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Sex, Society, and Syphilis: A Social, Ecological, and Evolutionary History of Syphilis in Late Medieval and Early Modern England (c. 1494-1865)

By

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B.A., Pennsylvania State University, 2004

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Abstract

Sex, Society, and Syphilis: A Social, Ecological, and Evolutionary History of Syphilis in Late Medieval and Early Modern England (c. 1494-1865)
By Molly Kathleen Zuckerman

This study presents a social, ecological, and evolutionary history of acquired syphilis in early modern England (c. 1495-1864). Specifically it examines the influence of different proximate ecological factors, such as biological sex and overall health, on the pathophysiology of syphilis, explores the influence of social identity on access to treatment, and assesses whether the disease evolved in response to changes in human behavior and ecology. I synthesized my own and previously published data on sex, health indicators, and evidence of syphilis in several 15th to 19th century skeletal samples with published and unpublished archaeological and historical data, my own trace element data on evidence of treatment with mercury, and re-analysis of 19th and 20th century studies of untreated infection to address four research questions. First, did syphilis evolve in virulence (attenuate) soon after its emergence? Controversial historical evidence suggests that syphilis became milder soon after its 15th c. emergence, making it the first credible example of this valuable phenomenon. Instead, results show no evidence of attenuation and fail to support the most popular explanation: that syphilis altered to become less evident to potential mates (Knell 2004). Second and third, did overall health and biological sex (e.g., sex steroid hormones) affect the pathophysiology of syphilis? Analysis of 18th-19th c. skeletons and clinical and epidemiological data suggest a strong relationship between the former, particularly in regards to early life stressors, which potentially supports the Barker hypothesis. The same was not found for the latter, which contradicts a large body of 19th -20th c. medical knowledge and invites further study. Lastly, results demonstrate that gender, but not socioeconomic status influenced access to mercury treatments, indicating that women may have had more equitable access to treatment than documentary evidence indicates or that they pursued undocumented avenues for access to treatment. This study is the first to address the social and ecological aspects of syphilis in a large skeletal sample using multiple lines of evidence and joins a small but growing body of literature that uses skeletal evidence to elucidate the evolution and ecology of infectious disease.

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Dedication

This dissertation is dedicated to my mother and to William White, at the Museum of London. This dissertation would not exist without his sanction and support.

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Chapter One: Introduction

Introduction

Kevin P. Siena concludes his 2004 text, *Venereal Disease, Hospitals, and the Urban Poor: London's "Foul Wards", 1600-1800,* with a vignette about an impoverished English couple, Elizabeth and John Byon, infected with "the pox" (as syphilis and venereal disease in general was commonly called in England (see below)). On the bitterly cold night of February 7th, 1774, they paid for a night's lodging in the house of Magdalen Jones in London. Well aware of the great stigma associated with his wife's infection, John Byon lied to Jones about his wife's affliction, stating that she was drunk and when pressed for the truth, that she had a cold. However, near midnight, upon discovering that Elizabeth was severely ill with the pox, Jones and her husband cast them out into the night without, as court testimony attests, even allowing them to finish dressing. They made it two blocks before Elizabeth perished in the street.

John Byon promptly brought murder charges against Magdalen Jones. In court, Jones' serving maid testified that both Byon and his wife were '"rotten with the pox"' and the city coroner pronounced only that Elizabeth was '"full of blotches"'. Despite the absence of any testimony challenging the charges against Jones, the jury acquitted her of all charges (OBSP 1734; cited in Siena 2004). Both the London legal system and its citizens seemed to fully condone and legitimate what boiled down to negligent, voluntary manslaughter of victims of the pox.

Siena employs this vignette at the end of his analysis to demonstrate the plight of the very poorest members of London infected with the pox. Instead, as it captures many

of the aspects of the experience of having the disease in early modern London, here it is used to introduce these elements. With only a few pence to their names on the night of the 7th, they would have been unable to afford private medical treatment and instead have sought the less guaranteed and more exposed and potentially humiliating option of public institutional care for their infections. Indeed, court testimony indicates that the Byons had lain for two nights in front of their local parish churchwarden's residence but had been unable to qualify for parish relief or secure a bed at a local workhouse. Either of these two options would most likely have led to treatment with mercury, the most common treatment for the pox during the period. As will be discussed in Chapter Six, 'Mercury in The Midst of Mars and Venus: Treatment of Acquired Syphilis with Mercury in 17th to 19th century England', while higher and middling status sufferers in early modern London had a variety of treatment options open to them, far more limited options were open to those of lesser means. A review of the historical evidence suggests that for a poor woman like Elizabeth Byon, options for therapeutic treatment for syphilis may have been limited to nearly non-existent.

Elizabeth Byon may also have been suffering from an especially severe case of the disease. The maid's testimony explicitly states that Byon was '"rotten"' with the disease and seems to have died of it. As is noted throughout the following analyses, modern syphilis and that most commonly documented in the early modern period is infrequently fatal, though it is responsible for varied and often severe morbidity (see Chapter Five for a full discussion of the pathophysiology of untreated syphilis). However, at the time of its emergence, which is likely to have been in the late 15th century (though this is hotly contested), historical evidence indicates that syphilis may have been an all-

together different animal. As is discussed in Chapter Three, 'Sex Gets Less Dangerous? Investigating an Evolution of Virulence in Syphilis', syphilis may have been an acute and aggressive disease in the late 15th and early 16th centuries in Europe and Asia but quickly evolved into its modern chronic and less severe incarnation. As such, later, severe cases like Byon's may have been exacerbated by different ecological and social conditions rather than being products of the virulence of the untreated disease. As Chapters Four, 'The Effect of Biological Sex on Manifestations of Syphilis in the Pre-Antibiotic Era' and Five, 'Overall Health and the Pathophysiology of Tertiary Syphilis', discuss, the health status of sufferers as well as their biological sex may have had a mediating effect on the expression and manifestations of syphilis. Elizabeth Byon's disease could have been worsened by her presumably poor health or have been affected by the influence of endocrine pathways on the pathophysiology of syphilis.

This study employs an integration of historical, archaeological, skeletal, clinical, and biochemical evidence to investigate the evolutionary, social, and ecological history of acquired syphilis in early modern England (c. 1494-1864). Specifically it examines the influence of different proximate and ultimate ecological factors on the expression of syphilis, explores how social constructions of a disease affected the experience of having it, and assesses whether syphilis may have evolved over time in response to changes in human behavior and ecology. From this larger schema, four research questions are addressed: Did syphilis evolve in virulence in the late 15th and early 16th century? What effects did overall health status have on the expression and manifestations of syphilis? Did biological sex have a moderating effect on the expression and manifestations of syphilis as well? And lastly, what effects did components of the social identity of past

sufferers, specifically gender and socioeconomic status, have upon access to mercury treatments for syphilis?

Background

According to many contemporary chroniclers (Diaz de Isla 1539; Fernandez de Oviedo y Valdes 1526; von Hutten [1519] 1945) and modern day historians, microbiologists, and physical anthropologists (Meyer et al. 2002), the first known epidemic erupted in Italy in 1495 during the Siege of Naples. From there, facilitated by the movement of returning mercenaries (Brown et al. 1970; Williams et al. 1927), the disease spread across the continent, becoming widespread across Europe by 1500 (Pusey 1933). Combined with other factors and the suspicious proximity of the date of Columbus's voyage to the beginning of the epidemic, these observations made the theory of a New World origin for syphilis popular for the next four centuries.

In the 20th century this theory was reformulated as the Columbian hypothesis, which proposes that syphilis originated in the New World and was transmitted to the Old by Columbus in the 1490s (Baker and Armelagos 1988; Crosby 1972a; Dennie 1962; Goff 1967; Harrison 1959). This is supported by the 15th and 16th century accounts of syphilis's rapid spread and extreme virulence, which some argued suggested a novel infectious disease set loose on virgin populations (Hudson 1963; Knell 2004). It has also received additional support from phylogenetic evidence suggesting that the migrant was a venereal or non-venereal progenitor of modern syphilis-causing strains (Harper et al. 2008a; Harper et al. 2008b; contra Mulligan et al. 2008) and an absence of Old World

Pre-Columbian skeletal disease (Harper et al. Accepted). Therefore, it is the hypothesis for the origins of syphilis that is adopted and employed in this study.

However, some critics argued for the Pre-Columbian presence of syphilis in the Old World (Hackett 1963; 1967; Holcomb 1934; 1935). The associated 'Pre-Columbian Hypothesis' asserts that delayed recognition of the disease until the 1490s was because the disease was very mild, not distinguished from other bone-remodeling diseases, particularly 'venereal leprosy' (Buret 1891; Castiglioni 1941; Hackett 1963; Hudson 1961; 1964; Sudhoff 1925), that the introduction of the printing press or an especially virulent New World strain facilitated its recognition (El-Najjar 1979; Kampmeier 1984), or that the epidemic was caused by another disease entirely (Andre 1994). Evolutionary and biocultural variations on this theme propose that syphilis evolved in response to the social, cultural, and environmental changes that humans have experienced since the Pleistocene, such as urbanization (Brothwell 1981b; Cockburn 1961; Hackett 1963; Willcox 1972).

Other hypotheses have been forwarded, such as Livingstone's (1991) Alternative Hypothesis, which posits that syphilis originated in Africa, or the Unitarian Hypothesis, which argues that syphilis and its variants, yaws and endemic syphilis (bejel) are the environmentally produced forms of a singular disease (Hudson 1963; 1965). However these are ill supported by archaeological data and discredited with genetic evidence, respectively (Centurion-Lara et al. 2006; Gray et al. 2006; Harper et al. 2008a; Hollander 1981; Morris 1988; contra Mulligan et al. 2008).

Due to concerns with the bias and incompleteness of documentary and ethnographic data, primary evidence—skeletal material and its specific context—has

become central for elucidating the origins, antiquity, and evolution of syphilis (Roberts 1994; Siena 2005b). As syphilis is one of the few infectious diseases to leave distinctive traces on the skeleton, skeletal evidence has been used to exhaustively trace its temporal and geographic distribution throughout the pre-Columbian eastern and western hemispheres (Dutour et al. 1994; Harper et al. Accepted; Meyer et al. 2002; Powell and Cook 2005a). However, without the motivation of resolving the 'syphilis enigma', comparatively little attention has been paid to post-Columbian Old World syphilis. Scattered cases have been documented in Italy (Fornaciari et al. 1989b), Denmark (Rasmussen et al. 2008), the Czech Republic (Horáčková and Vargová 2001), Russia (Buzhilova 1999), Spain (Malgosa et al. 1996b), Portugal (Codinha 2002), Japan (Suzuki 1984a; 1984b; 1984c), and England (e.g., Mays et al. 2003; Roberts and Cox 2003a; WORD database 2010). Overall, these reports present differential diagnoses and lesion summaries or frequencies; these make little contribution to understanding the evolution, ecology, and social impact of syphilis. Only two studies have attempted to briefly reconstruct general socioeconomic data for three English skeletons (Brickley et al. 1999; Molleson and Cox 1993). This is largely a product of the low prevalence of syphilis in the archaeological record, meaning that even large Post-Columbian skeletal samples have more than a handful of cases. The low prevalence is likely due to the rarity of skeletal involvement in syphilis—with estimates ranging from .5% to 10% of cases (Resnick and Niwayama 1995)—though many other, likely secondary, explanations for its low prevalence in the record have been raised (see Miles et al. 2008; Molleson and Cox 1993; Roberts 1994; Watts 1997). This study attempts to circumvent this limitation by creating a larger artificial sample of syphilitic skeletons by pooling those found at multiple

different sites throughout post-medieval England. As is discussed in Chapter Two, 'Research Design', each research question in this study employs a different subset of this larger skeletal sample.

Other factors have also limited attempts to specifically trace the evolutionary history of syphilis, as in Chapter Three, or reconstruct lived experiences of the disease in the past, as in Chapters Four, Five, and Six. An important revisionist history has stressed that syphilis was identified by Renaissance and early modern physicians and laity alike by an inclusive set of symbolic, socially constructed symptoms (Harris 1996; 2005). Commentators employed their own disease concept—the 'venereal disease'—that encompassed a range of conditions, including gonorrhea, in the vernacular of terms like the 'French Disease,' 'Mal Francese,' and in England, 'the pox' (Arrizabalaga et al. 1997). 'Syphilis' was not commonly used until the 1700s (Quétel 1990). In part because of its frightening, disfiguring, and leprosy-like effects on the body, and the added humiliation of moral transgression that infection implied, syphilis also functioned as one of the period's most significant cultural markers and a rich discursive tool (Siena 2005). When combined with linguistic nuances and differences between modern and Renaissance and early modern-era medical terminology (Arrizabalaga et al. 1997), these factors preclude the use of modern diagnostic criteria—known as retrospective diagnosis—to identify an ancient disease (Harley 1999; Siena 2005c). According to Arrizabalaga et al., Harris, and others, these factors even preclude the assumption that an entity identifiable as 'syphilis' existed in the past. Problematically, this also precludes studying the longer continuities of disease history (Healy 2001). This position also butts up against the entire enterprise of paleopathology, which is largely premised on the

identification of pathological conditions in the past using bio-medically derived diagnostic criteria (Ortner 2003)[1]. Instead, these issues demand attention to how the disease was defined, conceptualized, and experienced historically (Arrizabalaga et al. 1997). As Watts (1997) characterizes it, a history of syphilis must tread in the "swampy frontier lying between objective medical (in this case skeletal) "truth" and subjective, culturally derived, perceptions. Consequently, this study employs biocultural, social constructionist, and political economic, as well as evolutionary approaches (e.g., Goodman 1998; Goodman and Leatherman 1998; Lindemann 1999) to both trace the history of syphilis and reconstruct lived experiences of the disease in early modern England. For the purposes of clarity—and because this study is dependent on skeletal evidence of infection by a specific pathogen (see Chapter Three)—'syphilis' is the most commonly employed term in this study but 'the pox' is used when specified by related historical material.

In the midst of its rapid spread across Europe and Asia, the pox arrived in England in approximately 1497 (Fabricius 1994; Merians 1996a). According to the earliest reports of the disease, its capacity for transmission through sexual activity was identified almost immediately after its emergence (Arrizabalaga 2005; Tognotti 2009) (see Chapter Three for a complete discussion), and this knowledge appears to have spread with the disease simultaneous to or quickly following its arrival in England (Fabricius 1994; Qualtiere and Slights 2003). While its arrival and initial spread were widely commented upon, the pox does not resurface in the historical material from England until the late 16th century. During this period the infection's prevalence seems to have steadily

[1] See Zuckerman, MK., Turner, BL., and GJ Armelagos. In Press. Evolutionary Thought in Paleopathology. In: A Companion to Paleopathology. Grauer, AL, Ed. New York: Wiley-Liss, for a discussion of the potential pitfalls of this approach.

increased; contemporary observers believed that it was endemic by 1579 (Clowes 1579 cited in Qualtiere and Slights 2003). As is discussed in Chapter Three, this may have been facilitated by contemporary economic and demographic factors, such as high rates of rural emigration into urban centers and the effect of the English Civil War, enclosure practices, and the dissolution of the monasteries (Ross 1995). While prevalence is difficult to calculate for pre-modern diseases, that of syphilis seems to have increased steadily in the 17th and 18th centuries, making syphilis one of the later period's most significant health problems (Roberts and Cox 2003). By the end of the 16th century, all social strata were affected (Braudel 1967), though, the largest affected group, as in all pre-modern European epidemics, were the urban poor, largely because of urban density and sheer numbers (Fabricius 1994). While it did not have a significant *discernable* demographic impact (Roberts and Cox 2003c; Watts 1997), it did have a powerful effect on the imaginations of early modern English society.

Social constructions of syphilis—and those whom these were inflicted upon—shifted over time in response to major social, religious, and economic transformations in England (see Sontag 1978). Throughout, these associations reflected cultural, economic, and social anxieties, such as maintenance of a social structure dependent on female subordination, and were used to engineer social boundaries, regulate sexuality, and marginalize low status groups, such as the poor and women (Hentschell 2005; Milburn 2004). While many beliefs about syphilis, including its treatment (see Chapter Six), were recycled from medieval understandings of leprosy in the early stages of the epidemic (Foa 1990; Gilman 1987; 1988), later ones were novel and specific to the disease.

The sudden and dramatic emergence of syphilis on the European stage in the 1490's provoked significant social anxiety (Siena 2005b). Astrological, miasmic, humoral, and divine origins theories were advocated, in keeping with popular Renaissance-era etiologies. Potentially because of Renaissance-era humanistic and objective values and a confusion over its capacity for sexual transmission (see Chapter Three), in the early stages of the epidemic sufferers seem to have been uniformly regarded with a mix of pity, fear, and disgust rather than contempt (Arrizabalaga et al. 1997; Quétel 1990; Temkin 1977).

