REVIEW ARTICLE

History of Syphilis

Bruce M. Rothschild

The Arthritis Center of Northeast Ohio, Youngstown, and Northeastern Ohio Universities College of Medicine, Rootstown, Ohio; Carnegie Museum of Natural History, Pittsburgh, Pennsylvania; and University of Kansas Museum of Natural History, Lawrence, Kansas

Evidence-based research now allows clear separation of syphilis from other diseases in its class of treponematoses. Examination of skeletons from populations with clinically diagnosed bejel and yaws revealed bone alterations distinctive to those diseases, clearly separating them from alterations due to syphilis, transcending the limitations of current DNA and immunologic technologies. These insights allowed confident identification of the New World origin of syphilis. Absence of skeletal evidence of any treponemal disease in continental Europe before the time of Columbus excludes it as site of origin of syphilis. Treponemal disease appears to have originated in East Africa with late transmission to England, perhaps as a complication of the slave trade. The original treponemal disease apparently spread from Africa through Asia, entering North America. Approximately 8 millennia later, it mutated to syphilis. Presence of skeletal evidence of syphilis at the site in the Dominican Republic where Columbus landed suggests the route by which it was transmitted to the Old World.

The dichotomy between science and the folk history of treponemal disease and a resistance to data-based analysis have been at the very heart of the controversy about the origins of syphilis [1–15]. Those speculations can be divided into 3 hypotheses, 2 of which pertain solely to the European question [2, 3, 16–18]. Was syphilis a contagion from the New World (i.e., the Columbian hypothesis), or was it a mutation of another treponematosis already present in Europe (i.e., the pre-Columbian hypothesis)? The third hypothesis about treponematosis suggests that syphilis was transported from the Old to the New World. The key questions would appear to be whether any treponemal disease was present in pre-Columbian Europe (i.e., before 1492), and if pre-Columbian presence of treponematosis were confirmed, was it syphilis?

ACTUAL RECOGNITION OF DISEASE

Before examining the biologic evidence that the 3 major pathologic treponematoses actually represent distinct diseases, what is the anthropologic evidence that any treponemal disease existed in pre-Columbian Europe? Fortunately, treponemal disease leaves an osseous signature, most prominently marked by periosteal reaction, tibial remodeling (sabre shin formation), and, occasionally, by bone destruction, referred to as "gumma" [19–21].

Recognizing periosteal reaction and distinguishing it from postmortem bone damage (taphonomy) is an art with a learning curve that has confounded many "seasoned" anthropologists [8, 11, 22–24]. When examination of the same set of skeletons results in reports of 0%–100% involvement [9], it is obvious that there is a severe problem with technique standardization and reproducibility. Validity could be established by use of an independent measurement, but what measures bone surface integrity? Microscopic examination of the cut surface of bone clearly distinguishes periosteal reaction and taphonomic (postmortem) damage.

However, I have devised an approach unfettered by previous (and now invalidated) perceptions of how to distinguish taphonomic damage. Periosteal reaction, by definition, is a process that occurs external to the original cortical margin [25]. Identify that margin and it is generally quite easy to assess whether any bone alteration is present, internal or external to that cortical surface. The resultant approach, which will henceforth be referred to as "macroscopic," has demonstrated re-

Received 31 October 2004; accepted 23 December 2004; electronically published 1 April 2005.

Reprints and correspondence: Dr. Bruce M. Rothschild, The Arthritis Center of Northeast Ohio, 5500 Market St., Youngstown, OH 44512 (bmr@neoucom.edu).

Clinical Infectious Diseases 2005; 40:1454–63

1058-4838/2005/4010-0011$15.00

markable reproducibility, yielding data clearly comparable across population lines [4, 19, 26, 27].

An independent technique confirmed the accuracy of the macroscopic assessment. Noncolligative properties of matter, such as entropy, depend on qualitative aspects of structure, not quantitative ones [28, 29]. As a surface-dependent thermodynamic property, entropy is independent of the extent and amount of damage but reflects only surface alteration—taphonomic damage (e.g., loss) or periosteal reaction (e.g., accretion) [9, 28, 29]. Uniformity of thermal emission of the entire tibia was assessed by heating bones to 30°C and noting time for heat dissipation to 27°C. Normal bone internal to the periosteal membrane (exposed by taphonomic damage) has a different rate of heat dissipation than does bone with an intact outer layer (periosteum). Bone architecture, characteristic of endothermic individuals, results in uniform thermodynamic characteristics [30]. Pathologic alteration of that outer layer (periosteal reaction) produces a different pattern [9]. More importantly, there was no overlap in the time course of taphonomically affected bone and that of bone with periosteal reaction [9], as measured by the reproducible technique described above on 261 tibia. Not only is the technique precise, it is also accurate.

Because bone has only a limited repertoire of responses to any stressor (e.g., disease or injury) [25, 27, 31], alterations in a single bone (unless pathognomonic) are unlikely to allow specific diagnosis, even for a category of disease (e.g., infection or neoplasia), let alone variety (e.g., syphilis vs. yaws). Examination of the skeleton of a single individual is compromised by the "outlier phenomenon." If 1 in 20 affected individuals has a variant form of a disease (e.g., spondyloarthropathy) that mimics another disease (e.g., rheumatoid arthritis), chance selection of that outlier would lead to misdiagnosis. However, examination of the population reveals a spectrum of manifestations for each disease [25, 27, 31]. That spectrum is highly characteristic, and the outlier simply becomes a part of the spectrum and can be recognized as such [20, 21, 27, 31]. This has been clearly documented for a series of diseases, including rheumatoid arthritis, spondyloarthropathy, calcium pyrophosphate deposition disease, tuberculosis, leprosy, and the treponematoses [20, 21, 27, 31].

Examination of afflicted populations reveals identical spectra, reproducible even across species lines [27, 31]. It overcomes the outlier issue and adds an additional testable characteristic: population frequency. Although trauma can cause isolated periosteal bumps, involvement of >1 bone in a given individual would be uncommon [25, 27, 31]. Examination of populations might reveal isolated periosteal bumps but no widespread involvement, with the exception of cases involving combat or battered child syndrome. Few phenomena or diseases actually produce nonfocal periosteal reaction in more than a very small percentage of individuals [25, 27, 31]. Paget disease, for example, can occasionally produce periosteal reaction (in association with other findings). However, it has never been found with frequency greater than 1% in populations under the age of 40 years. Thus, the presence of periosteal reaction in >1% of individuals under the age of 40 years should not be attributed to Paget disease. The cortical thickening in persons with Paget disease affects the posterior portion, in contrast to anterior tibial cortical thickening in persons with treponematoses [25, 27, 31].

