findings of the early investigators that viable treponemes can be found in CSF with otherwise normal laboratory parameters obtained from patients with early syphilis. A positive rabbit inoculation, however, tended to correlate with CSF abnormalities. Posttreatment CSF from seven patients was inoculated into rabbits. No treponemes were isolated from the three patients who received 4.8 MU or more of benzathine penicillin. Treponemes were isolated from three of the four patients given only 2.4 MU; all three were HIV seropositive while the fourth (the patient with a negative posttreatment infectivity test) was HIV seronegative. Based on this data, the accompanying editorial (59) claimed that 2.4 MU can no longer be considered adequate therapy for HIV infected patients with early syphilis.

While this claim may eventually be borne out, several points must be made. First, the numbers were extremely small. Second, the patients were not randomized. In fact, while only one third of the patients in the entire study were HIV positive, 75% (3 of 4) of the patients whose CSFs

were analyzed after 2.4 MU of benzathine penicillin were HIV positive. Finally, as pointed out above, clinical treatment failures have been well documented in presumably HIV seronegative patients who received the same dose of penicillin. As pointed out by Dr. Musher (59), the current recommendations for all patients with early syphilis, not just those who are HIV seropositive, needs to be reconsidered.

In view of the above, how is syphilis to be treated? Every patient with syphilis should have his HIV serological status determined. In the absence of additional data, and given the overall track record for currently recommended treatment schedules, HIV seronegative patients with early syphilis should continue to receive standard therapy according to the CDC treatment guidelines (53). Based upon the limited data available, a conservative approach should be taken towards HIV positive patients. They should undergo lumbar puncture and recieve a minimum of 4.8 MU of benzathine penicillin regardless of the results (since treponemes may still be present in "normal" CSF). CSF abnormalities, although often related to HIV infection (61), should be presumed secondary to syphilis and followed as one would any patient with neurosyphilis.

Patients with late syphilis should undergo lumbar puncture to dand should be treated for neurosyphilis is the CSF is abnormal (pleocytosis and/or reactive VDRL). No patient with neurosyphilis, asymptomatic or otherwise, should be treated with benzathine penicillin G. Numerous reports have consistently shown that the CDC regimen employing 7.2 MU of benzathine penicillin G has a 10% failure rate (62). Although such failures are generally asymptomatic, neurological catastrophes also have occurred in such patients (63). Patients with symptomatic neurosyphilis should always receive high dose (10-20 MU daily) intravenous aqueous penicillin G. Asymptomatic patients can be given the procaine penicillin G plus probenicid regimen (64), although this is a difficult regimen to administer as an outpatient. Alternative regimens, such as high dose oral amoxycillin, have been found to be effective in a limited number of patients (65), but have not been approved by the CDC. Penicillin allergic patients with neurosyphilis should be desensitized and given high dose penicillin. One particularly safe and effective method for penicillin desensitization was recently published by Wendel and co-workers (66) of this institution. Ceftriaxone, a third generation cephalosporin with an extremely long half-life, shows promise as an alternative agent for penicillin-allergic patients. The drug has excellent activity against *T. pallidum* (67), but only one report of ceftriaxone treatment of a patient with neurosyphilis has appeared in the literature (68).

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