Nonetheless, many initial perceptions of the pox adhered to existing social status- and gender-based social divisions. In particular they ascribed blame for the disease to women, especially prostitutes. This association occurred simultaneously with the emergence and initial spread of the disease, despite the ambiguity over its potential for sexual transmission in the early years of the epidemic. In Scotland in 1497, for example, simultaneously with the arrival of the pox, legislation was introduced to isolate and police prostitutes with the specific, explicit goal of quarantining the new infection (Spongberg 1997). The association grew more specific over time with increased understanding of syphilis' pathophysiology and modes of transmission. By the mid 16th century, for example, knowledge of syphilis' capacity for sexual transmission had become widespread, disseminated in pamphlets and books intended for lay readers. Its symptoms quickly came to symbolize vice, adultery, prostitution, and sexual deviance (Milburn 2004). Simultaneously, women and prostitutes in particular were pervasively characterized as the source, agent, and active transmitters in medical and popular literature (Quétel 1990; Schleiner 1994). McGough and others (Harris 1996; McGough

2005a; Siena 1998) attribute this association to the existing pathologization of women's bodies in Galenic medicine, the maturation of Paracelsian and Fracastorian ideas of contagion, and the threat that prostitutes' sexuality posed to social order. This may have also been tied to a continent wide shift in the moral climate associated with the Protestant Reformation, which produced ideologies that tied sexuality to vice and moral ruin. In England the rise of Puritanism may have also contributed to this, as it propagated providentialist ideas of divine intervention and retribution (Allen 2000; Davenport-Hines 1990); while all disease came to be interpreted as evidence of moral failure, syphilis became the most tightly linked with sin (Arrizabalaga et al. 1997; Cunningham and Grell 2000). At the same time, Luther's work on welfare reform in the 1520's effectively moralized poverty; the poor were divided into 'deserving' and 'undeserving' groups, with syphilitics falling into the latter category (Siena 2005c).[2] In the late 16th century, these beliefs were joined by the 'putrefaction theory' on the origins of the disease. Following this ideology, the pox independently arose from the wombs of womnen who were sexually active with multiple male partners; the infectious poison arose from the combination of heat, female fluids, and a venomous mixture of semen deposited by multiple male partners. Embraced widely and highly influential for a century, this theory hardened public and medical attitudes towards lower class women and prostitutes (Siena 1998).

By the end of the 18th century, new moral ideologies arose which prioritized the sanctity and fundamental economic and social importance of the family and the

[2] Jütte (1996) among others argues that the simultaneous coincidence of the rise of Puritanism and of syphilis is conspicuous. In a similar vein, Ross (1995) and Andreski (1982; 1989) have also tied syphilis' emergence to the rise of both Puritanism and witch-hunts. Siena (2005b) however, advises that caution should be employed in giving monocasual arguments for complex historical developments.

importance of virtuous domesticity in women (Merians 1996b). Temkin (1977), Spongberg (1997), Siena (1998) and others have allied these with the rise of the European bourgeoisie, and the rise of increased religiosity, Methodism, and Calvinistic Evangelicism. Starting in approximately the 1780s, attitudes towards women and poor syphilitics bore the greatest evidence of this ideological shift (Davenport-Hines 1990). As is discussed in Chapter Six, the motivations of civic obligation and pubic health concerns that fueled institutional care for sufferers in the 16th century dissolved in favor of fees, public differentiation of 'clean' (non-poxed) *vs*. 'foul' (poxed) patients, and an emphasis on moral reform for female patients. Calvinism and its model for the penitent transformation of 'sinners' ('Calvinistic sadism') encouraged what some scholars have viewed as punitive treatment with mercury (see Chapter Six) and public whipping (Davenport-Hines 1990). Many scholars have found evidence of English chroniclers, physicians, and social reformers promoting treatment of only 'innocent' sufferers and denying the distribution of prophylactic advice with the intention of discouraging licentious acts (Allen 2000; Boehrer 1990; Schleiner 1994b; Siena 1998; Stewart 1996; Temkin 1977). Lower status female patients were increasingly subject to strategies for moral reform, such as quarantine and uniform wearing (Merians 1996b; Siena 2004; 2005a).

As is discussed further in Chapters Five and Six, these linked ideologies of pollution, sex, morality, and poverty may have had a powerful effect on the lives, livelihood, and health of sufferers. As Gowing (1998b) and Siena (2001; 2004) note, stigma surrounding the disease and consequent damage to sufferers' social and sexual honor could easily translate into economic instability, job loss, and a spiral into poverty.

This real threat seems to have been feared—and experienced—by members of all genders and social strata. Cultural attitudes and medical theory were also inexorably linked. These linked ideologies quickly disseminated in 16th and 17th century medical treatises. Impoverished individuals and women in particular, seeking to avoid the moralizing increasingly inherent to public options for health care, may have rejected their already limited options for medical care (Siena 2004).

However, these dynamics can be difficult to detect in the available historical evidence. As is discussed in Chapter Six, studies of patient experiences and lived experiences of disease are biased by nature of the surviving source material towards the experiences of elites (Porter 1985a; Siena 2004). Consequently, experiences of non-elites often must be derived from second hand, institutional sources and interpreted with this lens in mind (Siena 2004). Uniquely, the integration of skeletal and historical evidence, which is employed here, can help to circumvent these limitations. Interrogating historical evidence against the more direct skeletal evidence can be used to reveal historiographic bias, nonconformities, and incompleteness following established procedure in historical bioarchaeology (Buikstra 2000; Grauer and McNamara 1995; Saunders et al. 1995). Ultimately, the interdisciplinary integration of direct and historical lines of evidence generates more information than the separate consideration of these sources (Swedlund and Herring 2003). This is especially true for reconstructing the disease experiences of socially marginalized groups, such as women and the poor, which are otherwise obscured or invisible in the historical and archaeological record (Grauer 2003). As such, Chapter Six addresses whether differences in disease experience—specifically in access to therapeutic treatment with mercury corresponding to gender and socioeconomic status—

can be discerned from skeletal evidence. This analysis employs trace element analysis via XRF spectrometry to examine differences in levels of mercury in skeletons from several archaeological sites throughout London dated to the 17th to 19th centuries. This technique is established for non-destructive trace element analysis of inorganic remains in archaeometry but is novel for the same in human skeletal remains. This represents the first use of this technique to detect biochemical evidence of treatment of pathological conditions in the archaeological record.

Integrations of historical, skeletal, and archaeological material also enable critical insight into the murky effects of different degrees of overall health among individuals on susceptibility to infectious disease in the past (hidden heterogeneity in frailty) (Wood et al. 1992). This issue remains a major impediment to using skeletal samples to reconstruct patterns of health and disease, particularly in stratified societies (Wright and Yoder 2003). While bioarchaeologists have produced a growing body of literature tackling this concern in a variety of contexts, for a range of conditions, and employing a growing number of skeletal indicators to infer differing degrees of frailty (e.g., Armelagos et al. 2009; Boldsen 2007; DeWitte 2009; DeWitte and Bekvalac 2010; DeWitte and Wood 2008; Sullivan 2004), it has yet to be addressed for syphilis. As such, working off of a large body of medical literature which suggests that the manifestations of untreated syphilis may vary by sex, Chapter Four addresses whether any evidence of sex-based differences in the expression and manifestations of syphilis are evident in both the pooled skeletal sample from post-medieval England and in primary data on the manifestations of syphilis from three major 19th and 20th century studies of untreated syphilis. Chapter Five explores whether any relationship can be discerned between skeletal indicators of overall

health, specifically dental caries, periodontal disease (periodontitis), and linear enamel hypoplasia, and the pathophysiology of tertiary disease in skeletons from two London archaeological sites.

Lastly, as is addressed in Chapter Three, tracing the early evolutionary trajectory of syphilis grants a unique opportunity to examine interactions between a novel, emerging infectious diseases and 'virgin soil' host populations in an extended and well-documented context. Given the stronger support for the Columbian Hypothesis (*vs*. the pre-Columbian) (Harper et al. 2008a; Harper et al. 2008b; Harper et al. Accepted; contra Mulligan et al. 2008), syphilis stands as the sole major infectious disease to have made the reverse trip across the Atlantic in the Columbian Exchange (Diamond 1997). In turn, this makes it one of the first biological products of globalization. As mentioned briefly above, syphilis is also distinguished by being the first credible known example of the evolution of virulence in a human disease (Knell 2004; Hudson 1963).

It has become increasingly well appreciated that to understand and predict the processes, epidemiology, and evolution of current and future emerging and re-emerging infectious diseases, those of the past must be equally well understood (Morens et al. 2008). Shared, fundamental general factors, such as increased mobility, trade, social disorder, and social inequalities underlie the emergence of all epidemic infectious diseases in history. Knowledge of the effects of these social and ecological factors on disease experiences in the past can provide comparative counterpoints and critical predictive insight into new and recently emerged diseases (Armelagos et al. 2005; Fischer and Klose 1996; Morens et al. 2008). As such, because an evolution of virulence in syphilis in the 15th and 16th centuries has been widely assumed but never directly tested

(e.g., Hudson 1963; Knell 2004), Chapter Three analyzes direct skeletal evidence of syphilis dating to the late 15th and early 16th centuries to assess whether manifestations of the disease changed in the ways suggested by the historical literature and in turn, what selective or ecological processes may be responsible.

Chapter Two: Research Design

The aim of this study is to create a longitudinal characterization of the social, evolutionary, and ecological history of acquired syphilis in early modern England. This characterization is based on in-depth osteological and pathological profiles of archaeologically derived skeletons with evidence of acquired syphilis (N=57) (see Table 1). It also incorporates trace element profiles of a subset of these skeletons (N=30) as well as a larger control sample of individuals from the same archaeological sites without evidence of syphilis (N=75) as well as associated soil samples (N=13) in order to control for endogenous and diagenetic background exposure to mercury (see Table 18). Re-analysis of clinical and autopsy data on the manifestations of syphilis derived from several previously published 19th and 10th century surveys of syphilis are also included to address manifestations of syphilis not apparent on the skeleton, such as the timing of different stages and various soft-tissue manifestations associated with infection (see Table 3).

Materials

With the exception of the clinical and autopsy data, these chapters primarily employ different subsets of an overall, larger data set. This parsing out of the sample reflects the specific aims of each chapter and the data best suited to addressing each. Chapter Three, 'Sex Gets Less Dangerous? Investigating the Evolution of Virulence in Syphilis', uses a much smaller dataset than the other analyses. It incorporates skeletal data from all reported, currently accessible cases (N=17) of acquired syphilis recovered from England that date to the 15th and 16th centuries (see Table 1). As the manifestations of syphilis reportedly

changed in the early 16th century, this represents an attempt to accurately represent and evaluate any changes in the nature of the disease—at least as is discernable from skeletal evidence—over this time period in a given region (see Chapter Three, Discussion, for rationale for the use of England as the 'given region' for investigating this phenomenon). Consequently, later cases dating to the 17th to 19th centuries are not included. Problematically, all of the 'currently accessible cases' does not exactly overlap with all of the 'reported' cases. Due to a continuing embargo against access by outside researchers to the St. Mary Spital skeletal sample curated at the Museum of London pending publication of results by internal researchers, ten or eleven (the reported numbers vary) of the earliest cases of reported syphilis, dated to the 16th century, are not included in this analysis. As is discussed in Chapter Seven, the Conclusion, further analysis and the resultant publication will include this data. The estimated effects of not including these individuals on the results for the present analysis are discussed in the Discussion section of Chapter Three.

The Fourth, Fifth, and Sixth chapters incorporate a variably larger subset of skeletal data. This includes data from skeletons deposited in cemetery sites between approximately AD 1550 and 1856. This subset was chosen because these chapters address variation in the manifestations of syphilis and in its treatment that are unrelated to any adaptive shifts that the pathogen (*T. pallidum*) may have experienced. Accordingly, this subset incorporates only skeletons for whom variation in their pathological lesions is likely due to proximate (ecological and individual) rather than ultimate (evolutionary and population-level) variables. Chapter Five, 'Overall Health and the Pathophysiology of Tertiary Syphilis,' examines associations between skeletal indicators of overall health and both the presence of tertiary syphilis and skeletal manifestations of tertiary syphilis in individuals from the New London Bridge/ St. Thomas Hospital and Lower St. Bride's/ Farringdon Street sites

in London. These samples were selected because they include the largest numbers of skeletons with lesions consistent with syphilis—seventeen in the New London Bridge/ St. Thomas Hospital sample and seven in the Lower St. Bride's/ Farringdon Street sample—in any reported assemblage recovered from England. In each sample, the frequency of oral pathologies and stress indicators (i.e., periodontitis, linear enamel hypoplasias, and dental caries) were compared between those with and without lesions associated with syphilis. Then, within the smaller, combined sample of syphilitics from both sites, frequencies of oral pathologies and stress indicators were compared between those with and without specific tertiary manifestations.

Chapter Four, 'The Effect of Biological Sex on Manifestations of Syphilis in the Pre-Antibiotic Era,' incorporates both skeletal data (N=41) from the overall dataset and non-skeletal data on the stages of the disease and the soft-tissue manifestations associated with syphilis. As is described below, this constitutes primary data collected from 19th and 20th century clinical, epidemiological, and autopsy studies of the natural history of untreated syphilis. Lastly, Chapter Six, 'Mercury in the Midst of Mars and Venus: Treatment of Acquired Syphilis with Mercury in 17th to 19th century England', employs a subset (N=30) of the larger skeletal sample, dating to the 17th to 19th centuries and excavated from six cemetery sites in London. As controls, additional individuals selected from each of these sites provide indicators of background endogenous levels of mercury (N=75) (see Table 18). Soil samples found in close proximity to several of the skeletons allow an estimation of diagenetic exposure to mercury.

Skeletal Individuals: Pathological Sample

Sample Treatment and Selection

The overall skeletal sample includes the great majority of currently accessible, archaeologically derived skeletons with macroscopic evidence of syphilis in England[3] (N=57). They have been excavated over the past forty years from multiple archaeological throughout England and are currently curated a variety of research, public, and educational institutions in England. At each location, they are stored in acid free paper or plastic bags within cardboard boxes in both basement and above ground facilities.

Overall, the skeletal sample dates to approximately the late 15th to mid 19th centuries (see Table 1). An English skeletal sample was selected because the country offers, on the whole, the world's largest and most comprehensively curated body of skeletons. A survey of the published literature suggests that this body of evidence also contains the largest known number of skeletons with syphilis recovered from the archaeological record. These are accompanied by a large, detailed, and high quality body of contextual historical data on the samples (Roberts 2006) and the world's largest and most comprehensive body of literature on contemporary economic and demographic data, and social and medical history (Higgs 2004).

All of the skeletal individuals included in the study are listed and referred to by context codes, or unique identifying numbers, and prefaced by a site code. These are

[3] Excluded are approximately ten individuals from St. Mary Spital, mentioned above; several cranial fragments with caries sicca from Bristol, which have no temporal provenience; and several individuals from the reburied and currently unpublished St. Pancras cemetery site, London.

specific to each archaeological site and were assigned during initial examination by excavators and osteologists at the curatorial institutions.

Selection Criteria

All of the skeletal individuals included in the sample exhibit gross or macroscopic lesions associated with acquired syphilis. Biomolecular techniques were not used to assist diagnosis. Despite initial optimism (Kolman et al. 1999; Ortner et al. 1992), uniformly unsuccessful attempts to recover pathogenic antigens and aDNA since then have established that it is currently impossible to use these for diagnostic purposes in archaeological material (Barnes and Thomas 2006; Gray et al. 2006; von Hunnius et al. 2007). Pathology associated with syphilis was diagnosed following Hackett (1976), supplemented by Ortner (2003) and Steinbock (1976), and Aufderheide and Rodrìguez-Martìn (1998b). Syphilis is a multi-stage disease with protean manifestations, both in soft tissue and on the skeleton (Peeling and Hook 2006). While primary and secondary stage disease both produce periosteal reactions and in the latter (Ehrlich and Kricun 1976b; Hoeprich 1994), osteitis, these are mild, transient, and non-diagnostic (Hazen 1921; Ortner 2003; Powell and Cook 2005b; but see Rothschild and Rothschild 1995). Only tertiary stage infection can be diagnosed in dry bone with any certainty. Tertiary disease produces the above lesions in addition to osteomyelitis, gummata, and joint involvement. Lesions are characteristically systemic and bilateral, and predilect multiple elements, including diaphyses, clavicles, scapulae, ribs, the sternum, bones of the hands and feet, and the cranium.

Because of this diversity, establishing which lesions are specific to syphilis has been historically problematic. This study followed the guidelines established by Hackett (1976), in which skeletons of clinically diagnosed cases of treponemal disease, cases of other pathological conditions, and healthy controls were compared. This study is the only published analysis that has rigorously assessed the specificity of the many associated lesions to the actual disease. It revealed two diagnostic markers. The first is caries sicca, a sequence of gummatous focal destruction, necrosis, pitting, and excessive sclerosis that, over time, can generate radially grooved stellate scars and a 'worm-eaten' appearance. The second are osseous expansions and nodes with superficial cavitations on long bones. Hackett found that variations upon these—both rugose and finely striated nodes and expansions, and coarsely striated and pitted expansions on long bones—were not diagnostic but instead strongly suggestive of treponemal disease. Several lesion types that have been employed in other studies as diagnostic of syphilis, such as tibial bowing, striated cortical expansions, systemic periostitis, and histological structures (Rothschild and Rothschild 1995; von Hunnius et al. 2006; Waldron 2009) have been demonstrated by Hackett (1976) and others to be merely consistent with infection (Blondiaux et al. 2002; Hackett 1976b; Webb 1995; Weston 2008; 2009). Following Hackett (1976) and Powell and Cook (2005a), macroscopic lesions on were divided into those *consistent*, *suggestive* of and *specific* to syphilis; only skeletons with specific or suggestive lesions were included. These stringent criteria, while excluding consistent cases, avoid inclusion and analysis of false positives for infection. This is particularly critical for the analysis performed in Chapter Three.

Pathological sample selection for the trace element analysis

From the overall pathological sample, a subset of individuals (N=30) from several archaeological sites in London was selected for trace element analysis. Most importantly, individuals were selected from samples that had not been reburied as control individuals from each site were also analyzed to detect background levels of endogenous exposure to mercury. The selected individuals date to the 17th to 19th centuries. Samples from London sites were selected because the majority of published analyses of therapeutic care and treatment of syphilis in the early modern period focus on London, allowing direct comparison of historical and skeletal evidence for treatment.