Few diseases actually produce periosteal reaction, except as very isolated occurrences in afflicted populations [25, 27, 31]. Exceptions include treponematoses, hypertrophic osteoarthropathy (a phenomenon related to intrathoracic disease, cirrhosis, and inflammatory bowel disease), and perhaps renal failure [4, 25, 27, 31–33]. Those disorders produce a periosteal reaction that often affects the entire bone, but it may be limited to 1 region (e.g., diaphyseal or metaphyseal) and not be focal.

TREPONEMAL DISEASE IN EUROPE

Proof of European origins of syphilis would first require proof that any treponemal disease existed in pre-Columbian Europe. Actually, there is little evidence even of periosteal reaction, let alone of its existence as a population phenomenon in pre-twelfth century A.D. Europe [34, 35]. All evidence represents isolated cases for which alternative diagnoses are more likely [5, 8, 14, 27, 36–41].

The individual from Lisieux, France, from the fourth century A.D. described by Blondiaux and Alduc-le Bagousse [8] had parietal nodularity, suggesting pyogenic osteomyelitis. The bones lacked frontal involvement characteristic of syphilis. Peripheral periosteal reaction was focal in nature, which is more suggestive of trauma. Henneberg and Henneberg [11] suggest that there was a high frequency of periosteal reaction in Metaponte, Italy, in the sixth century B.C.. However, the most extensively involved cases had quite minimal involvement, and focal and taphonomic confusion was suspected as a diagnosis [34]. Hurley et al. [36] and Power [37] separately diagnosed syphilis in a 14th century A.D. individual aged 12–13 years. However, bone changes were unlike those associated with treponemal disease, and on examination, they were found to be typical of lytic damage due to histiocytosis.

Findings from the hard palate lesion from the 11th–14th century A.D. and thickened skull with pyogenic tibial osteomyelitis from the 12th–14th century A.D. from Poland described by Gladykowska-Rzeczycka [38] are certainly not diagnostic of syphilis. The isolated first or second century B.C. skull from Agripalle, India, has tabula externa scars [39] that are difficult to distinguish from taphonomic changes and are not diagnostic for syphilis [27]. Zhang [40] reported a skull from the Song dynasty–era (960–1279 A.D.) Fujiang province with frontal and parietal lesions, which he believed were similar in appearance

Figure 1. Lateral view of proximal tibia. Periosteal reaction is prominent.

to caries sicca. Again, this was not a definitive diagnosis and represented the only possible case he found in all of China. A macroscopically nonspecific condition in bone fragments from a knight, Gottfried von Cappenberg (who lived from 1097 to 1127 A.D. but who traveled extensively), were attributed by Kuhnen et al. [41] to an isolated case treponarid (bejel), but not syphilis.

Attempts to attribute conditions to syphilis in isolated individuals would, at best, identify outliers of a different disease, because the population spectrum of periosteal reaction is much rarer than that found for any of the treponematoses. Furthermore, it is critical to distinguish periosteal reaction from fetal membrane calcification. The latter led to the famous misdiagnosis [5] of a fifth century A.D. lithopedian as a case of congenital syphilis in the abdomen of a 53-year-old woman.

Cases from 13th century A.D. England and Ireland are more complicated. Something new was found: a high frequency (20%–40%) of polyostotic periosteal reaction in the population that was already common among subadults [15, 35, 42]. The frequency and character of this reaction at an English monastery and at other sites were much more extensive than what is found for syphilis (see Skeletal Criteria, below) but are classic for another treponemal disease, yaws [20, 21, 26, 42, 43].

A 1987 report of a case of treponemal disease in an 11,000-year-old bear [44] was possible because immunologic study confirmed that treponemal disease was responsible. Neither the immunologic studies that were state-of-the-art then nor DNA analyses now allow distinguishing among the treponematoses [45–47]. The reporting scientists suggested a diagnosis of yaws—for which the current criteria (see Skeletal Criteria, below) [27, 48] allow diagnostic confidence of 70%—as only an isolated case due to this rare species. But questions about a specific diagnosis of treponematosis in a 13th century A.D. English skeleton are really tangential. Columbus came from continental Europe, where there is no evidence of any cases of trepone-

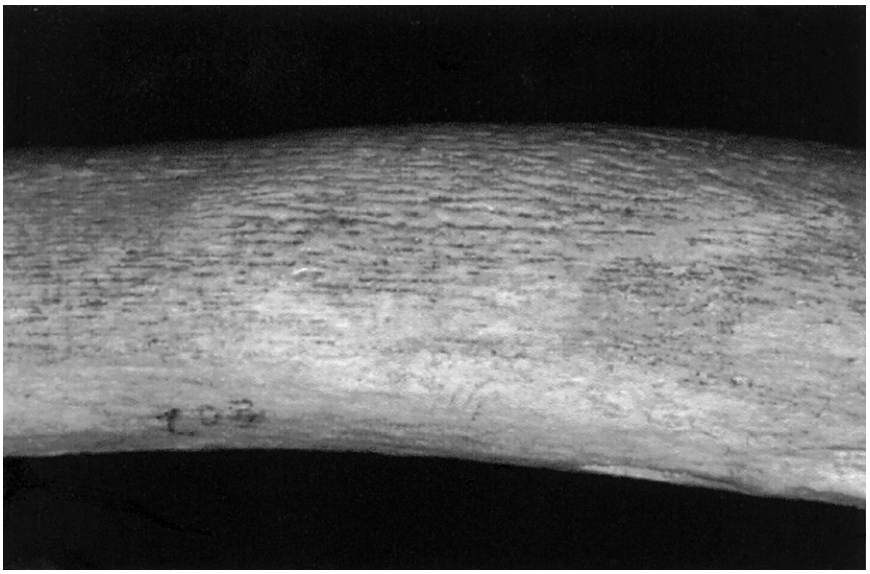

Figure 2. Lateral view of proximal tibia showing subtle periosteal reaction

Table 1. Comparative characteristics of osseous involvement in treponemal disease.

