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When Is Syphilis Not Syphilis? Or Is It?

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The correspondence by Mikalova *et al.*¹ in this issue of Sexually Transmitted Diseases makes the important and very interesting observation that the genital lesion of a man diagnosed as having primary syphilis in Paris, France², contained a *Treponema* strain that displays several molecular signatures that suggest infection not with *Treponema pallidum* subsp. *pallidum* as expected, but with *T. pallidum* subsp. *pertenue*, the causative agent of yaws.

Syphilis is usually transmitted sexually and now has a global distribution. Yaws is characteristically an infection acquired during childhood through skin contact in remote regions of Africa, South Asia, and the Western Pacific islands. A close relative of the syphilis and yaws treponemes is *T. pallidum* subsp. *endemicum*, which causes bejel (also known as endemic syphilis) and is traditionally found in the Middle East and in desert regions of West Africa. These 3 treponemes share the ability to infect humans and to cause chronic infections that appear initially as single lesions, progress to disseminated lesions, and ultimately may cause serious and destruction of tissues including skin, cartilage, and bone. Dogma states that the major differences among the subspecies include the mode of transmission (venereal vs. nonvenereal) and the inability of the nonvenereal treponematoses to cause neurosyphilis or congenital infection (reviewed in Ref.3). The finding of this organism in an apparently sexually acquired genital lesion reopens a decades-long nature versus nurture debate about the classification of the pathogenic *Treponema*. In 1963, Hudson⁴ proposed the “unified” theory in which he suggested that all of the treponemal infections--syphilis, yaws, and bejel--were caused by the same etiological agent and that the mode of transmission and clinical characteristics of infection were dictated by various aspects of the environment. According to Hudson, in warm and humid tropical conditions, lesions would appear on the extremities exposed by the limited clothing required in such a climate, resulting in yaws. Transmission occurs when children with chronic ulcerative lesions play, wrestle, and sleep with siblings and playmates. In contrast, in the hot and dry conditions of the Middle East and North Africa, bejel lesions would be seen primarily on the oral mucosa, and the infection would be transmitted by sharing of prechewed food, by moisture-seeking flies, and by sharing of drinking vessels. Venereal syphilis, which was originally recognized in the temperate climate of Europe where clothes typically cover most of the body, found a niche in the genital regions, thus becoming largely sexual transmitted. Hackett⁵, on the other hand, argued that the etiological agents of these infections were genetically distinct and that the differences in clinical manifestations among the infections were due to biological differences of the causative agents. The advent of comparative genomics permits us to reexamine this debate and to critically evaluate the long-held dogma concerning the treponematoses.

Early genetic analyses of the existing strains of *T. pallidum* subsp. *pallidum*, *pertenue*, and *endemicum* revealed several genetic signatures that can be exploited to differentiate these 3 subspecies, supporting the Hackett argument.^{6–10} Application of these tools to a number of strains, however, revealed some inconsistencies. For example, the Haiti B strain, which had been isolated from a typical frambesiform yaws lesion on a boy in Haiti and had been studied extensively in the hamster model of yaws, was shown to have the molecular signatures of the *pallidum* subspecies.⁶ The Mexico A and Sea81-3 syphilis strains had some, but not all, signatures in common with *T. pallidum* subsp. *endemicum* strains.⁹

More detailed genetic analyses have led to both further divisions and further blending of the subspecies. The *tpr* gene family had been identified quite early as a repository of genetic diversity among the subspecies, along with several other genes. Comparison of the full sequences of the *tpr* genes among a large number of *pallidum*, *pertenue*, and *endemicum* strains revealed that the *pallidum* subspecies can be divided into at least 5 genogroups and that some of the unusual hybrid gene sequences seen in *pallidum* strains are also found in some members of other subspecies.¹¹ Full genome sequence comparisons have also confirmed the finding of overlapping genetic characteristics among subspecies.^{12–15} For example, the sequencing of the Seattle 81-4¹⁵ and Mexico A¹² strains, both isolated from penile chancres, revealed many typical *pallidum* genetic signatures, in addition to some *pertenue* markers. Thus, although some molecular signatures clearly differentiate strains into the 3 subspecies, other signatures result in cross-subspecies groupings. Furthermore, comparative analysis of the syphilis versus yaws strain genomes failed to provide an explanation for the long-claimed lack of invasiveness of the yaws and bejel strains.¹⁴

Is the dogma concerning the lack of serious invasive disease in the nonvenereal infections actually true? The literature contains reports of neurological and cardiovascular involvement in patients diagnosed as having yaws,^{16–19} and reports of genital lesions and sexual transmission in bejel.²⁰ Furthermore, a significantly increased rate of miscarriage, consistent with transplacental infection, has been documented in women with bejel.²⁰ In the hamster model of congenital infection, one study demonstrated that the Nichols strain of subsp. *pallidum* caused congenital infection, whereas the Haiti B strain (then thought to be *pertenue*) failed to cause infection.²¹ This was claimed to confirm the lack of congenital infection in yaws, although later molecular typing clearly showed Haiti B to be a *pallidum*. Knauf and colleagues^{22, 23} have recently reported highly destructive genital lesions, apparently sexually transmitted, in wild baboons in Tanzania; these lesions seem to be caused by a treponemal strain most closely related to subspecies *pertenue* strains.

We now return to the Parisian man with a penile chancre caused by a “yaws” strain. Is there anything special about sexual transmission, such that only the subsp. *pallidum* strains can cause genital lesions? We certainly know that *pallidum* strains can be transmitted nonvenereally; in the days before universal precautions, dentists developed chancres on the fingers after exposure to oral lesions of syphilis, and wet nurses could develop nipple chancres from nursing infants with congenital syphilis. Is there any reason to believe that *pertenue* strains should be less able to infect the skin of the penis, compared with the skin of the arms and legs? As stated by Mulligan *et al.*,²⁴ “mode of transmission appears to be defined by opportunity, rather than biology.”

Although no details have been provided about the likely source of the genital infection in the Parisian man and no further genetic characterization has been provided by Grange et al., several molecular signatures identified by Mikalova et al. have indicated a close relationship to the Gauthier strain that is considered to be a *pertenue* strain. This observation by Mikalova *et al.* provides yet another chink in the armor of the Hackett view of treponemal infections. With increased examination, clinical evidence for a clear distinction between the venereal and nonvenereal treponematoses is receding, and a biological or genetic basis for the purported clinical differences is still lacking.

It is possible that the few genetic signatures described in the strain from the Parisian man might be compatible with sexually transmitted infection with a “yaws-causing” strain, but we further propose that the accumulated evidence is very suggestive that pathogenic *Treponema* may represent a genetic continuum of organisms whose modes of transmission, clinical manifestations, and even host ranges can overlap. Molecular tools have provided the ability to examine many more strains of infectious agents rapidly and to examine them at a greater genetic depth. Such studies in the *Treponema* and in other species are likely to reveal a more ecumenical view of pathogens and their capabilities.

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