Control sample selection for the trace element analysis

To accommodate endogenous exposure, a large sample of non-pathological control individuals was also analyzed (N=77). The control group contains approximately three adult skeletons for every syphilitic skeleton recovered from each site. Selection criteria include, first, proximity, and second, health status. Selected individuals were recovered in close spatial and stratigraphic proximity (within 5 m horizontally and 1 m vertically; for vault burials, within 1 m horizontally) to each syphilitic individual. Control individuals also do not display non-specific (e.g., periosteal reactions) or specific indicators of infectious disease; wholly non-pathological skeletons were preferentially included but not always available. In these situations, individuals were employed who demonstrated evidence of conditions that, according to documentary evidence, were not

treated with mercury. These included tramautic injuries and metabolic conditions, such as scurvy.

Exceptions to these criteria, however, existed. In some cases, fewer than three non-pathological or spatially proximate control individuals were available. This is clearly noted in Table 1. Uniquely, at NLB91, all of the excavated individuals were recovered from a 6m x 3m pit and as such, a mass control sample rather than a pathological-individual specific one was the only amenable alternative. Numbers of available control individuals fitting the second criteria were also limited at both NLB91 and REW92, which represent cemeteries for a hospital and a very impoverished community, respectively (see Site Descriptions, below).

In an attempt to control for any status-based differences in endogenous mercury, individuals were also selected whose funerary artifacts (e.g., coffin presence, shape, type, hardware, and decoration) most closely matched those of the associated syphilitic skeleton. Control sample skeletons were identified using unpublished archaeological site maps, site reports, skeletal reports, and osteological recording forms (context sheets). Individuals were then independently aged as adult (18 ≥ 45+ yrs) and checked for pathologies by the author, following established standards (Buikstra and Ubelaker 1994; Ortner 2003).

Site descriptions

The Hull Magistrate's Court site, Hull, Humberside, is the cemetery site of a medieval Augustinian friary located on the Humber River on the east coast of England (Gillett and MacMahon 1985), which is now the modern city of Kingston upon Hull. The

site (HMC-94) was excavated in 1994, yielding two hundred and forty five burials (Evans 2000; Holst et al. 2001). Many of these exhibited periosteal lesions consistent with syphilis (Holst et al. 2001), but only four cases had suggestive or specific lesions, all of which are thus included in the following analysis. Burials at this site range from high status religious officials to lower class members of the urban poor. According to historical records, skeletons were interred here between 1316 and 1540 AD (Holst et al. 2001), but the primary publication for these cases, von Hunnius et al. (2006) provided a date of AD 1300 to 1450, based on stratigraphic and dendrochronological evidence. Direct radiocarbon dates on several of the individuals confirmed this, spanning approximately 1310 AD to 1435. However, published descriptions of the site and personal communications from the excavators indicate that the dendrochronological material was not found in stratigraphic proximity to the treponemal burials, rendering it irrelevant (Evans 2000; 2007a; 2007b). However, re-dating of the specimens has produced a significantly later date range, spanning 1428 to 1611 AD. Furthermore, uncertainty in the radiocarbon dates generated by the marine reservoir effect (which is caused by the presence of 'old carbon' in dated material due to dietary consumption of marine reservoirs (Cook et al. 2001a)), has significantly extended the date ranges for several of these skeletons substantially into the 17th century (Roberts 2009) (see Table 1). The overwhelming majority of skeletons from the site have been reburied.

The Blackfriars site is the cemetery site of the Dominican Friary of Blackfriars, Gloucester. According to historical records, the site was in use for burial between AD 1246 and 1538. One hundred and forty burials were excavated (Wiggins et al. 1993), a mere fraction of the estimated burials at the site, only one of which yielded lesions

specific for syphilis. This individual has been stratigraphically dated to the early to mid-16th century and radiocarbon dated to AD 1438-1635 (Ortner 2003; Roberts 1994) (see Table 2).

The Hospital cemetery of St James and Mary Magdalene, Chichester (CH 86), a medieval leprosy hospital, served as a burial ground between the late 12th to 18th centuries. Interred individuals were of very low status: paupers, lepers, or hospital patients. Excavations of a portion of the cemetery, between 1986 and 1987 and in 1993, produced three hundred and thirty skeletons and forty-four skeletons, respectively. One skeleton recovered has lesions highly specific for syphilis—a stage 1-2 caries sicca lesion—but combines this with rhinomaxillary changes characteristic of leprosy, making the cranial lesion more likely to be a product of tuberculosis (Magilton et al. 2008). This skeleton was not included here (neither was a skeletons with consistent lesions), but a suggestive case is included below. Dating for this skeleton (sk 277) is uncertain, but using relative dating it has been attributed to the late 17th to mid 18th century. Interestingly, this individual as buried at a distance from the remainder of graves, perhaps signaling social exclusion related to infection with syphilis (Magilton et al. 2008) (see Table 1).

The Rivenhall site is the churchyard cemetery of St. Mary and All Saints Church. Excavations in the 1980s recovered two hundred and twenty nine burials (Rodwell and Rodwell 1985; Rodwell and Rodwell 1993), of which one individual demonstrated lesions suggestive of syphilis; the remainder have been reburied. All of the burials represent 'ordinary parishioners' (Mays et al. 2003), presumably of the lower to middle classes. According to historical records, the churchyard was in use for burial between the

9th and 19th centuries; the individual in question has been radiocarbon dated to AD 1295 to 1445 (at 95% confidence) (Mays et al. 2003). With adjustment for the marine reservoir effect, the date range stretches from AD 1295 to 1632 (Harper et al. Accepted). As this new date has been submitted but not yet published, the earlier date is employed in analysis with the strong assumption that it dates to the very earliest part of the Pre-Columbian period (see Table 2).

The Ipswich Blackfriars site, Ipswich, is the cemetery site of the Ipswich Blackfriars Dominican Friary site (IAS). The cemetery was in use for burial from the Friary's foundation in AD 1263 until its dissolution, on the orders of Henry VIII, as part of his suppression of the monastic orders in AD1538 (Page 1975). Excavations of the site recovered two hundred and fifty burials, of which one yielded skeletal lesions suggestive of syphilis. This individual has been radiocarbon dated to AD 1440 to 1620, unadjusted for the marine reservoir effect. This individual is presumed to be of higher status than the majority of other burials as the site, as it was recovered from the nave of the conventional church, which was reserved for lay benefactors (Mays et al. 2003) (Table 1 & 2).

Excavations were carried out at the Barbican Leisure Center site (OSA 07), York, between 2003 and 2008. Preliminary dating suggests that of the six hundred and sixty seven recovered, five hundred and fifty date to the medieval period (one hundred and thirteen are post-medieval). These burials are thought to be associated with the lost church of All Saints, Fishergate. The first known reference dates for the church are 1091 to 1095 and the church seems to have perished soon after 1539. Of all of the burials, only one displays evidence of syphilis (McIntyre and Chamberlain forthcoming). Intriguingly, this skeleton (which displays specific lesions) has been hypothesized to be Lady Isabella

German, a well-known anchoress who resided in the churchyard between 1428 and 1448 (Raine 1955). This is based on her burial at the apse of the church, which indicates that she was of high social status, as well as the unusual position, location, size, and shape of the grave cut, which suggest that she represents some one other than a wealthy benefactor (McIntyre and Chamberlain forthcoming). The osteoporotic character of her skeleton also corroborates this, as anchorites were famously permanently confined within small cells within church foundations (Sauer 2004). Corroboration of this would make this find Pre-Columbian. As such, radiocarbon dating of this specimen is currently being conducted at the Oxford Radiocarbon Accelerator Unit, Oxford University, funded by an NFRC grant (1478.0410), to ascertain the date of this specimen. As this individual is not yet radiocarbon dated, it is assumed, for the purpose of analysis here, to date to the early part of the Pre-Columbian period, prior to 1539 AD (Table 1 & 2).

The majority of excavations at the Chelsea Old Church site (OCU00), London, the cemetery of the All Saints Church in Chelsea, occurred in 2000. The site yielded two hundred and eighty-eight burials, mainly in wooden coffins, although a few lead coffins were found, of which one hundred and ninety-eight were analyzed (Cowie et al. 2008). Coffin plates were found with ninety-three burials of which twenty-five produced legible inscriptions. Only one skeleton, not of known name, exhibited lesions suggestive of syphilis. Biographical information from the plates and the location of the cemetery in a high status community in a rural London suburb suggests that the majority of interments were of high status individuals. Coffin plates date the cemetery to between 1712 and 1842 AD (Table 1).

The Cross Bones Burial Ground on Redcross Way (REW92), Southwark,

London, was partially excavated in 1993, producing one hundred and forty-eight skeletons, mostly dating to the early 19th century (AD 1800-1853). The cemetery was thought to have been originally established in the 17th century as a prostitutes' burial ground (Miles 1993) but served as the ('paupers'') cemetery for poor residents of the parish of St. Savior's, Southwark, in the early 19th century. Most of the skeletons were buried in cheap coffins—only a small number of decorated coffins were recovered—and the cemetery was highly crowded. Two cases of syphilis from the site, one suggestive, the other specific, likely date to 1800 to 1853 (Brickley et al. 1999). Analysis suggests that the population was very poorly nourished and highly susceptible to infectious disease. The site yielded a high prevalence of dental and post-cranial pathologies, including syphilis: seven subadults exhibited evidence of congenital syphilis and 60.1% of all individuals demonstrating non-specific periosteal reactions, which are consistent with syphilis (Brickley et al. 1999) (Table 1).

The St. Bride's Lower Churchyard, Farringdon Street (FAO90), and St. Bride's Fleet Street Crypt (SB) represent two components of the burial ground for the parish of St. Bride's, London. The lower cemetery accommodated overflow from the overcrowded Fleet Street churchyard and vault. Individuals buried therein were poor and lower status servants, infants, residents of the nearby Bridewell workhouse and Fleet prison, vagrants, and visitors from other parishes. A burial ground was opened on the site in 1610, but the excavated and analyzed burials all date to the late 18 to 19th century (AD 1770-1849). Most of the burials were in wooden (elm) coffins, stacked up to eight deep, which formed nine intercutting north-south rows across the site, in at least two phases. The west end of the site contaned a brick burial vault, which contained forty-seven burials in coffins and

seventy-five individuals piled at the end of vault. Excavations of the site in 1991-92 yielded a total of six hundred and six skeletons, of which five hundred and forty-four were analyzed (Miles and Conheeney 2005). This yielded eight skeletons with lesions suggestive of or specific to syphilis (Table 1).

In contrast, burials in the crypt of St. Bride's Fleet Street (SB), were of primarily 'middling sort' to high status individuals. This sample is unique for being a documented skeletal sample, for which, courtesy of coffin plates and parish records, names, ages, and background information is known for a large portion of the skeletal sample. Interments in the crypt date from the 17th to mid 19th century and, of more than two hundred skeletons, have yielded two cases of syphilis, one suggestive and one specific. Both are from the known-named sample, and have respective dates of death of AD 1788 and 1828 (Schuer 1998) (Table 1).

The Church and graveyard of St Benet Sherehog, London (Number One Poultry) were excavated between 1994 and 1996 (ONE94). Parishioners were primarily of English descent, with only a few northern European immigrant families (Miles and White 2008) and affluent by Victorian measures of wealth (e.g. median rent, wills, etc.) in the 16th and 17th centuries (Rappaport 1989; Slack 1985). It remained one of the wealthier areas of the city after the Great Fire (Jones and Judges 1935-6; Miles and White 2008), though lower status parishioners were also entombed in the burying ground. Excavations of the site yielded two hundred and seventy-four burials, of which two hundred and thirty were post-medieval, dating primarily to the period between the Fire and 1849. The post-medieval burials were retained for analysis. Of these four displayed syphilitic lesions (Miles and White 2008), three of which were consistent but only one specific for syphilis

(Table 1).

In 1991 excavations were carried out on a small portion of the site of New London Bridge House, Southwark, which covered a very small part (6m x 3m) of a post-medieval cemetery north of St. Thomas Street (NLB91). These revealed at least three burial trenches identified as mass graves associated with St. Thomas Hospital. They are believed to represent either pauper or epidemic graves. The two hundred and twenty seven articulated individuals recovered were found beneath a presumed charnel pit and dated to the 17th century based on pottery; St. Thomas was one of only three hospitals to survive the dissolution of the monasteries in 1538. Of the one hundred and ninety-three analyzed, twenty-four had lesions attributable to syphilis, of which seventeen were suggestive or specific. The prevalence of non-specific periosteal lesions was also very high (35.2%) and may in some instances have been a precursor to specific infection. The high prevalence is attributed to the cemetery representing a hospital population for an institution that provided care to patients with syphilis throughout the early modern period (Jones 1991) (Table 1).

The cemetery of St. Marylebone served the parish of St. Marylebone, Marylebone Road, Westminster, between the 18th and 19th centuries (MBH04). Parishioners were of middling to high status, with documentary evidence indicating that overall, the parish was affluent. Excavations in 1992 and 2004 of a portion of the cemetery recovered over three hundred and seventy two burials. Analysis of three hundred and two from the post-medieval period revealed two suggestive cases. These date to 1767 to 1859 AD. The entirety of skeletons from the site have been reburied (Miles et al. 2008) (Table 1).

The hospital cemetery of the Newcastle Infirmary at the Forth, Newcastle Upon

Tyne, was in use between 1753 and 1845 AD. Patients at the infirmary, and thus individuals interred in the cemetery were not necessarily paupers, only those who could not afford private medical care (e.g., impoverished to lower status) and those suffering traumatic injuries. The majority however, were poor. The hospital did not provide long-term care. Excavations of a portion of the cemetery between 1996 and 1997 recovered four hundred and seven skeletons. Six specific cases (i.e., caries sicca) were recovered from disarticulated material at the site but these are no longer available for observation (6/ 295 crania or 2% CPR). Three additional cases, one two suggestive and on specific, were recovered and are included in the following analyses. Interestingly, burial registers from the hospital indicate that five individuals dying of 'lues venerea' were interred here (5/129 patients or 3.9% CPR), suggesting a congruence between historical and skeletal evidence (Boulter et al. 1998) (Table 1).

The cemetery of the church of St. Margaret Fyebriggate, Magdalen St, Norwich, was excavated in 1985 and 1987. Activity at the site dates to the Roman era but excavated and analyzed burials date to c. 1200 to 1468. While historical evidence suggests that the cemetery fell out of use between 1468 and 1600 AD (Stirland 2009), archaeological evidence cannot be used to rule out later burials (Bown, personal communication). Radiocarbon dates of several of the syphilitic skeletons found at the site, when uncertainty for marine reservoir effects has been incorporated, stretch into the 17th century (see Table 1)(Stirland 2009). In total, four hundred and thirty-six burials were excavated, of which four hundred and thirteen were analyzed. Of these, one displayed consistent lesions and has been omitted; five displayed suggestive or specific lesions and are included here.

The St. Helen-on-the-walls site, in York has yielded an isolated cranium with lesions specific for syphilis. This cemetery was the burial grounds for the St. Helen-on-the-walls parish, which historical documentation suggests was impoverished (Palliser 1980). The site was excavated between 1973 and 1978, yielding one thousand and fourteen skeletons. Analysis of these detected several other individuals displayed periosteal reactions consistent with syphilis (Grauer 1993), and one with osteitis and pitting suggestive of infection (Dawes and Magilton 1980), but as this was on an isolated tibia it was not included. The site is dated to 1100 to 1550 AD but the cranium has been radiocarbon dated to the 13th to 15th centuries. Even with correction for the marine reservoir effect, the date spans 1208 to 1425 AD (see Table 1 & 2). However, this date was generated several decades ago, before significant improvements in the accuracy of radiocarbon dating (Harper et al. Accepted). As such, radiocarbon dating of this specimen is currently being conducted at the Oxford Radiocarbon Accelerator Unit, Oxford University, funded by an NFRC grant (1478.0410), to ascertain the date of this specimen. Corroboration of this would make this find Pre-Columbian. As such, radiocarbon dating of this specimen is currently being conducted at the Oxford Radiocarbon Accelerator Unit, Oxford University, funded by an NFRC grant (1478.0410), to ascertain the date of this specimen. It is assumed, for the purpose of analysis here, to date to the earliest years of the Pre-Columbian period, prior to 1550 AD.

The Augustinian priory and hospital of St Mary without Bishopsgate (later known as St Mary Spital), East London was one of about two hundred hospitals founded in 12th-c. in England. It became one of the largest hospitals in the country in the medieval period, providing shelter for the sick, the poor, elderly and homeless. Extensive investigations

have occurred at this site over the course of the 20th century, yielding approximately 10,000 skeletons. While more recent work has yielded approximately ten cases of suspected syphilis that are reported to date to the Pre-Columbian period, these individuals are not accessible to outside researchers and thus have not been included in the following analyses. A solitary cranium excavated in the early 20th century, however, has been included. This cranium bears evidence of classic caries sicca lesions and is a specific case. While the site has been dated to AD 1197 to 1537, the crania is believed to be dated to the early 16th century (Brothwell 1961; Morant and Hoadley 1931) (see Table 1).