Variable	Treponemal disease		
	Syphilis	Yaws	Bejel
No. of samples	296	290	85
Rate of periosteal reaction in at-risk population, %	2–13	20–40	20–40
Youth affected	Rare	Common	Common
Skull lesions	Present	Present	Present
Sabre shin	Present	Present	Present
Sabre shin without periostitis[a]	Occurs	Absent	Absent
Unilateral tibial involvement	Yes	No	No
Bone groups affected, mean no.	1.3–2.3	3.0–7.0	1.5–2.7
Mean no. of bone groups affected of $\geqslant 3$[b]	No	Yes	No
Hand or foot commonly affected	No	Yes	No

NOTE. Data are from [19–21, 77].

[a] Indicates a degree of remodeling such that there is no longer any surface evidence of periosteal reaction.

[b] Tibia(e), fibula(e), and femora(e), etc., each represent a bone group independent of unilaterality of bilaterality of involvement.

matosis prior to 1492 [34, 35]. Treponematosis originated in Africa in the form of yaws [48]. It passed through Asia to North America, spinning off a mutation (in the form of bejel) on the way [49]. Bejel also passed through Asia into North America [50]. However, it was in North America that another mutation took place, creating syphilis [51].

ORIGINS OF TREPONEMAL DISEASE

Kenya National Museum 1808 was a *Homo erectus* whose cause of death was originally diagnosed as a vitamin A overdose [52]. However, the distinguished scientists who made the original report had actually never seen a case of bone afflicted by hypervitaminosis A (M. R. Zimmerman, personal communication). Bone reaction in hypervitaminosis A is calcification within tendons starting at the site of enthesial attachment [27, 31], not periostitis [27, 31, 53]. That recognition and presence of periosteal reaction from another *H. erectus* from that area revealed a disease that epidemiologically could only represent yaws [48].

It is perceived that bejel represented an early mutation of yaws as it passed through northeast Africa [51]. Confidence in diagnoses of bejel and yaws through time is high because the reproducibility of findings in these diseases in general [27, 31, 32] and for treponematoses in particular [4, 26, 50, 51] through time and geography has been clearly demonstrated. Curiously, continental Europe stayed free of treptonemal disease until it was contaminated by Columbian syphilis [34, 35]. Even the British Isles remained free of treponemal disease until the 13th century A.D., when yaws appeared [42], possibly related to initiation of a slave trade from yaws-afflicted West Africa.

WHAT IS HISTORY?

History is a complicated concept and is often the product of the victors' (e.g., in a conflict) desires to control how they or their causes are portrayed. The history of syphilis, therefore, can be approached from several perspectives: by name ascription, by actual origins, and according to the efforts to disassociate from it.

LITERARY RECORD

The actual designation "syphilis" originates in an ancient myth about a shepherd named Syphilis [54]. In 1530, Girolamo Frasastoro first derived the appellation "syphilis sive morbus gallicus." Because of the associated rash (pox) and as a means to distinguish the disease from smallpox, the term "great pox" arose. Although that term saw 2 centuries of use, syphilis early on became a cultural embarrassment, which prompted various attributions: Germans and English called it "the French pox"; Russians, "the Polish sickness"; Poles, "the German sickness";

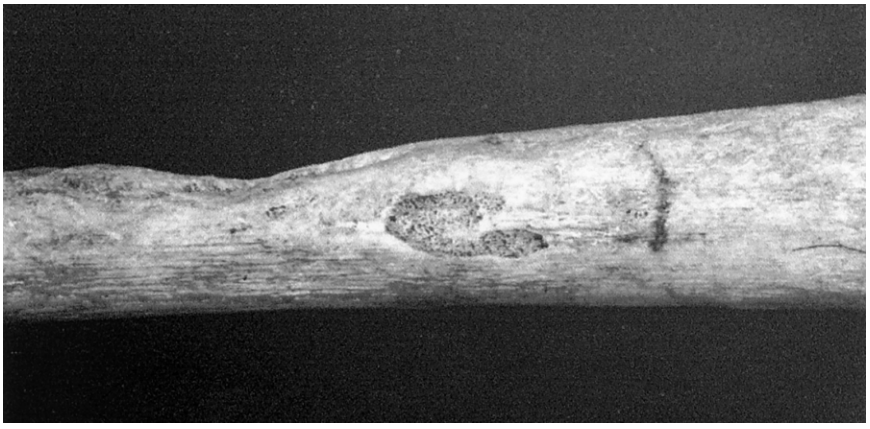

Figure 3. Lateral view of tibia showing gummatous defect with periosteal reaction

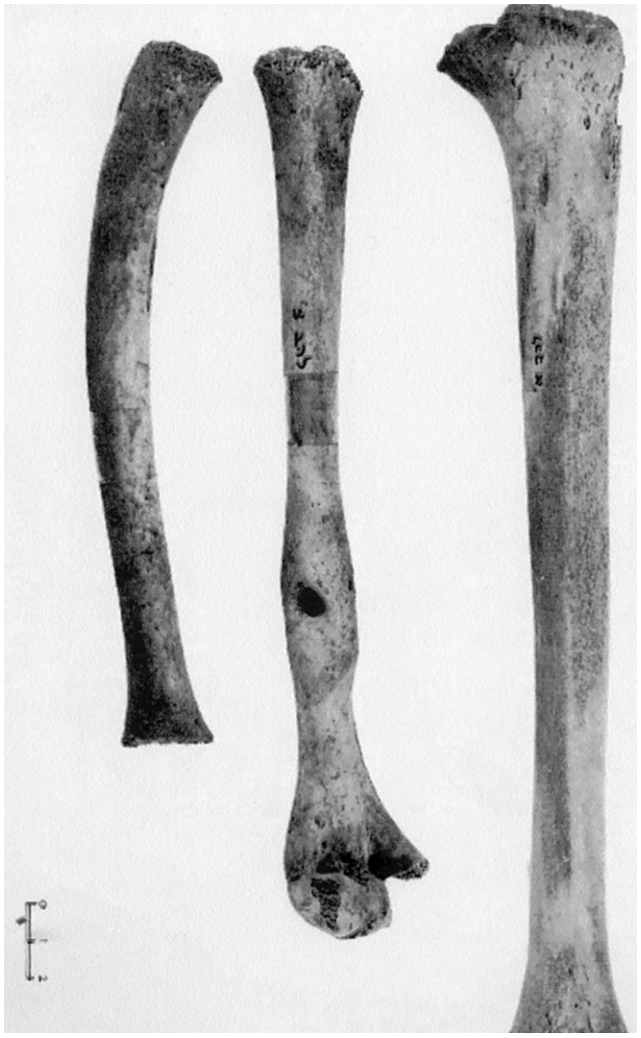

Figure 4. Posterior views of radius, ulna, and tibia showing ulnar bowing, ulnar draining gumma, and tibial periosteal reaction.

