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Perspective Piece

Pinta: Latin America's Forgotten Disease?

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Abstract. Pinta is a neglected, chronic skin disease that was first described in the sixteenth century in Mexico. The World Health Organization lists 15 countries in Latin America where pinta was previously endemic. However, the current prevalence of pinta is unknown due to the lack of surveillance data. The etiological agent of pinta, *Treponema carateum*, cannot be distinguished morphologically or serologically from the not-yet-cultivable *Treponema pallidum* subspecies that cause venereal syphilis, yaws, and bejel. Although genomic sequencing has enabled the development of molecular techniques to differentiate the *T. pallidum* subspecies, comparable information is not available for *T. carateum*. Because of the influx of migrants and refugees from Latin America, U.S. physicians should consider pinta in the differential diagnosis of skin diseases in children and adolescents who come from areas where pinta was previously endemic and have a positive reaction in serological tests for syphilis. All stages of pinta are treatable with a single intramuscular injection of penicillin.

The endemic treponematoses, pinta, yaws, and bejel, are caused by spiral-shaped, not-yet-cultivable bacteria of the genus *Treponema*.[1–3] These neglected infectious diseases (NIDs), for which there are no vaccines, present a diagnostic dilemma to physicians because their clinical manifestations must be differentiated from those of other diseases that affect the skin. Moreover, serological tests cannot differentiate the endemic treponematoses from each other or from venereal syphilis, which is caused by the closely related spirochete, *Treponema pallidum* subspecies *pallidum*. Unlike venereal syphilis, the endemic treponematoses are usually acquired by children or adolescents living in poor rural communities in tropical climates (see references 1 and 2 for maps showing the geographical distribution of endemic treponematoses). Whereas venereal syphilis has a global distribution and is transmitted primarily by sexual activity, the endemic treponematoses are transmitted by nonsexual, direct skin-to-skin contact with infectious lesions.

Pinta, also known as mal del pinto or carate, is the most benign of the endemic treponematoses since it affects only the skin.[1–3] Pinta was first described in the sixteenth century in the Aztec and Carib Amerindians by Spanish conquistadors and missionaries.[4] In the 1950s, there were an estimated 1 million cases of pinta in Mexico, Central America, and northern South America. Although pinta was most highly endemic in Mexico and Columbia, cases declined in these countries due to treatment campaigns and possibly due to improvements in living standards, access to health services, and hygiene.[4,5] The World Health Organization (WHO) lists 15 countries in Latin America where pinta was previously endemic. Because of the lack of surveillance data, the current prevalence of pinta is unknown. However, some findings suggest that pinta has not disappeared. For example, in 1982 and 1983, clinical evidence of pinta was discovered in 20% of the examined inhabitants of a remote village in Panama.[6] In 1987 and 1993, pinta cases were reported in native Indians (Ticuna) living in the Amazon border region of Brazil, Columbia, and Peru.[7,8] Although the last reported case of pinta in Cuba was in 1975, an active, early pinta lesion was identified in a Cuban female who was visiting Austria in 1999.[9] On the basis of these data, it is plausible that pinta has remained endemic in some remote areas of Latin America where access to health services is limited and living standards have not yet risen.[1,2]

Like syphilis, pinta is classified into stages (see references 1–3 for pictures of the clinical stages of pinta). The primary stage is characterized by the presence of one or several papules or erythematous scaly plaques that develop about 3 weeks after infection. The body area most commonly affected is the exposed skin of the extremities. The papule or plaque, which is teeming with infectious treponemes, does not ulcerate, but expands to a diameter of 10 cm or greater. Regional lymphadenopathy is common. During early infection, serological tests for syphilis (STS) may be negative for antibodies to nontreponemal (cardiolipin) and treponemal antigens. Plaques may last for months to years and pigmentary changes may be observed in the plaques. The lesions may heal spontaneously or they may persist and become indistinguishable from the lesions of secondary pinta.

The secondary stage usually appears several months after the initial manifestations of the primary stage.[1–3] Small disseminated lesions known as "pintids" may coalesce into plaques. The pintids change from an initial red color to brown, slate-blue, black, or gray colors. Different pigmentation may occur within a pintid. The secondary lesions can remain active and infectious for a long time, leading to extensive depigmentation. STS are positive in the majority of untreated cases.

The late (tertiary) stage usually develops 2–5 years after initial infection and is characterized by pigmentary abnormalities (i.e., from dyschromic treponeme-containing lesions to achromic treponeme-free lesions), skin atrophy, and hyperkeratosis.[1–3] The degree of lesion pigmentation can be different in the same patient, resulting in a mottled appearance of the skin, which can persist lifelong. Lesions may turn into various colors (e.g., brown, gray-blue, or black). STS are positive in virtually all untreated cases.