The crypt of Christ Church with All Saints, Spitalfields, East London was excavated between 1983 and 1986 (SRP98), producing nine hundred and eighty-three interrments. The crypt was in use between 1729 and 1859 AD. Approximately 40% of the individuals in the named sample were of Huguenot descent, who were involved in the textile industry. The majority of the vault burials (and the surrounding community) were members of the 'middling sort', particularly those deposited in the 18th century. In the 19th century, the parish's demographic shifted and the community became poorer. It is unique for being a documented skeletal sample, for which—courtesy of coffin plates and parish records—names, ages, and background information are known for a large portion of the skeletal sample (39.9%). The 'named sample' yielded one case specific for syphilis, with a date of death of 1729 AD. The non-named sample yielded an additional specific case, with an attributed date between 1729 AD and 1857 (Cox 1996; Molleson and Cox 1993) (see Table 1).

Excavation of the Quaker Burial Ground, Kingston-upon-Thames, London in 1996 produced three hundred and sixty burials (QBK 96) (see Table 1). The cemetery

was in use for burial between 1664 and 1814, but the majority of interments occurred during the early period of the site's use, between 1664 and c. 1739, when the cemetery primarily served the local Religious Society of Friends or Quaker community. As such, this site represents one of the few excavated cemeteries for Nonconformist communities in early modern England. The sample includes both middling sort and high status individuals and yielded a solitary skeleton with evidence of syphilis, which bears lesions specific for the infection. Excavators of the site noted with interest that unlike at some other sites that have yielded syphilitic skeletons, such as St James and Mary Magdalene, Chichester, this individual was buried in the same overall manner as the majority of interments and in the exact same location. This might signify reduced or non-existent social exclusion, at least for this individual, for those infected with a highly stigmatized disease (Bashford and Sibun 2007; Start and Kirk 1998).

Pathological sample: Clinical and autopsy studies

Very few large-scale analyses of the natural history of untreated syphilis exist. There are two clinical studies, the Oslo and Tuskegee Studies of Untreated Syphilis, and several autopsy studies in the published literature (see Table 3). These constitute four types of data sets. The first are anamnestic or recall studies, such as Kemp and Menninger's (1936), of self-selected samples of infected individuals who did not seek treatment or were ignorant of their infection and were examined only during late stage infection. These studies are few in number, rarely include benign or asymptomatic cases, and are significantly biased towards symptomatic, severe outcomes (Gjestland 1955).

Because of these concerns, none of these studies were included in the following analysis.

The second is retrospective, represented by the Oslo Study of Untreated Syphilis. This study presents data, recorded between 1891 and 1910 by Dr. Caesar Boeck, on two thousand, one hundred and eighty-one patients admitted to the University Hospital of Oslo, Norway with primary or secondary syphilis. Patients in the study were clinically diagnosed, as darkfield and serological tests were not employed before 1910. They were hospitalized until their lesions ameliorated and left largely untreated. Patients were hospitalized until their lesions had healed, a duration which ranged from one to twelve months, with an average of 3.6 months. Potassium iodide treatments were given to 40% of patients and mercury to 3.6%, but the majority were left untreated following Boeck's belief that patients' own 'defense mechanisms' were more effective against the disease than the currently available anti-syphilitics: mercury, iodine, and arsenic (Gjestland 1955). Between 1925 and 1927, Boeck's successor, Bruusgaard (1929) attempted a follow up analysis of four hundred and seventy-three patients from the original study, three hundred and nine of whom were still living and one hundred and sixty-four of whom were deceased. Bruusgaard examined medical records for the deceased. For living patients who responded to entreaties to return to the venereal disease clinic, he conducted personal, neurological, and cardiovascular examinations, the latter via roentograms. Wasserman tests were also given to the majority, though CSF was examined in a minority of patients. Patients who returned to the hospital for unrelated ailments were only subjected to personal examination. While Bruusgaard's findings formed the foundation of prognostic statements on the course of untreated syphilis for a quarter century after its publication (Clark and Danbolt 1964), neither Boeck's or Bruusgard's

data was incorporated into this analysis because of profound and irreconcilable selection biases within the data set (Gjestland 1955; see Harrison 1941; Sowder 1940).

Instead, data from Gjestland's retrospective reanalysis of Boeck's data has been employed (see Table 3). Gjestland, concerned about the selection bias in both data sets, performed clinical examinations on two hundred and sixteen of the remaining one thousand four hundred and fourteen remaining living patients in addition to reexamining the original medical records for the entire sample (see Clark and Danbolt 1964). The original study by Boeck had been conducted to determine the course of untreated syphilis, specifically the outcomes of late syphilis, duration of life, and causes of mortality. In contrast, Gjestland's reanalysis was directed towards answering five primary questions about the duration, timing, and manifestations of the stages of untreated syphilis, one of which conveniently enough, was whether sex influenced outcomes and in turn, whether these were consistently more severe in males than females.

The third type is that of retrospective plus prospective studies, wherein no treatment is supplied upon diagnosis, which is represented by Tuskegee Study of Untreated Syphilis and Turner's (1930) analysis of clinical data from the patients of the Syphilis Division of the Medical Clinic of the Johns Hopkins Hospital. Data from the Tuskegee Study is not included in the following analysis as females were not included in the study population (Olansky et al. 1956; Vonderlehr et al. 1936). Turner provides information on sex differences in the manifestations of 10,000 cases seen at Clinic in MD between 1916 and 1928. All patients in this sample were above the age of 12 years and the great majority had a confirmed diagnosis of syphilis via a positive Wasserman reaction. The intent of the study was to demarcate differences in incidence of the stages

and manifestations of syphilis between white males and females and African American males and females in the clinic population. No information was provided on the age of the patients. As data presented in this study is highly standardized, it was included in the analysis in Chapter Five (see Table 3). Like Boeck's sample, however, some individuals included within this sample received treatment for infection (including arsenical injections, heavy metal treatments, trypsaramide, and hyperpyrexia). Which patients received treatment and for what duration is not indicated.

Lastly, the fourth are autopsy studies, conducted in the early 20th century, which have been surveyed and summarized by Rosahn and Black-Shaffer (1946; 1947; 1943a; 1943b). There are two data sets of this type: that derived from the Yale Autopsy Series and that derived from a number of smaller studies conducted in Germany. The latter note frequencies of specific manifestations of syphilis infection within the larger autopsy samples. However, very few provide the sex of the surveyed cases. Problematically, all of these studies involve profound, irreconcilable variability in the employed diagnostic criteria, which are ambiguous and most often left unstated (Frates 1934; Melchior 1922; Teodori 1938; Warthin 1918). This impedes comparison of the studies and precludes incorporating their data into the following analysis. In contrast, data was more rigorously collected in the Yale Autopsy Series (Black-Schaffer and Rosahn 1943; Rosahn 1946; 1943a; Rosahn and Black-Schaffer 1943b), making them amenable to re-analysis here (see Table 3). This series represents three thousand nine hundred and seven autopsies conducted between 1917 and 1941 at the Yale University School of Medicine. This yielded three hundred and eighty cases of syphilis, which were diagnosed antemortem, either serologically or clinically. Postmortem diagnoses (gross and histological) were

made on a smaller number of individuals in this sample. Like Boeck and Turner's samples, however, some individuals included within this sample received treatment for infection (including arsenical injections, heavy metal treatments, trypsaramide, and hyperpyrexia). Which patients received treatment and for what duration is not indicated.

Hypotheses

This study addresses four central questions: Did syphilis evolve in virulence? What effects did components of social identity, such as gender and socioeconomic status, have upon access to mercury treatments for the disease? What were the effects of overall health on the likelihood of pathophysiology and progression of tertiary syphilis? Lastly, does biological sex have any discernible effects on the manifestations of syphilis? To address these questions, this study tests four major hypotheses ($\mathbf{H_{1\text{-}4}}$).

Hypothesis 1 (H_1): Syphilis underwent an evolution of virulence in the 15th and 16th centuries.

Historical evidence suggests that several aspects of syphilis changed markedly within decades of its emergence, becoming substantially milder. To assess this, evidence of specific manifestations in a subset of skeletons dating to the late 15th and early to mid 16th century are analyzed for any significant changes in frequency over time.

Results consistent with an evolution of virulence or attenuation of the virulence of syphilis would include a negative (or indirect) correlation between time and the frequencies at least one of the destructive lesions associated with syphilis (mortality and

the duration and tempo are not assessed here). Time here is expressed as the mean of the date range (15^{th}-16^{th} c.) assigned to individuals with evidence of syphilis. This would suggest a decrease in the severity of syphilis over time. Results inconsistent with this hypothesis would include: 1) a positive correlation between time and the frequency of at least one of the lesion types, which would suggest that syphilis increased in severity over time; or 2) no correlation over time, indicating no temporal changes in the manifestations of the disease.

H_1a: The manifestations of syphilis changed in the manner suggested by historical material in the late 15^{th} and early 16^{th} centuries.

This hypothesis posits that (and assesses whether) changes in the manifestations of syphilis occurred in the manner specifically suggested by the historical literature. The literature suggests a reduction in amputation (i.e., element destruction), facial destruction (i.e., caries sicca, gangosa, gondou), and in general, a reduction in the number of gummata.

Results consistent with this hypothesis would include a systematic, statistically significant decrease in the frequencies of all of the above lesions over time (negative or indirect correlation). Results inconsistent with this hypothesis would include: 1) a positive correlation between time and the frequency of any of the lesion types, which would suggest that syphilis did not alter in the manner suggested, or if more than one lesion type increases in frequency, that syphilis increased in severity over time; or 2) no correlation over time, indicating no temporal changes in the manifestations of the disease.

Results inconsistent with either **H_1** or **H_1a** suggest that syphilis did not attenuate, or evolve in virulence, as has been suggested by various theorists. Instead, these results would support the claims of various historians that reports of a decline in the virulence of syphilis are related to other factors. These may include in changes in contemporary social or sexual mores or a progressively increased familiarity with the disease and thus reduced fear over its gruesome manifestations.

H_1b: Syphilis evolved in virulence in response to direct selection for milder symptoms.

This hypothesis is intended to address the cause of evidence for a change in the manifestations of syphilis **(H_1 and (H_1a)**. This hypothesis is that proposed by Knell (2004) as the most likely evolutionary explanation for an evolution of virulence in syphilis as suggested by historical literature. Knell proposed that features which are evident to potential sexual partners and that would impair mobility and thus sexual activity would be selected against. This argument infers that over time, the lesions most obvious to potential partners and thus discouraging of sexual activity, should decrease in frequency. For syphilis, these lesions include amputation (i.e., element destruction), facial destruction (i.e., caries sicca, gangosa, gondou), and gummata.

Results in support of this hypothesis would include a systematic, statistically significant reduction in the frequencies of the above lesions over time. Specifically, it is expected that frequencies of facial destruction will decrease over time (negative or indirect correlation) as these lesions are the most conspicuous. Results not in support of

this hypothesis would include an increase in the frequencies of these lesions over time. In particular, this hypothesis would be directly nullified by results indicating either 1) an increase in the frequency facial destruction over time (positive correlation), or 2) no alteration (no correlation) in the frequency of facial destruction over time. These results would suggest that if changes are detected in the manifestations of syphilis, they are more likely due to other causes, as are discussed in Chapter Three.

Hypothesis 2 (H_2): Biological sex has a mediating effect on the manifestations of syphilis and on expression of the stages of infection.

Clinical literature from the 19th and early 20th centuries clearly states that the manifestations of syphilis and expression of each of the stages varies between males and females. To assess whether this variation is evident in archaeologically derived skeletal material as well as in data on the incidence of the stages and manifestations of syphilis from several large studies of untreated syphilis from the 19th and 20th centuries, two sub-hypotheses were evaluated.

H_2a: Sex is associated with differences in the manifestations and syphilis.

Physician's reports from the 19th and 20th century state that the timing and duration of the stages of syphilis and manifestations of the disease vary greatly between male and female cases of infection. This hypothesis was assessed in both the clinical and autopsy series

and the skeletal data set. To assess this, the frequency of different types of syphilitic lesions (i.e., cutaneous lesions, skeletal involvement), of different stages of the infection (i.e., secondary, secondary recurrent, and tertiary; primary was excluded for methodological reasons), and involvement of organ systems (i.e., neurological and cardiovascular) in males and females was assessed in the clinical and autopsy sample. Lesion types (i.e., gummata) were also assessed in the skeletal sample (male and female, skeletons of intermediate sex were not included).

Results in support of this hypothesis include systematic, statistically significant co-variance between sex and the frequencies of the above variables. It is specifically expected that, 1) overall, females will exhibit significantly lower frequencies of syphilitic lesions, organ system involvement, and of progressive infection—in other words, lower frequencies of tertiary disease than males. In a specific test of the general conclusions reported in clinical literature—primarily that while syphilis is generally milder in females, there is a certain degree of variation—it is secondarily expected that 2) frequencies of secondary and secondary recurrent infection and associated manifestations (i.e., cutaneous involvement) are more common among females. Results inconsistent with this hypothesis would include an absence of systematic, statistically significant co-variance between sex and the frequencies of at least one of the above variables. In regards to the first expectation above, they would also include results suggesting that overall, frequencies of specific lesions, organ involvement, and progressive infection are lower in females (and thus higher in males), or again, that there is no association. In regards to the second, secondary expectation, inconsistent results would also include a finding that frequencies of secondary and secondary recurrent infection and associated manifestations

(i.e., cutaneous involvement) are less common among females, or again, that there is no association.

H_2b: Sex and age (reproductive status) are associated with differences in the manifestations and syphilis.

There are clear indications in the clinical literature that the frequency and severity of the stages and manifestations of syphilis were perceived by physicians to vary by age and specifically by reproductive status in females (e.g., pre-menarche, pre- and post-menopause) but not in males. As such, skeletal data was assessed for differences in the type of lesions present in relation to whether skeletons (male and female; skeletons of intermediate sex were not included) were aged as being under 18 years of age, between 18 and 45 years of age, or above 46 years of age. Systematic data on age was not provided in any of the available large clinical and autopsy series and so this hypothesis was not assessed in this data set.

Results in support of this hypothesis include systematic, statistically significant co-variance between the presence of gummata, skeletal sex, and skeletal age categories: <18 yrs; 18-45 yrs; and >46 yrs of age. Specifically, it is expected that 1) gummata will be found at higher frequencies among males than among females. It is also expected that 2) the presence and frequency of gummata will be positively correlated with age, specifically with the highest age category (>45 yrs), reflecting the effects of menopause; negative correlations are expected with the lower age categories. It is expected that 3) among males, the presence and number of gummata will be positively correlated with

age, but with the two highest age categories (18-45 and >45 yrs). This would reflect the hormonal effects of puberty and the progressive, destructive effects of senescence on the immune system rather than specific age-dependent hormonal effects on the immune system (i.e., the striking changes in hormonal profiles associated with menopause). Results inconsistent with this hypothesis include an absence of systematic, statistically significant co-variance between the presence of gummata, skeletal sex, and skeletal age categories. They also include a 1) negative correlation between age and the presence and number of gummata among females, particularly in older individuals, which would indicate that immunological changes associated with reproductive status have a limited to nonexistent effect on the immunological and inflammatory processes associated with syphilis.

Hypothesis 3 (H_3): Overall health has a mediating effect on the pathophysiology of tertiary stage syphilis and on manifestations of tertiary infection.

The underlying cause for the variation seen in the expression of late stage infection—that only 15 to 40% of cases express tertiary syphilis—and its manifestations—that only a small but variable portion of tertiary cases experience debilitating, disfiguring levels of morbidity—is not well understood. As immunocompetence and inflammatory responses seem to play a role in the progression of the disease, this hypothesis proposes that overall health may be linked to variation in late stage infection. To assess this, two sub-hypotheses are addressed.

H_3a: Overall health status is associated with the pathophysiology of tertiary syphilis.

This assesses whether there are differences in overall health status between individuals with and without evidence of syphilis in the skeletal sample. Health status was estimated via frequencies of periodontal disease (periodontitis), dental caries, and linear enamel hypoplasia. It is assumed that overall health is linked to immunological mechanisms that either prevent or allow the infection's progression to tertiary stage disease. Presence of tertiary infection is expected to be associated with higher frequencies of these skeletal stress indicators. This hypothesis was evaluated in a sub-set of the overall skeletal sample.

Results in support of this hypothesis include 1) systematic, statistically significant co-variance between frequencies of a) linear enamel hypoplasias (LEH); b) periostitis; and/ or c) dental caries and individuals exhibiting lesions associated with syphilis. Specifically, individuals with syphilis are expected to have higher frequencies of LEH, periostitis, and/ or dental caries than those without evidence of syphilis. Results not supporting this hypothesis would include an absence of systematic, statistically significant co-variance between the frequencies of these indicators and the presence of tertiary lesions. Equally, results inconsistent with this hypothesis would systematic, statistically significant, lower frequencies of these indicators on individuals with evidence of tertiary syphilis.

H_3b: Overall health status is associated with the manifestations of

tertiary syphilis.

This hypothesis proposes that the manifestations of tertiary syphilis, specifically the presence or absence of gummata, vary by the overall health of infected individuals. Overall health is estimated here through frequencies of periodontitis, dental caries, and linear enamel hypoplasias (LEH). It is assumed that these indicators, which are associated with frailty, reduced immunocompetence, and hyper-inflammatory responses, may elucidate to some degree the immunological and inflammatory processes associated with the manifestations of tertiary disease, specifically the formation of gummata. This hypothesis was evaluated in a subset of the overall skeletal sample.

Results in support of this hypothesis would include systematic, statistically significant co-variance between the presence of gummata and frequencies of at least one of the following indicators: linear enamel hypoplasias, periostitis, and dental caries. Specifically, it is expected that 1) frequencies of at least one of the indicators will be positively correlated with the presence of gummata in syphilitic individuals. Measures of frequency accommodate issues of skeletal preservation. Results not supporting this hypothesis would include an absence of systematic, statistically significant co-variance between frequencies of at least one of the above indicators and the presence of gummata. Additionally, results suggesting that frequencies of at least one of these indicators are not positively correlated with the presence of gummata would be inconsistent with this hypothesis.