French, "the Neapolitan sickness"; Flemish, Dutch, Portuguese, and North Africans, "the Spanish sickness" or "the Castillian sickness"; and the Japanese, "the Canton rash" or "the Chinese ulcer" [1, 2, 55].

Did syphilis develop independently in both the New and Old Worlds? Did Columbus bring syphilis back to Europe? Was syphilis a previously misdiagnosed European disease that was subsequently transmitted to the New World? Was the early 16th century A.D. European syphilis epidemic in fact not new, and did its recognition simply reflect a new ability to distinguish syphilis from leprosy?

EVIDENCE-BASED ANALYSIS

Preconceived notions have, until recently, compromised any opportunity to answer the questions above [56]. Furthermore, controversy raged as to whether syphilis was caused by a specific trepomene (e.g., *Treponema pallidum* as opposed to *Treponema pertenue*) or whether it was simply a climate-determined manifestation or a strain variation. Clarification of this question—and, therefore, of the origin of syphilis—has been complicated because of the diagnostic vagueness of the historical written record [1, 6, 7, 57, 58]. Laboratory analyses have not been helpful. Metabolic, histologic, microbiologic, immunologic, and even sophisticated DNA techniques have failed to distinguish between yaws, bejel (nonvenereal syphilis), and venereal syphilis [45–47]. The unanswered question in DNA analysis, however, relates to the choice of genome chosen for analysis. Although DNA analysis has allowed confident confirmation of the diagnosis of treponematosis, distinguishing among the treponemal diseases still

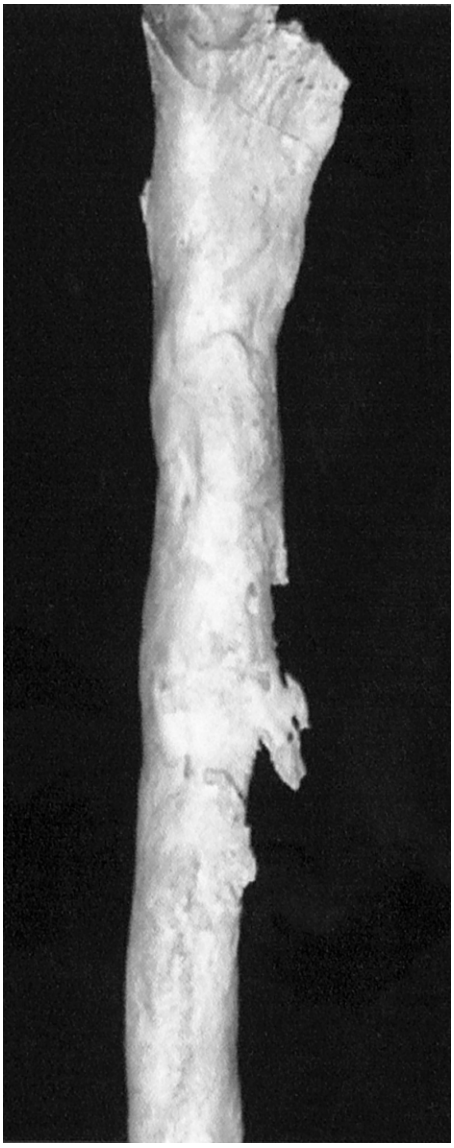

Figure 5. Anterior view of the midfemur showing spiculated periosteal reaction.

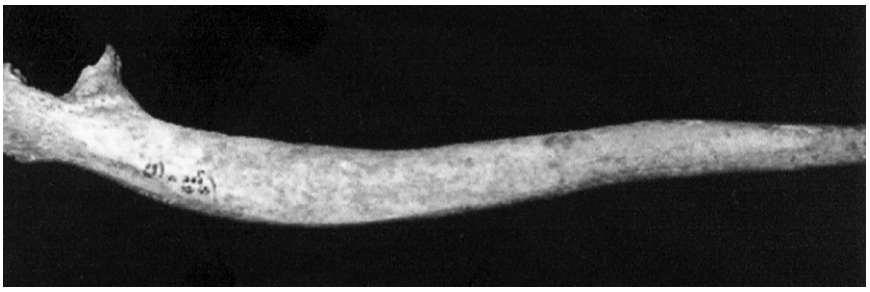

Figure 6. Lateral view of ulna showing cortical thickening and bowing

eludes us. Given that the *T. pallidum* genome has been sequenced [59], availability of the *T. pertenue* genome sequence should resolve that question for those who still have doubts.

Syphilis, as one form of pathologic treponematosis, has a skeletal signature. It alters the appearance of bones in a highly specific manner, which one can find if one knows how to look [20, 21]. The peculiar skull radial scarring and sabre shin alterations appear to be specific for treponematosis, but such findings do not allow one to distinguish among the types of treponematosis, and use of periosteal reaction has limited specificity. The special skeletal appearance of syphilis, however, is recognizable as a population phenomenon. "Outliers" in any disease process may mimic another disease (e.g., the pseudorheumatoid presentation of Wegener granulomatosis) [60].

Pre-Columbian evidence of treponemal disease abounds in cemeteries in both the New and Old World [8–15, 56, 61–69], with diagnoses given for what were perceived to have been isolated individuals with periosteal reaction. Population analysis, however, provides an opportunity to confidently distinguish among the treponematoses [19, 20].

Treponematoses are rather readily recognized as a population-based phenomenon on the basis of what percentage of the population manifests the condition. Alteration of the outer layer of bone (periosteum) is referred to as "periosteal reaction" (figure 1), which may be subtle (figure 2). Bone involvement occurs in 2%–13% of individuals with syphilis, as determined both by radiologic examination [25] and by examination of defleshed skeletons [20, 21]. The other pathologic treponemal diseases (yaws and bejel) have population frequencies of bone involvement of 20%–40%, easily facilitating distinguishing these diseases from syphilis. Although pinta has been referred to as a separate disorder with pathology limited to the skin, review of the literature about pinta actually revealed the presence of bone involvement due to pinta to be no different from that due to the endemic treponeme found in the same area [70].

