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SYPHILIS IN THE AIDS ERA

IT is difficult for those of us practicing modern-day medicine to comprehend how pervasive syphilis was in the pre-antibiotic era. For example, medical textbooks commonly divided the discussion of organ systems into sections on congenital defects, tumors, trauma, and infections, but listed syphilis as a separate category. Sir William Osler was often quoted: "Know syphilis in all its manifestations and relations, and all other things clinical will be added unto you."

All that has changed. No disease was more dramatically affected by antibiotics than syphilis. The incidence fell 18-fold from a peak of 72 cases per 100,000 population in 1943 to about 4 per 100,000 in 1956 (the current incidence is approximately 12 per 100,000). And the effectiveness of penicillin as a cure for syphilis has remained constant since its introduction over half a century ago.

The early regimens consisted of 8 to 10 days of painful intramuscular injections of short-acting penicillin, which severely hampered patient compliance. Thus, benzathine penicillin offered an effective simplified alternative. The exquisite sensitivity of *Treponema pallidum* and its slow growth rate (doubling time, 30 to 36 hours) permitted the use of benzathine penicillin, with a low but persistent blood level lasting 18 to 25 days. Furthermore, other commonly used antibiotics, such as tetracycline and erythromycin, were also highly effective. The imminent demise of syphilis was predicted by many an optimist.

But a steady flow of case reports documenting treatment failures, particularly in patients with neurosyphilis,[1] disturbed this otherwise hopeful scene and spawned a continuous debate about the adequate dosage of penicillin and other antibiotics and about how to assess an apparent cure. The problem was complicated by a more serious, albeit subtle, issue. Since spirochetemia developed in virtually anyone who contracted syphilis, everyone with primary syphilis was at risk of seeding of the central nervous system and the development of neurosyphilis. Since neurosyphilis was a devastating complication and one that could easily be cured if treated early, a few clinicians felt compelled to treat and follow all patients with syphilis, irrespective of the stage of illness,[2] to detect the development of neurosyphilis. Other physicians assumed that all patients were cured with a single course of treatment for any stage of disease. Still others chose to pursue an intermediate course and followed the results of the Venereal Disease Research Laboratory and rapid plasma reagin tests; a persistent titer three to six months after treatment for primary or secondary syphilis or five years after treatment for tertiary syphilis constituted a therapeutic failure.[3,4]

Why might an established regimen fail? One possible reason is that the organism has become resistant. But despite this theoretical possibility,[3] there is no evidence of this having occurred in the case of *T. pallidum*. A second reason may be an alteration in the immune status of the infected person. In this issue of the *Journal*, two articles[5,6] document the development of neurologic complications of syphilis in patients infected with the human immunodeficiency virus (HIV). Thus, the pathogenesis of syphilis is brought into sharper focus: the immunologic response of the patient has an important role in controlling the infection, even in the presence of adequate antibiotic therapy. In fact, these case reports suggest that penicillin alone is probably not adequate in the absence of a vigorous host response.

Practically speaking, this means that anyone who has a compromised immune status for any reason and has contracted syphilis must be treated with higher doses of antibiotics for prolonged periods. Antibiotic therapy for neurosyphilis appears to be the minimal acceptable regimen. The treatments used include aqueous penicillin, (2.4 million units per day given intravenously for 8 to 10 days), procaine penicillin (2.4 million units given intramuscularly) plus probenicid (1.5 g by mouth per day for 14 days),[7] amoxicillin, (3 g by mouth twice a day) plus probenicid (1 g by mouth per day) for 14 days,[8] and doxycycline, (100 mg by mouth twice a day for 21 days).[9] Furthermore, since the vast majority of patients with HIV infection

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have a personal behavior pattern that puts them at high risk of contracting syphilis, all HIV-infected patients should be screened for syphilis, and vice versa.[9] The same holds true for other sexually transmitted diseases.

But two potential problems remain. First, serologic tests remain the bedrock for the diagnosis of syphilis, since no attempt is made to isolate the infecting organism and no proved means of detecting *T. pallidum* antigens exists. The antibody response in HIV-infected patients, particularly in the later stages of AIDS, may be compromised,[10] and thus the diagnosis may be obscured. Should all HIV-infected patients with neurologic impairment be empirically treated for neurosyphilis? How do we determine whether the patient is cured? Until more is learned, one's clinical acumen must suffice.

Second, as suggested by Johns et al.,[5] "maintenance" therapy similar to that used for toxoplasmosis, pneumocystis infection, or cryptococcal infection may be required to control the disease in some HIV-infected patients. If so, which antibiotic that readily crosses the blood–brain barrier in the absence of inflammation should we choose?

One overriding fact remains: in patients with HIV infection, syphilis, like most other concurrent infections, follows a malignant and protracted course that challenges our diagnostic and therapeutic abilities. Indeed, Osler's quote may be recast: "Know *HIV infection* in all its manifestations and relations, and all other things clinical will be added unto you."

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