Hypothesis 4 (H_4): Evidence of mercury treatment for syphilis is associated with gender and socioeconomic status.

Controversy exists over the accessibility of mercury treatments for syphilis in early modern England. Previous scholarship has suggested that mercury treatments were exclusive to more affluent members of the society, though in the later 18th and early 19th century this dynamic may have switched, with the poor receiving large doses of the element. Women were presumed to have had systematically less access to treatment. More recent scholarship instead suggests that while this relationship may have been true for women, affluent individuals may have always avoided mercury treatments and the poor seem to have had free access to the drug through most of the period. To assess whether direct evidence supports these relationships, three sub-hypotheses are tested.

H_4a: Evidence of mercury treatment is detectable in human skeletal remains.

This hypothesis is premised on the assumption that evidence of therapeutic treatment with mercury is detectable via trace element analysis. Specifically it assumes that therapeutic exposure produces levels above 1 ppm that are detectable via non-destructive trace element analysis (via XRF) in skeletal material. This implies: 1) that levels are not expected to associate with levels of mercury detectable in the adjacent soil but instead to reflect endogenous exposure, and 2) that levels detectable in skeletons with evidence of syphilis are systematically elevated in comparison to skeletons without evidence of

syphilis. Support for this hypothesis has already been found in two published studies. Rasmussen et al. (2008) found elevated levels of Hg in a sample of post-medieval skeletons from Denmark. Tucker (2007) found the equivalent in a small sample of syphilitic skeletons from London, but did not use a relevant control to control for endogenous or diagenetic exposure (e.g., skeletal material or soil samples from the same archaeological site or time period).

Results in support of this hypothesis would be 1) a systematic, statistically significant absence of co-variance between Hg emission values in skeletal material and those from soil samples recovered in close proximity to the aforesaid material, and 2) systematic, statistically significant differences between the Hg emission values in skeletal material exhibiting lesions associated with syphilis and in non-pathological (e.g., non-syphilitic) skeletal material. This difference would be found systematically among the sample. Results not in support of this hypothesis would include 1) co-variance between Hg emission values in skeletal material and those from soil samples recovered in close proximity to the aforesaid material, and 2) insignificant differences between Hg emission values in syphilitic *vs*. presumably non-syphilitic individuals. The former would indicate diagenetic transfer of Hg between soil, groundwater, or adjacent materials and skeletal material. While possible, as mentioned above, evidence for this phenomenon has yet to be documented in studies of archaeological material. It would invalidate all of the results generated from the analysis of Hg, access to treatment, and syphilis. The latter might indicate several things: that exposure to high levels of mercury (i.e., levels high enough for detection of Hg in skeletal material at >1 ppm (see Background in Chapter Six))—for a number of possible reasons, including therapy or occupational exposure—was

ubiquitous among some communities in London, at least the ones represented by the analyzed skeletal samples. It might also indicate that individuals within the pathological sample selected did not receive treatment with mercury or that if they did, it involved dosages equivalent to the endogenous exposure received by many other contemporary Londoners. This result would preclude the remainder of analyses included in Chapter Six.

H_4b: Levels of mercury are not heterogeneously distributed throughout the skeleton or within skeletal elements.

This hypothesis is derived from literature examining the uptake of lead within the skeleton, following the assumption that as heavy metals, their routes of uptake may be similar. It is also premised on Waldron's (personal communication) argument that mercury is likely to distribute homogenously throughout the skeleton and within skeletal elements (see Tucker 2007). Both Tucker and Rasmussen et al. (2008) operated under this assumption, as indicated by their methodologies, in which only one element (ribs and femorae, respectively) were sampled to detect Hg concentrations.

Results consistent with this hypothesis would be 1) systematic, statistically significant co-variance between Hg emission values generated by ribs and mean values generated from the femora (i.e., a mean of the five locations sampled on each femur (see Methods, Trace Element Analysis); and 2) systematic, statistically significant co-variance between Hg emission values generated from the five locations sampled on each femur. Results inconsistent with this hypothesis would include be 1) an absence of systematic, statistically significant co-variance between Hg emission values generated by ribs and

mean values generated from the femora (i.e., a mean of the five locations sampled on each femur (see Methods, Trace Element Analysis); and 2) an absence of systematic, statistically significant co-variance between Hg emission values generated from the five locations sampled on each femur. These findings would indicate that Hg is deposited heterogeneously—and thus differently from lead—within the skeleton and within each element, at least among those sampled.

H_4c: Levels of mercury are associated with socioeconomic status.

This hypothesis is premised on historical literature suggesting a relationship between socioeconomic status and access to therapeutic treatment with mercury. Emission values of Hg detectable in human bone are expected to vary with categories of socioeconomic status (which was derived from indicators such as burial location, coffin hardware and type, and the overall socioeconomic status of the originating cemetery by the original excavators and osteologists for every given skeletal sample included in this analysis (see Methods, Chapter Six). Levels are detected using trace element analysis via XRF. As mentioned in **H_4a**, levels are not expected to associate with levels of mercury detectable in the adjacent soil but instead to reflect endogenous exposure.

Results in support of this hypothesis would include the systematic, statistically significant co-variance between categories of socioeconomic status (see **Table 6**) and Hg emission values found in skeletal individuals exhibiting lesions associated with syphilis. Co-variance may exist between any category and Hg emission values; a set relationship in any direction is not dictated by the relevant historical literature. Results not in support

of this hypothesis would include an absence of systematic, statistically significant co-variance between categories of socioeconomic status (see Table 6) and Hg emission values found in skeletal individuals exhibiting lesions associated with syphilis. The latter would suggest no relationship between categories of socioeconomic status and access to mercury treatments. This finding would be inconsistent with historical literature on the subject.

H_4d: Levels of mercury are associated with gender.

This hypothesis assesses whether direct evidence can be found for the differential access to mercury treatments between men and women that historians have proposed. It tests whether 'gender' is systematically associated with levels of mercury, i.e., access to treatment with mercury, among those infected with syphilis (see Chapter Six for a discussion of estimation of gender in this study). Levels of mercury are expected to systematically differ between skeletons of different sexes as well as between control and pathological skeletons of both sexes.

Results consistent with this hypothesis would be a systematic, statistically significant co-variance between sex (i.e., male or female) among skeletal individuals exhibiting lesions associated with syphilis and Hg emissions values. As discussed in the Methods section, individuals included in the analysis in Chapter Six were limited to those who could be assigned to categories of either 'male' or 'female' based on skeletal morphology. Those with more ambiguous morphology were excluded from this analysis. Results inconsistent with this hypothesis would include the absence of a systematic,

statistically significant co-variance between sex (i.e., male or female) among skeletal individuals exhibiting lesions associated with syphilis and Hg emissions values. This might suggest that biological sex, as estimated from the skeleton, is not clearly correlated with behavioral differences, being differences in access to mercury treatments. It might also suggest that gendered ideologies did not strongly influence the actual practice of seeking and receiving mercury treatments. Alternately, these results might suggest that such ideologies did not operate for individuals in the original communities for thess cemeteries.

Methods

Pathological and osteological inventory

Every skeleton in the pathological sample (N=57) was digitally photographed and subject to osteological and pathological inventory; in many cases the inventory duplicated that performed previously by other researchers (e.g., collections at the Museum of London and University of Sheffield), but at others, this represents the only systematic data collection performed on these skeletons. Data was collected following established standards (Buikstra and Ubelaker 1994; Powers 2008) and later coded for statistical analysis following Connell and Rauxloh (2003). Methods for the trace element analysis, via XRF, are described in Chapter Six.

Dates

Attributed dates for each individual have been derived from published and unpublished site reports, skeletal inventories, book chapters, or published, peer-reviewed articles. These were generated from radiocarbon, stratigraphic, and relative evidence. The method(s) used to date each skeleton are listed in (see Table 1). Radiocarbon dates for those individuals with a putatively Pre-Columbian date who were incorporated into the analysis in Chapter Three are separately reviewed in Table 2.

Element presence

Bone preservation was not recorded, but to accommodate the effects of preservation disparities on the presence, extent, and distribution of pathological lesions, element preservation was coded separately. Bones of the face and skull were recorded using binary code (0=absent; 1=present) to be crosschecked against the presence of pathologies (see *Pathology)*. The remainder was coded to incorporate the presence and type of pathology as well as the presence of a given element (see *Pathology: Syphilis &* Table 7). Ribs, and bones of the hands and feet were recorded and coded as present or absent by side (R/L & not sided). Long bones, clavicles, and the innominates were recorded and coded by sides as well as divided into three portions and scapulae into four portions (see Table 7). The sternum was divided into the body and manubrium. For the purposes of recording and coding data specifically on syphilis, the presence of the xiphoid process was recorded but not coded as syphilitic involvement has not been reported in the published literature. Likewise, vertebrae were divided into cervical vertebrae and general vertebrae, following the same rationale (see Ortner 2003). To be

recorded as present, 50% of each element or, when divided, the portion of each element had to be present.

The presence of all joints was recorded but only those reported in the published literature as having been involved in syphilitic pathology were coded (see *Joint Involvement*). Non-syphilitic involvement was recorded for all joints (see *Pathology: Other*).

Following Powers (2008) and Hillson (1996) tooth presence, dental stress indicators, and oral pathology were recorded using the *Fédération Dentaire Internationale* (FDI) (1971) system. This system allows a more precise estimate of the prevalence of oral pathology (Hillson 1996) (see Table 8).

Age

Age was estimated using auricular surface degeneration (Buikstra and Ubelaker 1994; Lovejoy et al. 1985) and pubic symphysis degeneration (Brooks and Suchey 1990; Lovejoy et al. 1985) for adults. Because of difficulty in ascribing age estimates to adult remains, particularly older adults, broad age ranges were used for analysis, following Powers (2008) (Table 8). Ages given for known-named individuals were crosschecked against skeletal indicators. For older sub-adults (>17yrs), age was estimated using dental eruption data and epiphyseal fusion. Eruption was coded following Buikstra and Ubelaker (1994). Estimated ages were based on the average age attained from both male and female data. Fusion was coded with reference to Scheuer and Black (2000) and Connell and Rauxloh (2003) and, in all observable epiphyses, visually quantified as

fused, fusing or unfused following Buikstra and Ubelaker (1994). Dental data were given priority when contradictory results were found. For the purposes of analysis for Chapter Five, age was recoded into a binomial variable to indicate whether adult individuals (>18 yrs) were of reproductive age (18-45 yrs) or generally reproductive age (>46 yrs) (see Table 4).

Sex

Sex of adult individuals was estimated using methods based on macroscopic assessment of skull and pelvic dimorphism and metric data on some post-cranial elements, following (Bass 1995 [1971]; Ferembach et al. 1980). Included features were graded using a scale, following Buikstra and Ubelaker (1994), and coded following Connell and Rauxloh (2003). Given the small sample size, for the purposes of analysis for Chapter Five, sex was recoded into a binomial variable. The categories of M and M? and F and F? were collapsed into three categories: M, F, and ? for those of indeterminate sex (see Table 5). Juveniles (<17 yrs), who cannot be reliably sexed (Wright and Yoder 2003) using macroscopic indicators, were not incorporated into this analysis.

Socioeconomic status

See Chapter Six for a discussion of the attribution of socioeconomic status.

Gender

See Chapter Six for a discussion of the attribution of gender.

Metric data

Limited dental and post-cranial metrics were recorded. Dental measurements—mesiodistal and buccolingual crown diameters—were recorded using sliding digital calipers on the maxillary and mandibular canines and first molars (permanent) (see Table 9). When possible, loose teeth were extracted to enable mesiodistal measurements. If caries, calculus, extreme attrition, post-mortem damage or the proximity of adjacent teeth obscured the crown, metrics were not collected. Post-cranial metrics were recorded only for the femur, preferentially for the left. Maximum femoral length (FeL1) was recorded (cm), using an osteometric board, for intact femorae or those with a single close fitting break only. This was collected following Buikstra and Ubelaker (1994). It was used to estimate stature using the regression formulae for 'white' males or females derived by Trotter (1970).

Dental pathology

Five main aspects of dental pathology are recorded (caries, calculus, enamel hypoplasia, periodontitis and periapical lesions (abscesses), though all other forms of pathologies and anomalies were recorded when found. All but calculus were included in the following analyses. All pathologies were recorded for each individual tooth and to

indicate the location and advancement of the pathology. To allow the most accurate assessments, it was noted (i.e., 999) when one pathology or alteration interfered with recording or obscured another. Each pathological lesion was coded separately. Caries are defined as destruction of the enamel, dentine and cement (from acid production by bacteria in dental plaque) manifesting as a cavity in the crown or root surface (Hillson 1996). They were recorded at the individual tooth level, noting the location and severity of the lesions (see Table 10); the most severe was recorded for each tooth. Location was recorded following Buikstra and Ubelaker (1994). Severity was recorded following Powers (2008). Calculus, or mineralized plaque adhering to the tooth surface (Hillson 1996), was recorded on individual teeth. Location and amount were recorded following Buikstra and Ubelaker (1994). Hypoplastic defects, both linear (LEH) and pit-shaped interruptions in enamel formation, were identified following Hillson (1996) and recorded on individual teeth following Buikstra and Ubelaker (1994). Periodontal disease (periodontitis), or severe gingivitis associated with alveolar porosity and bone resorption, was also recorded at an individual tooth level. The condition was recorded in stages, following Brothwell (1981a), based on the distance between the CEJ and the alveolus (mm). It was not recorded (i.e., 999) in the case of tooth loss or damage to the alveolus (see Table 9). Variation in dental eruption, attrition, and development must be incorporated into analysis of these measures Hillson (1996). Periapical lesions (abscesses) were diagnosed following Hillson (1996), and recorded at the parent tooth position according to the location of the largest sinus drainage (i.e., 999=alveolus absent; 0=absent; 1=present).

Pathology

Evidence of all pathologies and anomalies present was recorded but only those relevant to the following analyses were coded and incorporated. All of these were recorded following established standards (Buikstra and Ubelaker 1994).

Pathology: Syphilis

The full spectrum of syphilitic lesions was recorded and coded. These were recorded as discrete ordinal arrays. Lesion type, or the presence of gondou (periosteal reactions on the maxilla), gangosa (palatal perforation and rhinomaxillary destruction), and caries sicca was recorded for the vault. These variables were crosschecked against element presence. On the post-crania, the absolute number of gumma, presence of periosteal reactions, and lytic pitting (non-gummatous) was recorded for every element, element portion, or element group. Dactylitis was recorded for the hands and feet as well as periosteal deposition. Presence of osteitis, long-term healing, amputation or element destruction through lytic activity was also recorded and coded if present on any element in the skeleton. For all of the above, whether the lesions were also active (proliferative or lytic) was also recorded, as well as whether there was evidence of healing, both of which could co-exist in the same lesion. To control for bone preservation and element presence, this code also incorporated a variable for element presence. No evidence of other syphilitic manifestations, namely aortic aneurysms or pathological fractures, were found in the sample under study. Syphilitic pathology was recorded for major each skeletal

element of the appendicular and axial skeleton. As described above and denoted in Table 7 some elements were grouped, such as bones of the hands and feet, ribs, and vertebrae. Joint involvement caused by syphilitic and gummatous arthritis was also recorded and coded. As it is not possible to distinguish isolated syphilitic arthritis from osteoarthritis, joint involvement was only diagnosed when periosteal reactions and proliferation present on a non-joint surface extended onto a joint surface. Gummatous arthritis was recorded when gummata involved a joint surface. When present, a gumma on a joint was also added to the absolute count of gumma on that element, portion of an element, or group of elements. These were diagnosed following Aufderheide and Rodrìguez-Martìn (1998b).

Pathology: Other

The full range of observable non-syphilitic pathologies was recorded. From these, evidence of co-infection, trauma, metabolic disease, cribra orbitalia, osteoporosis or osteomalacia, and osteoarthritis and activity related changes (MSM) were coded. These were diagnosed following Ortner (2003). Cribra orbitalia was recorded for each orbit, following the grades established by Stuart-Macadam (1989) (see Table 11).

Pathological Data Collection: Clinical and Autopsy Sample

Data was derived from three primary publications: Turner (1930), Gjestland (1955), and Rosahn and Black-Schaffer (Rosahn 1946; Rosahn 1947; Rosahn and Black-Schaffer 1943a; Rosahn and Black-Schaffer 1943b). Information available and amenable to the analysis included here include the numbers of cases and, broken down, the

numbers of male and female cases manifesting specific disease stages and types of involvement and lesions (see Table 3).

Trace Element Analysis

A subset of the overall pathological sample (N=30) was subjected to non-destructive trace element analysis via X-Ray Florescence Spectrometry (XRF) to detect evidence of mercury treatment for syphilis. These individuals dated to the 17th through 19th centuries and were derived from the Chelsea Old Church site, St. Thomas's Hospital/ New London Bridge, St. Bride's Lower Churchyard, St. Benet Sherehog/ Number One Poultry, Red Cross Way/ Cross Bones, and the St. Bride's crypt sites, all in London. As mentioned above, an additional, larger sample (N=75) of non-pathological individuals was also analyzed to control for endogenous exposure and associated soil samples (N=13) to control for diagenetic exposure (see Table 28). See Chapter Six for methodology for the trace element analysis.