Infantile cortical hyperostosis (i.e., Caffey disease), thyroid acropachy, and hypertrophic osteoarthropathy do have significant nonfocal periosteal reactions, but these phenomena have low population frequencies and very characteristic patterns of periosteal reaction [25, 71, 72]. Caffey disease affects the jaws and clavicles of children—areas that are unaffected by treponemal disease [25, 73–75]. Thyroid acropachy is a disorder

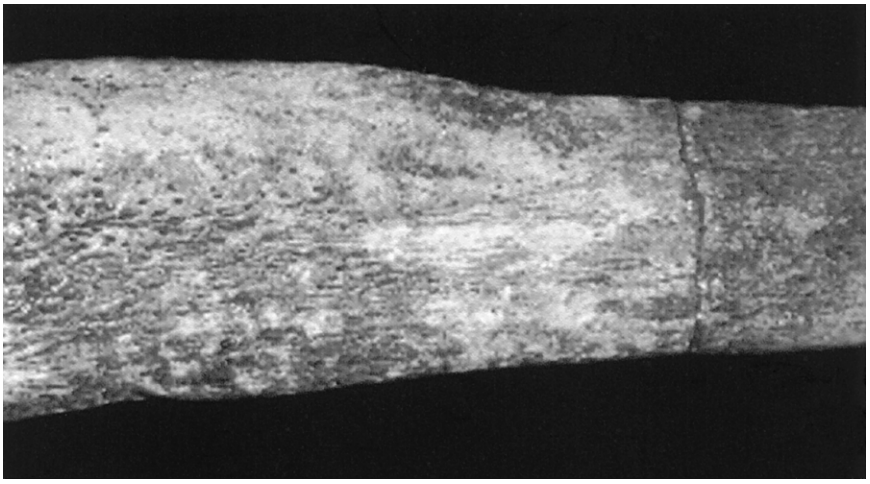

Figure 7. Lateral view of midportion of tibia showing sabre shin with residual surface periosteal reaction

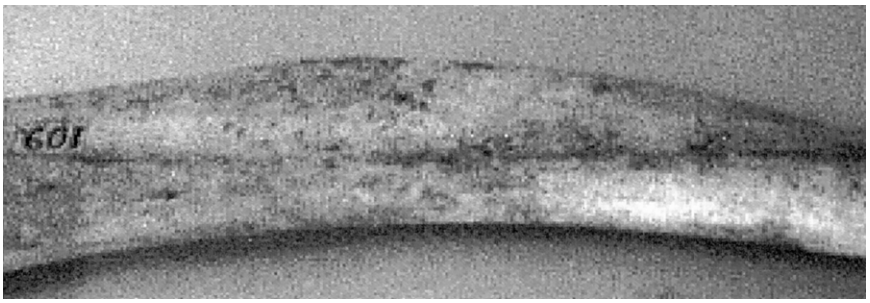

Figure 8. Lateral view of tibia showing sabre shin with total remodeling of surface bone

localized to the distal skeleton (hands and feet) and is quite distinguishable from the tibial predilection of syphilis [25, 76]. Hypertrophic osteoarthropathy is a predominantly intrathoracic disease–related polyostotic disorder with a unique predilection. It never affects the proximal diaphyseal region of the tibia unless the distal portion is also affected [32].

DISTINGUISHING THE TREPONEMATOSES

"Phenotype" and "genotype" are generally understood terms. To that terminology, I would offer the term "osseotype" (table 1), which describes the skeletal manifestations of disease. Examination of skeletons from populations with one documented treponematosis allowed identification of diagnostic criteria for distinguishing among them [20].

The autopsy-documented Hamman-Todd skeletal collection (Cleveland Museum of Natural History, Ohio) provided an opportunity to characterize the skeletal manifestations of syphilis [20, 21], with neurosyphilis and cardiovascular syphilis providing comparison groups. Because bejel has been documented as the only treponemal disease present among the eastern Mediterranean Bedouin [16, 17, 78–80], examination of cemeteries dated 1800–1849 A.D. [80] from that area allowed the character of this disease to be defined [77]. Similarly, yaws was documented as the only treponemal disease present in the region before 1668 [1, 81, 82].

SKELETAL CRITERIA

Examination of these populations revealed some shared characteristics and some that reproducibly distinguished among the treponematoses. Periosteal reaction (figures 1 and 2) is the primary osteologic clue, but variety (figures 3–6) of periosteal reaction (e.g., spiculated or thickened) does not allow the treponematoses to be distinguished. Similarly, gumma and stellate frontal bone scars do not differ in character or frequency among these populations.

Criteria unique to syphilis were the frequency of osseous involvement in the population and the extent of remodeling of the characteristic sabre shin lesion [20, 83–85]. These frequencies and osseotype characteristics are independent of sex and ethnicity [4, 26, 32, 50, 51]. Two percent to 13% of adults with syphilis had periosteal reaction, compared with 20%–40% of individuals with bejel or yaws. Less than 5% of children with syphilis have skeletal involvement, compared with the 10%–20% frequency of skeletal involvement in children with yaws and bejel. Although sabre shin occurs in all forms of treponemal disease (figure 7), only in syphilis can sufficient remodeling occur to hide all surface signs of periosteal reaction (figure 8). Syphilis is pauciostotic (the mean number of affected bone groups was 2), and hands and feet are rarely affected. This contrasts with polyostotic involvement in yaws, for which there is frequent hand and foot involvement.

Although tooth-related and congenital manifestations appear to be specific to syphilis, the occurrence of these conditions and the preservation of materials in the archeologic record are so infrequent as to preclude population comparisons [86–88]. Alterations at the epiphyseal line are extremely rare [89] and would be identified only if the affected individual had died prior to the routine bone remodeling that erases all evidence of congenital disease over the course of several months of growth [90]. Although Dutour and colleagues [5, 91] reported what they thought was a case of syphilis from medieval France, the case occurred in a lithopedian with calcified membranes and did not actually have the requisite periosteal reaction.

ORIGIN OF SYPHILIS

The osseotype characteristics of syphilis are absent in specimens from pre-Columbian Europe, Africa, and Asia [61, 91–93]. With regard to North and South America, these characteristics have been identified in North America as far back as 8000 years ago in sites as disparate as Windover, Florida; Frontenac Island, New York; Libben, Ohio; and Amaknak, Alaska [19, 92].