The etiological agent of pinta, *Treponema carateum*, was not identified until over 30 years after the 1905 discovery of the related agents of venereal syphilis and yaws.[4,10–12]

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Initially, it was thought that a pathogenic fungus caused pinta. However, two observations suggested otherwise. First, laboratory studies of pinta patients' sera showed that the Wassermann test, an early STS, was positive in the majority of cases. Second, treatments that were effective against syphilis (i.e., mercury and arsenicals) were also effective against pinta. In August 1938, Sáenz and others[10] using dark-field microscopy, demonstrated the presence of spirochetes that were morphologically indistinguishable from the *T. pallidum* subspecies in exudate from a Cuban pinta patient's lesions. Subsequently, other investigators reported the presence of spirochetes in pinta lesions. Because the presence of these bacteria was insufficient to prove causality, León-Blanco performed skin inoculation experiments on himself and human volunteers with lesion exudate that contained the spirochetes and succeeded in reproducing the early manifestations of pinta.[4,12] León-Blanco also showed that some immunity to reinfection develops during pinta. Patients with late-stage pinta could not be reinfected, whereas patients whose early-stage pinta had been cured could be reinfected. Furthermore, León-Blanco and Briceno Ross and Iriarte demonstrated that syphilis and yaws patients, respectively, were not immune to infection with pinta, despite the antigenic similarity of the etiological agents.[4,11,12]

Because animal models are necessary to propagate the *T. pallidum* subspecies for experimental studies, several investigators attempted to determine if laboratory animals could be infected with *T. carateum*.[11] León-Blanco and Oteiza[13] reported infection of one of the four rabbits that they inoculated intradermally with exudate from a pinta patient's lesions. However, they were unable to successfully passage *T. carateum* from the rabbit's lesion to other rabbits. Later, Kuhn and others[14] demonstrated that chimpanzees could be infected intradermally and that these animals developed lesions similar to those of pinta patients. Unfortunately, *T. carateum* isolates are not available for study. Although phylogenetic data obtained via genomic sequencing have enabled the development of techniques to differentiate the *T. pallidum* subspecies, comparable information is not available for *T. carateum*.[1,2] Thus, despite the morphological and antigenic relatedness of the agents of pinta and syphilis, molecular knowledge of *T. carateum* is currently insufficient to warrant classification of this spirochete as a *T. pallidum* subspecies.

Pinta can be treated with a single intramuscular injection of long-acting benzathine penicillin (1.2 MU for adults; 0.6 MU for children), which renders the lesions noninfectious in less than 24 hours.[1,3,11] Information is scant concerning the efficacy of other antibiotics. Although early pinta lesions heal within several months after penicillin administration, this treatment cannot reverse the skin changes of late pinta that can stigmatize those who were infected.[4] Penicillin treatment was the mainstay for the "National Campaign to Eradicate Mal del Pinto" conducted in Mexico (1960s) and for the WHO campaign against the endemic treponematoses (1952–1964).[1,2,4] A national campaign against yaws that was conducted in Columbia in the 1950s resulted in an almost parallel decline in the incidence of both yaws and pinta, even though pinta was not specifically targeted.[5] Despite the initial success of these campaigns, the endemic treponematoses, particularly yaws, have resurged due to the lack of sustained resources and political will. The WHO has initiated a campaign to eradicate yaws by 2020 that is based on mass treatment of endemic communities with an oral dose of azithromycin, a macrolide antibiotic with demonstrated efficacy against yaws.[1,2,15] If *T. carateum* is sensitive to azithromycin as is likely, this treatment strategy could have a concomitant effect on pinta in areas of Latin America where yaws and pinta may be co-endemic. Moreover, if the endemic treponematoses were rolled into the program area of the Pan American Health Organization's (PAHO's) Strategic Plan (2014–2019) that targets selected NIDs and focuses on strengthening national capacity for screening, treatment, and surveillance of NIDs, this could facilitate elimination of pinta and yaws in PAHO member countries and would aid WHO's yaws eradication campaign (www.paho.org/hq/).

The possibility of importation of NIDs such as the endemic treponematoses increases as record numbers of migrants and refugees from Latin America continue to enter the United States for economic or political reasons.[2,3,16] Accordingly, physicians should consider pinta in the differential diagnosis of skin diseases for Latin American children and adolescents who come from areas where pinta was previously endemic and have a positive reaction in STS.[3,16] This is critical to guide treatment as well as to avoid the inadvertent psychological harm and legal ramifications that can result from making an incorrect diagnosis of syphilis. Although pinta may be a forgotten disease, it is unlikely to be extinct.[9,17]

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