Chapter Three: Sex Gets Less Dangerous? Investigating the Evolution of Virulence in Syphilis

Introduction

As Naples fell before the army of Charles VIII in 1495, a plague broke out among the French King's troops (Gruner 1789). Early modern commentators and modern historians alike generally consider this to represent the first recorded epidemic of acquired syphilis (Clowes 1585; Crosby 1972b; Cunningham and Grell 2000; Lowe 1596; Quétel 1990; Rosebury 1971). When the army, composed largely of mercenaries, disbanded shortly after the invasion, the troops returned to their homes and disseminated the disease (Brown et al. 1970; Williams et al. 1927). By 1500, it was widespread across Europe and moving rapidly into Asia (Pusey 1933).

Initial reports of the new disease described it as a fearsome plague, which caused excruciating pain, severely disfigured sufferers, and was frequently and rapidly fatal. Reports describe foul smelling, black and green acorn-like scabs that covered the face and body, debilitating bone and joint pains, and gummy tumors and ulcers which frequently caused loss of the nose and eyes, genitalia, and even whole limbs. By the early 1500s, however, reports began circulating that the pox was growing weaker (Benedictus 1507; Fracastoro 1546; Grunpeckii de Mantalagra 1503), with milder symptoms and reduced mortality, and was also easier to cure (Fallopio 1564). Some particularly optimistic physicians even predicted that the disease would become extinct on specific calendar dates (Quétel 1990). Overall, available evidence indicates that within ten to

fifteen years after the start of the epidemic, the mortality associated with the disease decreased and the severity of its manifestations declined (Tognotti 2009).

These reports of attenuation in the disease have been interpreted in multiple ways. Some researchers have viewed them as evidence of the emergence of acquired resistance and herd or widespread immunity to a novel infection soon after the epidemic's onset (Cartwright and Biddis 2000; McKeown et al. 1975; Oriel 1994). Others have argued that it was due to the rapid death of the most susceptible individuals as the disease swept across Eurasia, leaving only less vulnerable hosts and thus milder cases in its wake (de Melo et al. 2010). The predominant explanation is that the causal agent of syphilis, *Treponema pallidum* subspecies *pallidum*, attenuated or evolved in virulence. To many authors, Renaissance-era syphilis thus represents the first credible known example of this evolutionary phenomenon in a human disease (Garnett 2002; Hudson 1963; 1965; Knell 2004).

Several scholars have questioned this claim. Carmichael (1990) has argued that such drastic genetic changes could not have occurred in either hosts or the pathogen in such a narrow time frame. Instead, Carmichael suggests that early reports of syphilis' lethality and severity were fueled by panic and fear over the outbreak of a new disease rather than the actual manifestations of the disease. Other historians emphasize that while the disease clearly changed over the years (Arrizabalaga et al. 1997), this well-accepted claim is based on second hand information reiterated over centuries by syphilographers and historians of medicine (Tognotti 2009). Even first-hand accounts are complicated by differences between Renaissance and modern nosologies, ambiguous information, and the stigma accompanying the disease (Arrizabalaga et al. 1997). A review of the

published literature reveals that direct evidence for a decline in the severity of syphilis' manifestations has yet to be evaluated.

To address this, this paper evaluates evidence for the evolution of virulence in syphilis using a sample of human skeletal remains from Post-Columbian England (c. 15th-16th c.). Suites of skeletal manifestations on individuals dated to specific time periods, collectively spanning the 15th to 16th centuries, have been evaluated against information on temporal changes in the manifestations of syphilis recorded in historical literature. This information has been gleaned from secondary translations of contemporary physicians' reports, chronicles, and patient narratives that were published throughout the 19th to 21st centuries. In doing so, this study attempts to cross the divide between historical and paleopathological approaches to the history of the disease. An important revisionist history has stressed that because syphilis was identified by Renaissance physicians and laity alike by an inclusive set of symbolic, socially constructed symptoms (Harris 1996; 2005), it is impossible to identify it using modern diagnostic criteria—the practice of retrospective diagnosis (Harley 1999; Siena 2005c). Renaissance commentators employed their own disease concept—the venereal disease—that encompassed a range of conditions, including gonorrhea, in the vernacular of terms like the 'French Disease,' 'Mal Francese,' and in England, 'the pox' (Arrizabalaga et al. 1997). 'Syphilis' was not commonly used until the 1700s (Quétel 1990). This approach, however, precludes studying 'syphilis' in the pre-modern era and thus longer continuities of disease history (Healy 2001). In marked contrast, paleopathological approaches to the history of disease use biomedically-derived diagnostic criteria to trace the presence of extant disease conditions throughout the archaeological record (e.g., Ortner 2003). While

it is acknowledged that diseases may not manifest the same pattern of skeletal lesions in each spatial, temporal, or cultural context (Weaver et al. 2005), this variation is assumed to be minimal (Cohen and Cane-Kramer 2003). To conduct this study, an underlying entity of acquired syphilis is assumed to exist (following Watts 1997, contra Arrizabalaga et al. 2007), grounded in gross skeletal evidence of a specific disease. This direct evidence is then evaluated against Renaissance-era reports of the disease's symptoms, following the assumption that the history of syphilis can be found in the middle ground between these two lines of evidence (see Watts 1997). Skeletal evidence is used to evaluate three questions: (1) did syphilis evolve attenuate or evolve in virulence? (2) If so, did it do so in the manner indicated in 15th and 16th century reports? Lastly (3), are any changes found in the manifestations of the disease consistent with the most popular hypothesis, that changes in the disease's manifestations are due to selection favoring milder strains of the pathogen, as suggested by Knell (2004)?

Background

Historically, prevailing theories assumed that virulence (defined here as morbidity and mortality of hosts caused by parasites and pathogens) was a deleterious side effect of novel host-pathogen associations that would eventually evolve to low levels (e.g., Dubos 1965). This assumption was implicitly based on the belief that group selection determined the course of pathogen evolution (e.g., Burnet 1953), along with prominent historical examples of disease attenuation, such as myxoma virus and syphilis, which seem to illustrate this trend (e.g., Fenner and Ratcliffe 1965). However, as the importance of group selection in nature was discounted, and observational studies and experiments

demonstrated that this attenuation was by no means universal, this simple hypothesis was rejected in favor of more sophisticated frameworks (Anderson and May 1982; Bull 1994; Ebert 1994; Herre 1993; Levin and Svanborg-Eden 1990).

Since the 1980s, variations in virulence have been reinterpreted as products of natural selection (Wallace 1989). Depending on the costs and benefits of virulence, host and parasite physiology, historical constraints, and variation in biological, ecological, and epidemiological aspects of host-pathogen interactions, almost any level of evolved virulence is now understood to be possible (Bull 1994). For the most part, these models are pathogen-centric. Known as trade-off models, they emphasize the role of virulence in pathogen fitness and model the direction of selection acting on virulence as an issue of optimality between levels of pathogen transmission and reproduction and host longevity and survival (e.g., Anderson and May 1982; Ewald 1983). This has led to goals of virulence management, wherein interventions would be designed to select for lower levels of virulence and avoid practices that encourage escalation of virulence (e.g., Dieckmann et al. 2002; Ewald 1994a; Gandon 2001). While these models and high ambitions of virulence management have been critiqued on both theoretical and empirical grounds (i.e. Ebert and Bull 2003), less ambitious aims, such as understanding the evolution of virulence to gain insight into the future of emerging infectious diseases like Ebola or bird flu, continue to provide practical reasons for investigating this phenomenon (Ebert and Bull 2008).

A growing body of literature employs models that instead approach virulence as a result of co-evolutionary associations between host and pathogenic genotypes. These are fueled by critiques that two dimensional trade-off models ignore the roles of immune

response, host genotypic heterogeneity, life history and behavior, and—with particular relevance to syphilis—that factors such as infectivity are not constant throughout the course of infection (i.e. Ebert and Bull 2003). In these models, virulence is associated with decreased host fitness but is not necessarily linked to transmissibility; it can be associated with decreased or increased pathogen fitness or, according to some models, even be selectively neutral to the pathogen (Ebert 1994; Frank 1996; Levin 1996). It is a product of antagonistic selection, lying somewhere between the host and pathogen's optima, and is not readily predictable (Ebert and Hamilton 1996). Epidemiological feedbacks can also vary the outcomes (Gandon et al. 2002; Restif et al. 2001). While the mechanisms underlying virulence remain incompletely understood, intra-population host heterogeneity is known to be common and play a major role in disease expression. Virulence across different combinations of host and pathogen genotypes has been demonstrated to vary profoundly (Carius et al. 2001; Hill 1991; Rauch et al. 2006; Singh et al. 1997). It is also increasingly realized that virulence is also often due to an over-reaction by the host immune system (Margolis and Levin 2007). This has been hypothesized for the Spanish flu virus (Kobasa et al. 2007) and may also be true for syphilis; its most destructive lesions, gummata, may be caused by exaggerated delayed-type hypersensitivity, a hyper-allergenic response to spirochetes or their antigens (Jaffe 1972; Musher and Baughn 1998; Salazar et al. 2002). However, methods for incorporating immune over-response into models for the evolution of virulence have yet to be developed (Ebert and Bull 2008). As discussed below, host heterogeneity may have exerted selective pressure on the virulence of syphilis, but given the speed with which the documented changes occurred, host evolution is not a viable consideration.

There are three successive phases in the progression of disease adaptation in a novel host. The first involves first contact between novel hosts and pathogens, either due to accidental infection, or, as with syphilis, emergence of a novel pathogen (Ebert and Bull 2008). Because the genes responsible for virulence did not evolve in the conditions in which they express in a novel host, their effect on the host is unpredictable and is not expected to follow evolutionary principles (Levin and Svanborg-Edén 1990). Novel infections are not necessarily more virulent; a bias towards reporting more virulent ones is likely to blame for this long-standing belief (Ebert 1994). The second constitutes the epidemic stage for pathogens, and also applies to the spread of novel variants of existing pathogens in old hosts. In this stage, the pathogen is generally not well adapted to the host, leading to rapid evolution of the host, the parasite, and potentially, of virulence, which may be far from optimal. Within-host evolution between strains also usually selects for higher growth rates and thus potentially higher virulence (Novella et al. 1995). Rabbit-myxoma virus is the classic example of this stage (Fenner and Kerr 1994). The third is an endemic phase. Trade-off models predict that diseases should approach equilibrium virulence as pathogens evolve to trade-off boundaries between their fitness components, namely transmissibility (Anderson and May 1982; Ewald 1980; Mackinnon and Read 2004). Virulence, transmission, and within host-growth are predicted to be positively correlated (Bull and Molineux 1992; Ebert and Mangin 1997) with an expectation that intermediate virulence is optimal (Anderson and May 1982; Fenner and Ratcliffe 1965; Jensen et al. 2006). However, subtle variations in the location of pathogen densities within an organism disprove this prediction (Levin and Bull 1994). Likewise, the evolved reduction in virulence selected by vaccination targeting specific toxins in

diphtheria has shown that virulence is not always a correlated trait but can be directly selected against.

The virulence of sexually transmitted infections (STIs) is also related to both heterogeneity in the transmissibility of infection, dependent on adaptive and innate immune responses, and host mating success (Knell 1999; Lena et al. 2005). Pathogen genotypic adaptation to one host genotype has been found to increase virulence on that genotype and reduce the pathogen's ability to exploit other host genotypes (Ebert 1998), but the generality of this is unclear (Ebert and Bull 2008). Garamszegi (2006) has found that generalist species of malaria are less virulent than specialist species, suggesting that in genetically diverse host populations, pathogens may have to adapt anew whenever they are transmitted, resulting in lowered virulence. The same has been proposed, but not yet evaluated, in HIV (Ariën et al. 2007). As phylogenetic and skeletal evidence strongly suggests that neither syphilis or related variants were present in the Pre-Columbian Old World (Harper et al. 2008a; Harper et al. Accepted), the effects of innate immunity on virulence (Lena et al. 2005) are presumably negligible. More simplistic trade-off models suggest that duration of infectivity and opportunities for transmission have the most selective influence. For example, higher virulence has also been predicted to be selectively favored in epidemic conditions (phase 1) but not in endemic ones (phase 2), dependent on the number of infected hosts. Short host-life spans have also been proposed to favor higher virulence, though tests of this prediction have failed (Ebert and Mangin 1997). As STIs depend on normal host activity for transmission, low virulence and/ or long latency periods may also be selected for to promote transmission. The same may also occur in populations with reduced potential for encounters with new hosts (Boots

and Mealor 2007). Some researchers have also proposed that pathogens that produce conspicuous lesions or affect the sexual attractiveness of their hosts are likely to be selected against (Hurst et al. 1995; Knell 1999), but this has yet to be evaluated in human sexual networks.

One of the most obvious difficulties in determining the mechanisms operating on the evolution of virulence is that attenuation has rarely been documented (Ebert and Bull 2003; Ebert and Bull 2008). Instances have been documented in plant parasites (Escriu et al. 2003), rabbit-myxoma virus (Best and Kerr 2000; Zuniga 2002), corona virus in pigs, potentially HIV-1 and 2 in some primates species (Fultz et al. 1990; Kestens et al. 1995), foot and mouth disease *in vitro* (de la Torre et al. 1988), and in humans, diphtheria. It has also been proposed, though with varying support, for the 1918 influenza pandemic (Kobasa et al. 2007) and the Black Death (Drancourt et al. 2006; Gage and Kosoy 2005). In addition, there are few studies of direct selection on virulence traits, such as with diphtheria, where evolutionary response would be much more rapid than that proposed in trade-off models where virulence is a correlated trait. Interestingly, the existing examples do not support any general model, and instead suggest that models must be specific to the details of the disease and its virulence (Ebert and Bull 2008).

Syphilis: natural history of the untreated disease

Syphilis is a multi-stage disease with protean manifestations. Primary stage infection, which begins approximately three weeks (avg. 3-90 days) after inoculation, involves a single painless indurated ulcer (chancre) at the infection site and regional

lymphadenopathy. Approximately two to twelve weeks later (max. 6 months), secondary infection ensues, causing a range of symptoms including rash, fever, malaise, systemic lymphadenopathy, mucus lesions, condyloma lata, alopecia, meningitis, and headaches. On the skeleton, periosteal lesions, or sub-periosteal bone deposition, and osteitis, the same in the marrow cavity, can occur but often quickly remodel (Ortner 2003). After a year or more of latent, asymptomatic infection, in which recrudescent infection occurs in 25% of modern cases, tertiary stage may follow in 15 to 30% of cases (avg. 10-30 yrs after infection) (Gjestland 1955). This includes cardiovascular involvement, neurosyphilis (i.e. meningitis, meningovascular involvement, paresis, tabes dorsalis), and gummata, or focal necrotizing gummy tumors that can affect any organ, including the skeleton, along with systemic periosteal deposition (see LaFond and Lukehart 2006; Singh and Romanowski 1999). Tertiary disease is thus the only stage that is reliably identifiable on the skeleton (Ortner 2003). Syphilis is transmissible in the primary, secondary, and early latent stages through sexual contact, though kissing and other routes have been documented. Estimates vary significantly, but transmission probability per partner is assumed to be approximately 60% (Garnett et al. 1997). However, only 16 to 30% of individuals who have sexual contact with an infected person (within thirty previous days) become infected (Moore et al. 1963; Schroeter et al. 1971). Increased bacterial load in the donor, and consequently the inoculating dose, increases the efficiency of disease transmission.

These three stages and their timing can be found in even the earliest descriptions of the epidemic (de Béthencourt 1527; di Silvestro 1922), but many of the manifestations reported in the early years of the epidemic are strikingly different. According to Tognotti

(2009), all contemporary sources, from physicians' treatises to chroniclers and patient narratives, emphasize the extremely malignant character of early syphilis and that a downshift to a milder form was witnessed within just a few years from the onset of the initial epidemic (Benedictus 1507; De Bordigné 1529; von Hutten [1519] 1945). Several stages are evident in this transformation: initial high virulence attenuating after several years, followed by a more rapid onset of florid secondary lesions though pustules, bone and joint pain, and necrotic lesions declined in severity. 'Bad smells' associated with the former also became rare. After several decades, alopecia and other novel symptoms arose and the disease began to exhibit the polymorphic phenotypes that would later grant it the moniker of the 'Great Imitator' (Astruc 1738; Tognotti 2009) (see Table 13)**.**

However, Tognotti and others emphasize that these historical sources must be approached with caution. Interpreting historical sources, particularly those dealing with a highly stigmatized medical condition such as syphilis, requires attention to the biases, limitations, and ambiguities inherent to the material. The principal concern is that descriptions of syphilis by different 15th and 16th century authors have much in common but are not all the same (Arrizabalaga et al. 1997). In particular, information on the timing of perceived shifts tends to be discordant. von Hutten's ([1519] 1945) estimate that syphilis had attenuated within 5 to 7 years of the initial epidemic was seconded by many contemporaries (Benedictus 1507; De Bordigné 1529; Grunpeckii de Mantalagra 1503) and has been accepted by many modern researchers (Knell 2004). However other sources indicate a significantly longer transition (Astruc 1738; Fracastoro 1530). Indeed, Tognotti's (2009) review of first-hand accounts of the transition suggest that it instead occurred in several stages over the course of ten to fifteen years. While some have argued

that von Hutten's estimate is far too short to accommodate pathogenic (or host) evolution, studies of myxoma virus (Fenner and Kerr 1994) and reversion to virulence in attenuated vaccines (Kew et al. 2004) have shown that virulence can evolve within a few years (Ebert and Bull 2008). This also aligns with Tognotti's estimate.