Somewhere between 2000 and 1800 years ago, the first identified osseotype of syphilis occurred [49]. The Mogollan Ridge proved to be the dividing line with respect to both the first appearance of syphilis and the climatic change that may have been responsible for the event [93, 94]. Its osseous signature is recognized to have occurred 1500 years ago in New Mexico, 1000 years ago in Wisconsin, 800 years ago in Ecuador, 700

years ago in Florida, and 600 years ago in Michigan and West Virginia [49].

It is clear that syphilis was present in the New World at the time of Columbus' arrival [19, 49]. Especially pertinent is documentation of syphilis in the area where he actually landed, the Dominican Republic [95]. The periosteal reaction characteristic of syphilis has been recognized in 6%–14% of skeletons from the El Soco (800 A.D.), Juan Dolio (1400 A.D.), La Caleta (1200–1300 A.D.), Atajadizo (1200–1300 A.D.), and Cueva Cabrera (1200–1300 A.D.) sites. The average number of bone groups affected ranged from 1.7 to 2.6. Sabre shin remodeling was often so marked as to erase all surface indications of periosteal reaction. The osseous evidence documents the presence of syphilis in the Dominican Republic where Columbus landed. Columbus' crew clearly had the opportunity and means to contract and spread the venereal disease we now call syphilis.

Acknowledgments

Appreciation is expressed to unnamed reviewers whose cogent queries directed appropriate clarification in this manuscript.

Financial support. The Arthritis Center of Northeast Ohio.

Potential conflicts of interest. B.M.R.: no conflicts.

References

1. Baker BJ, Armelagos GJ. The origins and antiquity of syphilis. Curr Anthropol **1988**; 29:703–20, 732–7.
2. Goff CW. Syphilis. In: Brothwell DR, Sandison AT, eds. Disease in antiquity. Springfield, IL: Charles C. Thomas, **1967**:170–87.
3. Harrison LW. The origin of syphilis. Brit J Vener Dis **1959**; 35:1–7.
4. Rothschild BM, Rothschild C. Pseudoscience and treponemal disease in the Western Pacific. Curr Anthropol **1998**; 40:69–71.
5. Dutour O, Panuel M, Palfi G, Berato P. Diagnostic differentiel des lesions observees sur le foetus Cristobal. In: Dutour O, Palfi G, Berato J, Brun J-P, eds. L'Origin de la Syphilis en Europe—Avant ou apres 1493. Toulon, France: Centre Archeologique du Var, **1995**:139–44.
6. Steinbock RT. Palaeopathological diagnosis and interpretation. Springfield, IL: Thomas, **1976**.
7. Quetel C. History of syphilis. Baltimore, MD: Johns Hopkins University Press, **1990**.
8. Blondiaux A, Bagousse A-L. Une treponematose du Bas-Empire romain en Normandie. In: Dutour O, Palfi G, Berato J, Brun J-P, eds. L'Origin de la Syphilis en Europe—Avant ou apres 1493. Toulon, France: Centre Archeologique du Var, **1995**:99–100.
9. Cook DC. Subsistence and health in the lower Illinois Valley: osteological evidence. In: Cohen MN, Armelagos GJ, eds. Paleopathology at the origins of agriculture. Orlando, FL: Academic Press, **1984**:235–69.
10. Haltrom WL, Shands AR Jr. Evidences of syphilis in Mound Builders' bones. Arch Pathol **1938**; 25:228–42.
11. Henneberg M, Henneberg RJ. Treponematosis in an ancient Greek colony of Metaponto, southern Italy, 580–250 BCE. In: Dutour O, Palfi G, Berato J, Brun J-P, eds. L'Origin de la Syphilis en Europe—Avant ou apres 1493. Toulon, France: Centre Archeologique du Var, **1995**: 92–8.
12. Powell ML. Treponematosis before 1492 in the United States of America: why call it syphilis? In: Dutour O, Palfi G, Berato J, Brun J-P, eds. L'Origin de la Syphilis en Europe—Avant ou apres 1493. Toulon, France: Centre Archeologique du Var, **1995**:158–63.
13. Roberts C. Treponematosis in Goucester, England: a theoretical and practical approach to the pre-Columbian theory. In: Dutour O, Palfi G, Berato J, Brun J-P, eds. L'Origin de la Syphilis en Europe—Avant ou apres 1493. Toulon, France: Centre Archeologique du Var, **1995**: 101–8.
14. Sanford MK, Bogdan G, Weaver DS, Sappelsa L. Possible treponematoses from the pre-Columbian Caribbean and costal North Carolina. In: Dutour O, Palfi G, Berato J, Brun J-P, eds. L'Origine de la Syphilis en Europe Avant ou Apres 1493? Toulon, France: Centre Archeologique du Var, **1995**:164–8.
15. Stirland A. Evidence for pre-Columbian treponematosis in Medieval Europe. In: Dutour O, Palfi G, Berato J, Brun J-P, eds. L'Origin de la Syphilis en Europe—Avant ou apres 1493. Toulon, France: Centre Archeologique du Var, **1995**:109–15.
16. Hudson EH. Non-venereal syphilis: a sociological and medical study of Bejel. London: Livingston, **1958**.
17. Hudson EH. The treponematoses or treponematosis? Brit J Vener Dis **1958**; 34:22–4.
18. Cockburn TA. The origin of treponematoses. Bull World Health Org **1961**; 24:221–8.
19. Rothschild BM, Rothschild C, Hill MC. Origin and transition of varieties of treponemal disease in the New World. Amer J Phys Anthropol **1995**; 36(Suppl 20):185.
20. Rothschild BM, Rothschild C. Distinction des maladies treponemiques: Syphilis, Pian et Bejel a partir des differences de leurs atteintes osseuses respectives. In: Dutour O, Palfi G, Berato J, Brun J-P, eds. L'Origin de la Syphilis en Europe—Avant ou apres 1493. Toulon, France: Centre Archeologique du Var, **1995**:68–71.
21. Rothschild BM, Rothschild C. Treponemal disease revisited: skeletal discriminators for Yaws, Bejel, and venereal syphilis. Clin Infect Dis **1995**; 20:1402–8.
22. Schultz M. Comparative histopathology of syphilitic lesions in prehistoric and historic human bones. In: Dutour O, Palfi G, Berato J, Brun J-P, eds. L'Origine de la Syphilis en Europe Avant ou Apres 1493? Toulon, France: Centre Archeologique du Var, **1995**:63–7.
23. Rothschild BM. Preconceived notions and hypothesis testing: holes in the blue hole. Chungara, Revista de Antropologia Chilena **2000**; 32: 141–6.
24. Rothschild BM, Rothschild C. Thermodynamic resolution of periosteal reaction and taphonomic change. Reumatismo **2003**:195–2001.
25. Resnick D. Diagnosis of bone and joint disorders. Philadelphia: Saunders, **2002**.
26. Rothschild BM, Heathcote G. Characterization of the skeletal manifestations of the treponemal disease, Yaws, as a population phenomenon. Clin Infect Dis **1993**; 17:198–203.
27. Rothschild BM, Martin LD. Skeletal impact of disease. Bull New Mexico Mus Natl Hist (in press).
28. Bull HB. An introduction to physical biochemistry. Philadelphia: FA Davis, **1964**.
29. Lewis GN, Randall M. Thermodynamics and the free energy of chemical substances. New York: McGraw Hill, **1923**.
30. Chinsamy A, Rich T, Vickers-Rich P. Polar dinosaur bone histology. J Vert Paleontol **1998**; 18:385–90.
31. Rothschild BM, Martin L. Paleopathology: disease in the fossil record. London: CRC Press, **1993**.
32. Rothschild BM, Rothschild C. Recognition of hypertrophic osteoarthropathy in skeletal remains. J Rheumatol **1998**; 25:2221–7.
33. Rothschild C, Rothschild B, Hershkovitz I. Clues to recognition of kidney disease in archeologic record: characteristics and occurrence of leontiasis ossea. Reumatismo **2002**; 54:133–43.
34. Rothschild BM, Coppa A, Petrone PP. Like a virgin: absence of rheumatoid arthritis and treponematosis, good sanitation and only rare gout in Italy prior to the 15th century. Reumatismo **2004**; 56:61–6.
35. Rothschild BM, Ruhli F, Rothschild C, et al. Virgin Europe: periosteal reaction prior to the 15th century and the potential influence of slavery. Paleobios (in press).
36. Hurley MF, Scully OM, McCutcheon SW. Late Viking age and medieval Waterford: excavations 1986–1992. Waterford, Ireland: Waterford, **1994**.