Differences in these reports may be due to a variety of factors. Some historians argue that syphilis, whether called 'the pox' or 'Mal Francese,' was used as a diagnostic catchall for a variety of conditions (Arrizabalaga et al. 1997; Siena 2005b), though others contend that syphilis was clearly differentiated from these soon after its emergence (Tognotti 2009). Drafts of chronicles may also have been altered at different stages (Arrizabalaga et al. 1997) and differ dependent on whether they describe first-hand experiences or derivatives from previous reports and oral traditions. Historians also often fail to distinguish between the dates when the first changes were observed and those when a major decline in virulence was could be seen, as well as not sufficiently attending to the new features the disease presented at various steps (Arrizabalaga et al. 1997; Tognotti 2009). In an attempt to accommodate these complications, descriptions of symptoms have been gathered from multiple historical sources written at various times from multiple regions (see Table 13).

Proposed explanations for the decline in virulence

While writers had mostly achieved an informed consensus that syphilis had attenuated by the mid 20th century (Guerra 1978; Hudson 1963; 1965), explanations for this that follow an evolutionary framework have only been recently proposed (Knell

2004). These are based on the Columbian Hypothesis, one of two dominant hypotheses for the origin of syphilis[4]. This proposes that syphilis originated in the New World and was transmitted to the Old by Columbus in the 1490s (Baker and Armelagos 1988; Crosby 1969). Recent phylogenetic work has confirmed this, further suggesting that the migrant was a venereal or non-venereal progenitor of modern syphilis-causing strains (Harper et al. 2008a; Harper et al. 2008b; contra Mulligan et al. 2008). This, combined with the absence of skeletal evidence for Pre-Columbian treponemal disease in the Old World, eliminates concerns of acquired immunity to the disease in these populations (Harper et al. Accepted) and its effect on transmission dynamics. Accordingly, Knell (2004) has argued that the initial high virulence may have been due to a switch in the transmission mechanism (non-venereal to venereal) or to the absence of constraints related to either host physiology or resistance mechanisms in Old World populations. Similarly, Oriel (1994), Cartwright and Biddis (2000), and O'Shea (1990) have attributed it to a lack of immunity in these populations. In turn, they have proposed that attenuation was due to acquisition of immunity, though Knell has pointed out that the time frame in question is too short for selection for host resistance. The same is true for Tognotti's (2009) expanded time frame. Instead, Knell (2004) proposes that syphilis may have attenuated in response to direct selection against traits which affect host mating success, such as mobility and host sexual attractiveness. According to Knell, many of the symptoms described in the early stages of the epidemic, such as foul-smelling ulcers and facial destruction, would have been discouragingly evident to potential sexual partners. Bone and joint pain may also have reduced host mobility and possibly sexual activity.

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[4] The other, the Pre-Columbian Hypothesis, asserts that treponemal disease was present in the Old World before the 1490s. See Meyer et al. (2002) for further discussion.

Changes in environmental conditions over the course of the 16th century as well as interactions with heterogeneous host genotypes could have also had a selective effect on virulence in syphilis. As Knell notes, direct selection is not necessarily sufficient to explain all of the changes seen in the disease, such as the lengthened latent period; these factors could have operated alone or in concert. For example, optimality arguments suggest that short host-life spans favor higher virulence, though there is no evidence for a marked increase in longevity in Europe in the early 16th century. Changes in the number of infected hosts could also have selected for reduced virulence (Lenski and May 1994, Bonhoeffer et al. 1996, Bull 2006), but this seems equally unlikely. While prevalence of syphilis in the past is extremely difficult to estimate, contemporary reports and records suggest that it may not have become endemic until the 17th century (Arrizabalaga et al. 1997; Siena 2004). Similarly, the speed of syphilis' spread and an overall high degree of population mobility in renaissance Europe means that scarcity of new hosts is an unlikely selective factor. Instead, the opposite may be true. Historical material suggests that syphilis spread rapidly throughout Europe and Asia, and in doing so, would have been exposed to genotypically heterogeneous host populations. Syphilis appears to have spread throughout Italy in 1495 and 1496, reaching France (Buchon 1828; Gruner 1789), Italy, Spain, the Netherlands, Germany by 1496, Holland, Greece, England, and Scotland by 1497, Hungary, Russia, and India by 1504, and China and Japan quickly afterwards (Fabricius 1994; Fernandez de Oviedo y Valdes 1526; Quétel 1990). These explanations, however, are unsuited to analyses based on skeletal material and await epidemiological modeling.

Another possibility is that syphilis did not evolve in virulence at all. Various environmental factors can affect virulence, such as nutrition and immunity. Malnutrition, particularly protein-energy malnutrition, and associated diminished acquired and innate immune functions increases susceptibility to infection and compromises immune responsiveness to infection. Particularly when widespread across a population, malnutrition can dramatically increase the prevalence, mortality, and morbidity of epidemic and endemic infectious disease (Schaible and Kaufmann 2007). Consequently, broad social trends can affect virulence over time, giving the appearance that virulence has evolved when it has not. The 15th and 16th centuries were an overall period of high living standards in Europe, due to the high mortality of the Black Death and protracted labor shortages, resulting in high wages, low food prices, and significant improvements in dietary adequacy across all social strata (Dyer 2002; Stone 2006; Woolgar 2006). In the midst of this, some historians suggest that the 1490s and early 1500s involved low living standards, which may have intensified susceptibility to a novel infection. In Italy for example, the 1490s were characterized by widespread crop failures, plague epidemics, famine, and war, marking one of the period's lowest standards of living standards (Arrizabalaga et al. 1997; Carmichael 1986). Resumption of higher standards of living, including improvements in nutrition, could have reduced susceptibility to syphilis, resulting in perceived reductions in virulence. Indeed, O'Shea (1990) attributed the early virulence to 'disease synergy,' caused by malnutrition and co-infection. There is excellent evidence that malnutrition synergistically exacerbated the severity of infectious disease epidemics in the past, such as in smallpox and tuberculosis (Cegielski and McMurray 2004; Scott and Duncan 1998), but this has yet to be documented for syphilis.

Study Aims

The following analysis employs skeletal evidence to satisfy three objectives, following the hypotheses ($\mathbf{H_1}$, $\mathbf{H_1a}$, and $\mathbf{H_1b}$) described in Chapter Two. The first is to evaluate whether skeletal indicators from individuals dated to different time period bear evidence of changes in the manifestations of syphilis. The second is to assess whether these are consistent with the reported changes, and the third is to evaluate whether skeletal evidence supports the most prominent and evolutionarily well-supported hypothesis, that these changes are due to selection for milder strains (Knell 2004).

Models of the evolution of virulence typically use parasite-induced host death rate (PIHD) to measure virulence (Ewald 1994b), but this measure does not encompass host fitness traits, such as host's attractiveness to mating partners and general morbidity, which are more relevant to discussions of STIs and syphilis (Lockhart et al. 1996). Instead, to accommodate this concern, the measure of virulence employed here, the frequency of different types of skeletal lesions, reflects the degree to which pathogens produce symptoms in infected hosts. Those assessed here are highly conspicuous, including gummata, limb and skeletal element amputation, skull lesions (i.e., caries sicca or gummatous involvement of the cranium), and facial destruction (i.e., gondou and gangosa). Contemporary observers suggest that these lesions changed substantially in frequency over the 15th and 16th centuries. They are also particularly well suited to this analysis because they are primarily found only in syphilis (see Background & Methods), greatly limiting the likelihood of incorporating false positives, or cases of other infectious

diseases, into the sample. They are not free of interpretive complications however, which are addressed below. See Table 13 for descriptions of these indicators.

Other indicators of virulence that are suggested by the historical literature include measures of general morbidity and mortality, such as that indicated by the duration (i.e., chronic vs. acute skeletal involvement, evidence of long term healing) and tempo of infection (i.e., episodic skeletal involvement), and evidence of mortality (i.e., absence of healed skeletal lesions). However, these indicators are significantly more ambiguous and difficult to interpret. A substantial body of literature within paleopathology strongly suggests that the duration of infection and the tempo of infection cannot be securely derived from skeletal evidence (see Ortner 2003). This is likely particularly so for syphilis. As noted above, syphilis is a chronic infection, which is often recurrent throughout the life course; the underlying cause of this variation remains unknown (Radolf and Lukehart 2006). Given this, any evidence of temporal variation in the duration and tempo of infection found in the sample would not be clearly attributable to evolutionary change within the causal pathogen or even to larger ecological factors. As such, these indicators are not assessed within this study.

Materials and methods

The skeletal sample includes all currently accessible, archaeologically derived skeletons with macroscopic evidence of syphilis in England dated to the 15th through 16th centuries (N=16). A solitary case from Scotland has also been included for the purposes of the present analysis. This sample excludes approximately ten putative cases of acquired syphilis recovered from the St. Mary Spital site, London, which are reportedly

dated to the Pre-Columbian period. These cases are pending publication and remain closed to analysis by outside researchers. The impacts of non-inclusion of these skeletons on the present analysis are included in the Discussion section.

While many of the manifestations of syphilis do not affect the skeleton, others do, such as gummata, facial destruction, ulcers, and limb amputation. Bone, limb, and joint pain have also been reported in association with periosteal deposition, lytic bone lesions, and syphilitic arthritis in clinical cases (Hansen et al. 1984; Kumar et al. 1989; Rademacher and Radolf 1996), though this is not clear-cut. Because syphilitic joint involvement is not distinguishable from non-infectious osteoarthritis, it was only recorded when proliferative or lytic activity associated with a non-joint surface extended on to a joint surface (see Aufderheide and Rodrìguez-Martìn 1998a). Joint involvement was recorded for multiple joints throughout the body (i.e., sternoclavicular, acromioclavicular, glenohumeral, humeroulnar, humeroradial, radioulnar, radio-ulnar-carpal, carpo-metacarpal, metacarpophalangeal, femoro-patellar, tibio-patellar, tibio-fibular superior, tibio-fibular inferior, tibio-talar, fibulo-calcaneal, tarsal, tarso-metatarsal). Lesion type, diagnosed following Hackett (1976), Ortner (2003), and Steinbock (1976), and number and distribution over the skeleton were recorded following Powers (2008) and Connell and Rauxloh (2008) (see Table 7 & Table 12). The presence and absolute number of gummata were recorded on several element categories (i.e., femur, tibia, fibula, humerus, ulna, radius, skull (i.e., caries sicca), rib, innominate (i.e., the ilium), scapula, clavicle, sternum). To control for element presence, all of the above were recorded for each joint and segment (thirds/ quarters/ right and left sides) of a given skeletal element.

Historical information on Renaissance-era transitions in the manifestations of syphilis was derived from secondary sources (Arrizabalaga et al. 1997; Quétel 1990; Sudhoff 1925; Tognotti 2009). An attempt was made to have this list be comprehensive, but relevant source material on syphilis is not available for many regions during the 16th century, including England (Lipenius 1679 cited in Schleiner 1994).

Dates for many of the skeletal individuals employed in this study are highly contentious (Harper et al. Accepted). This is primarily because many of the published radiocarbon dates for these specimens place them in the Pre-Columbian era (see Table 2). As such, many have been used to argue in support of the Pre-Columbian hypothesis, which, as noted before, posits that syphilis was present in the Pre-Columbian Old World (Brothwell 2005; Dutour et al. 1994). However, more recent re-analysis of these dates by Harper et al. (Accepted) has drawn attention to the great range of uncertainty involved in these date ranges, thus questioning their accuracy. This uncertainty is due to the continegnecies involved in radiocarbon dating, which have been increasingly appreciated in the past two decades (Arneborg et al. 1999). For example, many dates generated before the 1980s are of limited value, such as that provided for the St. Helen-on-the-Walls cranium (Table 2), because the introduction of the accelerator mass spectrometry technique subsequently increased the accuracy and precision of radiocarbon dates. Re-dating, using AMS, of specimens dated prior to the 1980s reliably generates substantially younger date ranges (Harper et al. Accepted). In addition to the analytic uncertainty incorporated in the 95% confidence intervals that accompany point estimates (Higham et al. 2006), the 'marine reservoir effect', from the presence of 'old carbon' from dietary consumption of marine reservoirs in dated material is now understood to generate dates

that can be hundreds to thousands of years too old. This marine 'reservoir effect' is caused by delayed exchange rates between atmospheric CO_2 and ocean biocarbonate and the dilution effect caused by the mixing of surface waters with 'old' upwelling deep water (Cook et al. 2002; Hedges and Van Klinken 1992; Molto et al. 1997). Correcting for potential reservoir effects remains complicated, due to uncertainty in estimating the percentage of the diet represented by different marine foods and their effect on the measurements performed. The uncertainty generated by these reservoir effects has been highlighted, addressed, and corrected fro by Harper eta l. (Accepted). These corrections (see Harper et al. Accepted), extend the date ranges for all but one of these individuals—the cranium from St Helen-on-the-walls—securely into the Post-Columbian period, and by such lengths that they are confidently reassigned as late 15th and early 16th c . Post-Columbian finds (Table 2). The St Helen-on-the-walls cranium is set to be re-dated, which is greatly expected to render a securely Post-Columbian date (see Materials, Chapter Two). However, since this analysis is forthcoming in the published literature, these new date ranges are not employed here. Instead, the previously published dates are employed, with a certainty that the skeletons they represent are Post-Columbian. Because of the small number of individuals included in this sample and the fact that few of the published date ranges overlap with each other, means were generated from these ranges.

Analysis

Preliminary statistical analysis of the skeletal sample was run using SAS©. To limit biases generated by an excess of degrees of freedom, elements (R/L) were subsumed into single categories for each skeletal element (e.g., R/L parietals, R/L

frontals subsumed into "skull"). In turn, preservation of each individual skeletal element (e.g., R parietal) within this category was added to generate a percentage of presence for each category of skeletal element (maximum possible: 100%). To accommodate an excess of degrees of freedom bias generated by the differing date ranges associated with each individual, a mean was generated for each date range using Microsoft Excel 2008©. For the purposes of the preliminary analysis, to evaluate $\mathbf{H_1}$ and $\mathbf{H_1a}$ a poisson regression was run to assess covariance between the mean date associated with the skeletal individual, element preservation, and lesion types associated with facial destruction (i.e., gondou and gangosa); between mean date, element preservation, and presence of element destruction (amputation); between mean date, element preservation, and the presence of joint involvement on any of the included joints; between mean dates, element preservation, and the average number of gummata and absolute number of gummata in each element category. To evaluate $\mathbf{H_1b}$, a poisson regression was run to assess covariance between the mean date associated with the skeletal individual, element preservation, and the presence of element destruction (amputation), gummata on the cranium, the presence of joint involvement on any of the included joints, and lesion types associated with facial destruction (i.e., gondou and gangosa).

Results

Few significant relationships were found in variation between any of the variables (see **Table 17**). No significant variation was found between mean dates and element destruction, the average number of gummata or absolute number of gummata, or the presence of gummata on any element category. Additionally, no significance was found

between mean date and joint involvement (see **Figure 5**). A significant relationship was only detected between mean dates and presence of gondou ($p=.0259$; $p<.05$) and highly significant relationship of between mean dates and gangosa ($p=.0041$; $p<.01$) (see **Figure 6**).

Discussion

The results of this preliminary analysis are largely inconsistent with the proposed hypotheses: that the manifestations of syphilis altered in the manner suggested by the historical literature (**H_1a**) and that such alterations may have occurred in response to selection for milder symptoms (**H_1b**). These findings also contradict previous preliminary analysis of the data set (Zuckerman et al. 2010). This analysis found that the same categories of skeletal involvement all significantly co-varied with time in the manner suggested by the historical literature, thus supporting the second hypothesis and indirectly, the third. This discrepancy suggests that differences in the employed methodology may be responsible. The primary difference between the present and previous analyses is that of sample size; the previous analysis included individuals with date ranges extending further into the 17th and 18th centuries, thus generating a sample size skewed towards later dates. In contrast, this study employed a smaller sample size with a more evenly distributed sample but one too small to generate much statistical power. Likewise, a great number of variables were incorporated into the present analysis, particularly in regards to controlling for element preservation. This expansion generated a degrees of freedom bias and may have produced a type one error. Future inclusion of the ten individuals from the St. Mary Spital site is expected to eliminate this source of bias.

Conclusive results on whether skeletal evidence suggests that syphilis evolved in virulence must await availability and analysis of these individuals.

Intriguingly however, two of the results, the increases in evidence of gangosa and gondou, support the first hypothesis, that the manifestations of syphilis altered during the 15th and 16th centuries. These findings suggest that the pathophysiology of syphilis altered in a systematic manner during this period—at least in the individuals included in this sample. These findings also directly nullify the third hypothesis, Knell's explanation for the disease's attenuation, that changes in the manifestations of the disease were produced by direct selection on *T. pallidum* to reduce the visibility of its manifestations to potential sexual partners and increase host mobility (and thus presumably the ability or desire to engage in sexual activity). In this analysis, this hypothesis was assessed by examining covariance in the frequencies of gummata on the skull, facial destruction (gondou and gangosa), and indicators of bone and joint pain, or periosteal deposition or gummata on joint surfaces. Results show no evidence of any changes in the frequency of caries sicca or indicators of joint and bone pain. However, these indicators are less clear-cut in their implications for Knell's hypothesis. The former can deform, scar, and ulcerate large portions of the skull, scalp, and forehead. However, these lesions are also concealable by head coverings and may thus have played a reduced role in determining host attractiveness and the advertisement of infection. Likewise, while early accounts of the disease mention that the joint and bone pain experienced by sufferers was excruciating, particularly during the night (Quétel 1990), physical discomfort, pain, and reduced mobility are not necessarily prohibitive of sexual activity.