37. Power C. The spread of syphilis and a possible early case in Waterford. Archaeology of Ireland **1992**; 6:20–1.
38. Gladykowska-Rzeczycka JJ. Syphilis in ancient and medieval Poland? In: Dutour O, Palfi G, Berato J, Brun J-P, eds. L'Origine de la Syphilis en Europe Avant ou Apres 1493? Toulon, France: Centre Archeologique du Var, **1995**:116–8.
39. Rao VV, Vasulu TS, Rector Bagbu AD. Possible paleopathological evidence of treponematosis from a megalithic site at Agripalle, India. Am J Phys Anthropol **1996**; 100:49–55.
40. Zhang Z. The skeletal evidence of human leprosy and syphilis in ancient China. Acta Anthrop Sinica **1994**; 13:294–9.
41. Kuhnen C, Schultz M, Bosse A, Weber A, Preuschoft H, Muller KM. Endemische Syphilis an den rekognoszierten Reliquien des Gottfried von Cappenberg: eine palaeopathologissche Studie. Der Pathologe **1999**; 20:292–6.
42. Rothschild C, Rothschild BM. Patterns of periosteal reaction in England from Roman through Elizabethan epochs. J Paleopath **1995**; 7:130.
43. Zimmer C. Can genes solve the syphilis mystery? Science **2001**; 292: 1091.
44. Rothschild BM, Turnbull W. Treponemal infection in a Pleistocene bear. Nature **1987**; 329:61–2.
45. Fieldsteel HA. Genetics of treponema. In: Schell RF, Musher DM, eds. Pathogenesis and immunology of treponemal infection. New York: Marcel Dekker, **1983**:39–55.
46. Noordhoek GT, Wieles B, van der Sluis JJ, van Embden JD. Polymerase chain reaction and synthetic DNA probes: a means of distinguishing the causative agents of syphilis and yaws? Infect Immun **1990**; 58:2011–3.
47. Norris SJ. Polypeptides of *Treponema pallidum:* progress toward understanding their structural, functional, and immunologic roles. The *Treponema pallidum* Polypeptide Research Group. Microbiol Rev **1993**; 57:750–79.
48. Rothschild BM, Hershkovitz I, Rothschild C. Origin of yaws in the Pleistocene. Nature **1995**; 378:343–4.
49. Rothschild C, Rothschild BM. Occurrence and transitions among the treponematoses in North America. Chungara, Revista de Antropologia Chilena **2000**; 32:147–55.
50. Molto Jel, Rothschild BM, Woods R, Rothschild C. Unique aspects of west coast treponematosis. Chungara **2000**; 32:1–12.
51. Rothschild BM, Rothschild C. Yaws, mine and ours: treponemal disease transitions in prehistory. J Comp Human Biol **1994**; 45:S115.
52. Walker A, Zimmerman MR, Leakey RE. A possible case of hypervitaminosis A in *Homo erectus.* Nature **1982**; 296:248–50.
53. Walker A, Zimmerman MR, Leakey RE. Nature **1982**; 296:248–50.
54. Baumgartner L, Fulton JF. A Bibliography of the poem "Syphilis sive Morbus Gallicus" by Girolamo Fracastoro of Verona. New Haven: Yale University Press, **1935**.
55. Hayden D. Pox: genius, madness, and the mysteries of syphilis. New York: Basic Books, **2003**.
56. Hackett CJ. Diagnostic criteria of syphilis, yaws and treponarid (treponematoses) and some other diseases in dry bones. Berlin: Springer-Verlag, **1976**.
57. Bourrieres C, Devant O. "La syphilis maligne precoce: Une explication a l'epidemie de 1493?" In: Dutour O, Palfi G, Berato J, Brun J-P, eds. L'Origin de la Syphilis en Europe—Avant ou apres 1493. Toulon, France: Centre Archeologique du Var, **1995**:170–3.
58. Froment A. Les treponematoses: une perspective historique. In: Dutour O, Palfi G, Berato J, Brun J-P, eds. L'Origin de la Syphilis en Europe—Avant ou apres 1493. Toulon, France: Centre Archeologique du Var, **1995**:260–8.
59. Fraser CM, Norris SJ, Weinstock GM, et al. Complete genome sequence of *Treponema pallidum,* the syphilis spirochete. Science **1998**; 281:375–88.
60. Rothschild BM, Calabro JJ, Staley H, Burnstein S, Garg S, Martin P. The arthritis of Wegener's granulomatosis. Clin Rheum Pract **1984**; 2: 29–35.
61. Anderson T, Arcini C, Anda S, Tangerud A, Robertsen G. Suspected endemic syphilis (trepanarid) in sixteenth-century Norway. Med Hist **1986**; 30:351–60.
62. Bogdan G, Weaver DS. Possible treponematosis in human skeletons from a pre-Columbian ossuary of costal North Carolina. Amer J Phys Anthropol **1988**; 75:187–8.
63. Brothwell D. Further evidence of treponematosis in a pre-European population from Oceania. Bull Hist Med **1976**; 50:435–42.
64. Bullen AK. Paleoepidemiology and distribution of prehistoric treponemiasis in Florida. Florida Anthropol **1972**; 25:133–74.
65. Cook DC. Dental evidence for congenital syphilis (and its absence) before and after the conquest of the New World. In: Dutour O, Palfi G, Berato J, Brun J-P, eds. L'Origine de la Syphilis en Europe Avant ou Apres 1493? Toulon, France: Centre Archeologique du Var, **1995**: 169–75.
66. El-Najjar MY. Human treponematosis and tuberculosis: evidence from the New World. Amer J Phys Anthropol **1979**; 51:599–618.
67. Gann T. Recent discoveries in Central America proving the pre-Columbian existence of syphilis in the New World. Lancet **1901**; 1:968–70.
68. Hudson EH. Treponematosis among the Bedouin Arabs of the Syrian desert. US Naval Med Bull **1928**; 26:817–24.
69. Iscan YM, Miller-Shaivitz P. Prehistoric syphilis in Florida. J Florida Med Assoc **1985**; 72:109–13.
70. Pardo-Castello V, Ferrer I. Pinta. Arch Dermatol Syphil **1942**; 45: 843–64.
71. Sakamoto A, Oda Y, Iwamoto Y, Tsuneyoshi M. A comparative study of fibrous dysplasia and osteofibrous dysplasia with regard to expressions of c-fos and c-jun products and bone matrix proteins: a clinicopathologic review and immunohistochemical study of c-fos, c-jun, type 1 collagen, osteonectin, osteopontin, and osteocalcin. Hum Pathol **1999**; 30:1418–26.
72. Thometz JG, DiRaimondo CA. A case of recurrent Caffey's disease treated with naproxen. Clin Orthop **1996**; 323:304–9.
73. McCarty DJ, Koopman WJ. Arthritis and allied conditions. Philadelphia: Lea and Febiger, **1993**.
74. Rothschild BM. Rheumatology: a primary care approach. New York: Yorke Medical Press, **1982**.
75. Silverman FN. Caffey's pediatric x-ray diagnosis. Chicago: Year Book Medical Publishers, **1985**.
76. Rothschild BM, Yoon BH. Thyroid acropachy complicated by lymphatic obstruction. Arthritis Rheum **1982**; 25:588–90.
77. Hershkovitz I, Rothschild BM, Wish-Baratz S, Rothschild C. Natural variation and differential diagnosis of skeletal changes in Bejel (endemic syphilis). In: Dutour O, Palfi G, Berato J, Brun J-P, eds. L'Origin de la Syphilis en Europe—Avant ou apres 1493. Toulon, France: Centre Archeologique du Var, **1995**:81–7.
78. Arensburg B. A short review of paleopathology in the Middle East. Mitekufat Haeven, Journal of the Israel Prehistoric Society **1985**; 18: 21–36.
79. Cockburn TA. The origin of treponematoses. Bull World Health Org **1961**; 24:221–8.
80. Goldstein MS, Arensburg B, Nathan H. Pathology of bedouin skeletal remains from two sites in Israel. Am J Phys Anthropol **1976**; 45:621–40.
81. Howells WW. The Pacific Islanders. New York: Charles Scribner Press, **1973**.
82. Stewart TD, Spoehr A. Evidence on the paleopathology of Yaws. Bull Hist Med **1952**; 26:538–41.
83. Jostes FA, Roche MB. Syphilis of the bones and joints. J Missouri Med Assn **1939**; 36:61–5.
84. Kampmeier RH. The late manifestations of syphilis: skeletal, visceral and cardiovascular. Med Clin N Amer **1964**; 48:667–97.
85. Stokes JH, Beerman H, Ingreham NR Jr. Modern clinical syphilogy. 3rd ed. Philadelphia: Saunders, **1994**:679.
86. El-Najjar M, Desanti MV, Ozebek L. Prevalence and possible etiology of dental enamel hypoplasia. Am J Phys Anthropol **1978**; 48:185–92.
87. Pinborg JJ. Pathology of the dental hard tissues. Philadelphia: WB Saunders, **1970**.

88. Sullivan NC. Enamel hypoplasia as an indicator of biologic stress in two Wisconsin populations. Wisc Archeol **1986**; 67:97–103.
89. Brion LP, Manuli M, Rai B, Kresch MJ, Pavlov H, Glaser J. Long-bone radiographic abnormalities as a sign of active congenital syphilis in asymptomatic newborns. Pediatrics **1991**; 88:1037–40.
90. Levin EJ. Healing in congenital osseous syphilis. Amer J Roentgenol **1970**; 110:591–7.
91. Berato J, Dutour O, Palfi G. Lesions pathologiques de 'Cristobal,' foetus du bas Empire Roman (Tombe N 1, Costebelle, Hyeres). In: Dutour O, Palfi G, Berato J, Brun J-P, eds. L'Origin de la Syphilis en Europe—Avant ou apres 1493. Toulon, France: Centre: Archeologique du Var, **1995**:133–8.
92. Rothschild BM, Rothschild C. Treponemal disease in the New World: a tale of two seeds. Curr Anthropol **1996**; 37:555–61.
93. Dean JS, Euler RC, Gumerman GJ, Plog F, Hevly RH, Karlstrom TN. Human behavior, demography, and paleoenvironment on the Colorado plateaus. Amer Antiquity **1985**; 50:537–54.
94. Euler RC, Gumerman GJ, Karlstrom TN, Dean JS, Hevly RH. The Colorado plateaus: cultural dynamics and paleoenvironment. Science **1979**; 205:1089–101.
95. Rothschild BM, Calderon FL, Coppa A, Rothschild C. First European exposure to syphilis: the Dominican Republic at time of Columbian contact. Clin Infect Dis **2000**; 31:936–41.