However, gondou and gangosa, which increased in frequency over the time period of interest, are arguably the most publicly visible and sexually unappealing symptoms of the disease. Gondou involves bony proliferation around the eyes, nose, and mouth, often resulting in a disfiguring proliferation of bubbly scar tissue on the face. Gangosa involves perforation of the hard palate and destruction of the nose, lips, and, and anterior upper jaw. This lesion often results in the loss of anterior teeth, and loss of anterior lower half of the face (Singh and Romanowski 1999). While prosthetic noses, often crafted of painted metal, were often employed to cover these lesions in the 18th and 19th century (Hayden 2003), they would have nonetheless been highly conspicuous to potential sexual partners. These findings suggest that Knell's hypothesis, and thus host sexual selection, may not sufficiently explain the underlying cause of any changes found in the manifestations of syphilis, including any revealed by future analysis.

Several issues related to Latin Galenism and renaissance-era ideas of disease transmission and treatment, and sexual behavior, also complicate this hypothesis. As Knell and others have noted, syphilis was *immediately* and uniformly associated with sexual transmission and this understanding spread with the disease (Benedicti 1497a; Boorde 1547; Fracastoro 1530; Massa 1537 [1507]; Scillacio 1495; cited in Quetel 1990 and Tognotti 2009). However, a survey of early European medical writings shows that even in the first decade of the 16th century, it was just as often attributed to divine retribution, corrupt air, astrological origins, non-sexual contact, humoural imbalances, and bad life regime, among others (Arrizabalaga 2005; Clowes 1585; cited in Hentschell 2005). Core preventative measures were focused on maintaining a humoral balance, of which frequent coitus played a key part, especially for men; while a few strongly

encouraged infected persons to desist from sex, many physicians prescribed 'moderate' coitus as a therapeutic remedy for syphilis. The great majority even prescribed it as a key preventative for men (Gil Sotres et al. 1996; Schellig 1496 cited in Arrizabalaga 2005)! Only a few discouraged sex with infected women and prostitutes; sufferers should instead seek out non-infected women (Torella 1497; Widmann 1497 cited in Arrizabalaga 2005). This aligns with popular belief, evident since the very early 16th century, that sex with a virgin could cure the disease (Schleiner 1994; Trumbauch 1998). While it is impossible to reconstruct sexual behavior from prescriptive literature, these complicated beliefs may have had a far reaching effect; the alleged barrier between disease views of physicians and lay people were far more permeable than traditionally believed (Arrizabalaga 2005; Lindemann 1999). Likewise, though foul-smelling ulcers and joint pains may have acted as deterrents to sexual activity, the most conventional signs of infection in pictorial renderings, dramatic literature, print culture, and thus presumably the lay imagination in 15th and early 16th century Europe and England, were visible spots or stains on the skin, especially the face. Facial destruction, for example, did not become representative of the disease until decades later. Unlike genital suppuration, ulcers, and bone decay, these spots were also publicly visible (Harris 2005), though none of the reports of syphilis's transition note their reduction.

The results still leave several aspects of the larger question unanswered: did syphilis evolve in virulence, and if so, why? This study suggests that many of the manifestations associated with syphilis and many of those specifically noted as changing in frequency and severity, show no such evidence of alteration. Instead, the positive results, while indicating a significant change in the manifestations of syphilis—and in the

most conspicuous lesions of the disease—directly contradict the historical literature. *None* of the documentary evidence on changes in the manifestations of syphilis (at least that which has been translated and interpreted by historians) records an increase in the frequency of facial destruction. Likewise, while these positive findings refute Knell's explanation, they do not necessarily indicate an alternate explanation. As is discussed throughout this document, very little is known about how *T. pallidum* produces the protean manifestations of syphilis. Existing evidence suggests that systemic and localized inflammation and the ensuing adaptive immune response cause all of the tissue destruction found in the disease (LaFond and Lukehart 2006; Radolf and Lukehart 2006; Salazar 2002; Stokes et al. 1944; Turner and Hollander 1957b). It is unknown what factors cause certain individuals to manifest some lesions—such as gangosa and gondou—and others to not, though scholars presume that this variation may be a byproduct of individual's distinctive immunological response to infection. Consequently, while the positive results contradict Knell, and their systematic nature suggests an underlying etiology beyond individual immunological variation, the ecological and evolutionary significance of this pattern remains unclear and subject to future research.

Additional ambiguities are generated by the nature of the source material. For example, because this study employs skeletal material, it can only infer rather than demonstrate evidence of pathogenic evolution. Future analyses of genes responsible for virulence factors in *T. pallidum* may demonstrate this directly (see Gray et al. 2006). A more fundamental concern is that skeletal evidence only demonstrates tertiary stage disease, at which point syphilis is no longer transmissible. This is a concern for trade-off models, wherein transmissibility is correlated with virulence but several aspects of the

documented transmission may also minimize this concern. Many of the symptoms described as having changed, such as facial destruction and ulcers, have skeletal correlates. Likewise, a lengthened latent period (and consequent drop off of transmissibility) was one of syphilis' documented acquisitions; prior to this, the disease may have been transmissible during early onset tertiary disease.

An additional limitation is that this sample represents only a subset of tertiary cases; those recovered from the archaeological record and manifesting diagnostic lesions. As such, individuals in this sample presumably experienced chronic infections, which endured for years. Those who experienced more acute, and potentially milder infections, or died early on, are less likely to be present in the sample. These conditions generate a substantial bias towards more chronic, severe cases.

All paleoepidemiological studies butt up against concerns over how representative skeletal samples are of their original living populations (Wood et al. 1992), in part due to very low rates of skeletal involvement from disease conditions, especially from acute ones (Ortner 2003). However, this potential bias is intensified by the characteristics of syphilis. As is discussed throughout this document, syphilis manifests skeletal lesions in a small number of overall cases—between 0.5 and 20%, with an average of approximately 10%, and unknown, smaller portion are diagnostic of the disease (Resnick and Niwayama 1995). As biomolecular techniques, like aDNA, are not useful for diagnosing infection in syphilis (such as for confirming its presence in skeletons with non-diagnostic markers) (Bouwman and Brown 2005; von Hunnius et al. 2007), all paleopathological studies of syphilis in the archaeological record thus by necessity employ a small subset of those who were actually infected in a given population and those with more severe and chronic

infections. This may be an intractable limitation for studies on the ecology and evolution of syphilis. Future work on this study, specifically with the inclusion of more individuals displaying a greater array of lesions, will attempt to accommodate and further explore this issue.

Lastly, it is arguable that analyzing a skeletal sample from one region in Europe is not adequate to assess the validity of what was described as a trans-continental phenomenon. However, several factors make it likely that results derived from this sample, as limited as they are, are representative of larger dynamics found within the overall pandemic. First among these is that with minor variation (Arrizabalaga et al. 1997), all of the reports from a wide variety of regions and authors describe a highly similar set of original manifestations gradually but contemporaneously transforming into another set of similar manifestations of the disease (Tognotti 2009). This suggests that living individuals, and thus their skeletons, should exhibit a highly similar set of manifestations at any given time or place in the 15th and 16th centuries. It also strongly suggests that if future analyses of skeletal evidence of 15th and 16th century syphilis do demonstrate temporal changes in the disease, that these are attributable to a selective event within the pathogen rather than a response to ecological conditions and disease synergy, as ecological conditions are often more regionally variable. Second, England boasts the largest number of reported cases of syphilis dated to the 15th and 16th centuries. This is largely a product of an intensive national history of archaeological investigation, federally mandated analysis of archaeologically derived skeletal material, and a comparatively larger number of paleopathologists and skeletal biologists than the remainder of Europe (Roberts 2006). Skeletal collections suitable for evaluating direct

evidence of an evolution of virulence do not exist outside of England at this time. Nonetheless, future research will be aimed at assessing contemporary skeletal evidence of syphilis derived from other countries in the interests of evaluating whether evidence consistent with an evolution of virulence is detectable in the regions for which it was originally reported.

Future analysis may clarify whether evidence exists for an evolution of virulence in syphilis, but the possibility remains that 16th century reports of milder, less fearsome cases of the disease are due to widespread, popular perceptions of the disease as less fear inspiring. By 1510, syphilis had spread widely across Europe and Asia and was quickly becoming well established as yet another contribution to the plague and pestilence that characterized Renaissance-era Europe. Reports of milder manifestations and a narrower range of symptoms may also be due to improved diagnostic clarity and increased familiarity with the manifestations of the disease by contemporary physicians. Likewise, reports of reduced mortality among sufferers may be due to progressive improvements in knowledge surrounding therapeutic caretaking of individuals or even simply that care was more commonly taken; as the disease became more familiar and less terrifying, sufferers were less often abandoned and ostracized by intimates (Arrizabalaga 2005; Arrizabalaga et al. 1997), which may have improved their longevity and reduced the likelihood of secondary infection of lesions. Continuing scholarly attention to the documentary evidence on the early years of the pandemic (e.g., Tognotti 2009) may provide opportunities to assess these possibilities.

Significance

As we enter an era wherein the optimism of the antibiotic era is being slowly being replaced by a new found respect for emerging and reemerging infectious diseases, it is critical to learn from the history of the human-pathogen relationship and to understand the evolutionary processes that unite humans and our pathogens (Baum and Kahila Bar-Gal 2003). Studies of epidemics and documented instances of the evolution of virulence have demonstrated that general models are not useful for predicting outcomes and that instead, models must be specific to host-pathogen inter-relationships (Dieckmann and Hessterbeek 2006; Dronamraju 2004; Hassel 2000). However, results could be used to inform the lower ambitions of virulence management: that of predicting whether and how syphilis may evolve in virulence in the future (Knell 2004). Syphilis remains a source of significant adult morbidity and, through congenital transmission, infant mortality on a global level (WHO 2001). The heaviest burden is in the developing world and Eastern Europe, though cases are on the rise in some sub-populations in the United States, United Kingdom, and Western Europe (CDC 2007; CDC 2002; Kahn et al. 2002; Nicoll and Hamers 2002). Recognition that infection with syphilis increases transmission and acquisition of HIV/ AIDs and exacerbates morbidity (Buchacz et al. 2004; Fleming and Wasserheit 1999; Greenblatt et al. 1988; Stamm et al. 1988) makes attention to variation in the manifestation of syphilis an especially pressing public health concern (Dar and Raza 2008; Radolf and Lukehart 2006). Effective treatments for syphilis may be selecting for strains that are harder to detect and more infective in the early stages of the disease. Reports of recent epidemics have found multiple asymptomatic cases as well as those with sufficiently mild symptoms that infected persons did not seek treatment (Battu et al. 1997; Cook et al. 2001b). The rise of less

virulent and thus less noticeable syphilis could exacerbate the spread and morbidity of HIV/AIDS in many regions.

Chapter Four: The Effect of Biological Sex on Manifestations of Syphilis in the Pre-Antibiotic Era

Introduction

The first documented epidemic of syphilis occurred in 1495, following the siege of Naples by Charles VIII (Crosby 1972; Quétel 1990). When the besieging army disbanded, the disease spread with them, quickly disseminating across Europe (Brown et al. 1970; Williams et al. 1927). By 1500, it was widespread across Europe and moving rapidly into Asia (Pusey 1933). While generating estimates of prevalence for infectious diseases in the past are often problematic (Waldron 2007), it is widely recognized that syphilis attained a high level of prevalence throughout many parts of the globe over the next four and half centuries. For example, by 1579 in England, syphilis was perceived as being endemic by contemporary chroniclers (Oriel 1994); by the 17th century, the numbers of infected were believed to be so high that the state of the nation was perceived as under threat and an apocalypse seemed eminent (Clowes 1579). Estimates of the prevalence and incidence of syphilis in modern times vary. In Europe prior to 1910, approximately 10% of urban inhabitants gave positive serological reactions for syphilis, though this is not identical to active disease (McElligott 1960). By WWII in the United States, incidence had risen to 500,000 infections per year. Following the introduction of penicillin, the incidence of early infection fell from 66.4 cases per 100,000 persons in 1947 to 3.9 cases per 100,000 persons in 1956 (CDC 2005).

Investigations of the origins of syphilis, its modes of transmission, and the search for an effective treatment began nearly simultaneously with the first epidemic and continued in the ensuing centuries (Quétel 1990). During the 19th and 20th centuries, a large and vigorous area of research on the disease was devoted to investigating variation in its symptoms and manifestations. Syphilis is infamous for provoking a wide, protean range of complications in cases, earning it the moniker, the ‘great mimicker’ (Peeling and

Hook 2006). Its progression also varies significantly between cases (Bruusgaard 1929). For example, only 16 to 30% of individuals who have sexual contact with a syphilis-infected person in the previous thirty days become infected (Moore et al. 1963; Schroeter et al. 1971), though actual transmission rates are assumed to be much higher (Alexander and Schoch 1949; Garnett et al. 1997). A small but varying proportion of cases exhibit early onset of late stage manifestations, such as meningitis and hepatitis, which are associated with significant morbidity (Mullick et al. 2004; Stokes 1934). More importantly, a highly variable number of cases—15 to 40% of early stage infections—progress to tertiary stage disease, which is associated with the most debilitating, disfiguring, and painful symptoms. Consequently, many researchers devoted great effort to discerning which 'constitutional' characteristics might be used to predict the course of infection. In an era with only minimally effective treatment available, and the looming prospect of dementia and disfiguring disease, the ability to forecast the future for trepidacious patients held great value (Fleming and Moore 1941). According to Kemp (1937), no aspect of syphilis received as much scrutiny or generated as much controversy as the differences in its manifestations between males and females, and particularly between males and pregnant females.

Observations from 19th and 20th century physicians, clinical studies of untreated syphilis, and autopsy studies document a suite of differences in the manifestations of syphilis in males and females. Clinical and autopsy studies that take sex into consideration—many do not—uniformly suggest that the complications of syphilis are more severe in males than females (Gjestland 1955; Sowder 1940). For example, in a large autopsy series, syphilitic lesions were found to be twice as frequent in males as

females at autopsy (Rosahn and Black-Schaffer 1943a; 1943b). Based on decades of clinical observations and hundred of autopsies, Warthin (1928) concluded that the manifestations of syphilis are both generally milder in females and substantively different in type from those in males. Likewise, milder manifestations in females have been documented in a variety of animal models (Chesney 1923). Several studies found that reproductive status may affect the manifestations of the disease, with pre-menopausal women experiencing milder symptoms or a delay in progression of the disease until the onset of menopause (Warthin 1928). More specifically, pregnancy was also reported to have a strong moderating effect on the course of disease, with pregnant females experiencing delayed or absent symptoms in the midst of an established infection (Kemp and Menninger 1936; Moore 1923).

Research on the underlying causes of variation in the manifestations of untreated syphilis largely ceased with the advent of the antibiotic era, except for one notorious exception.[5] However, a growing rise in the global incidence of syphilis and the largely unchecked progression of the HIV/AIDS pandemic has repositioned this issue as an important topic for contemporary research (Radolf and Lukehart 2006). Since 2000, there has been an increase in the number of cases of syphilis in the United States, United Kingdom, and Western Europe mainly among men who have sex with men (MSM) (CDC 2007). In comparison, the worldwide burden is formidable. In its most recent report, the WHO estimates that more than twelve million new cases occur each year (World Health Organization 2001), mostly in the developing world and Eastern Europe. Congenital

[5] The Tuskegee Study of Untreated Syphilis (1932-1972) was a collaborative study, sponsored by the Tuskegee Institute and the United States Public Health Service, of untreated syphilis in six hundred poor rural African American males. It was designed to measure the progression of untreated infection. It stands as one of the best-documented cases of unethical human medical experimentation in the twentieth century.

syphilis is a particular concern in developing nations, where lack of prenatal testing and antibiotic treatment of infected women results in frequent congenital infection. Congenital syphilis causes significant morbidity and mortality, including spontaneous abortion, stillbirth, and neonatal death; a recent report from Tanzania estimates that up to 50% of stillbirths in the country are due to congenital syphilis (Watson-Jones et al. 2002). Of particular importance to global health is the recognition that syphilis infection greatly increases the transmission and acquisition of HIV/ AIDS and exacerbates associated morbidity (Buchacz et al. 2004; Greenblatt et al. 1988; Stamm et al. 1988). These considerations, along with the highly destructive nature of tertiary disease make syphilis an important public health concern (LaFond and Lukehart 2006).

Variation in the manifestations of syphilis, particularly the presentation of mild or uncommon symptoms, can interfere with recognition, diagnosis and treatment of cases. The consequences of undiagnosed, untreated infection include morbidity from tertiary stage disease, the potential for continued transmission of congenital syphilis, and enhanced transmission and morbidity of HIV/AIDS. There are frequent reports of mild, variable, or anomalous manifestations that, because of their divergence from the 'classic' symptoms of syphilis, go undetected and untreated, sometimes for years. For example, Meier and Hollet (1986) report a case of periosteal reactions on the tibiae, which are characteristic but uncommon manifestations of early stage syphilis, but that were initially attributed to shin splints. Wang et al. (1991) describe a patient with a history of chronic headaches initially attributed to a brain mass but later diagnosed as a late stage syphilitic gummatous lesion. Primary chancres, the first sign of infection, which vary from the classic description or are very mild may go unrecognized by patients or undiagnosed by

clinicians, allowing the disease to continue unchecked (LaFond and Lukehart 2006). Even with modern diagnostic capabilities, the wide variety of CNS manifestations of neurosyphilis can greatly complicate diagnosis (Brightbill et al. 1995; Harris et al. 1997; Holland et al. 1986). For example, Bash et al. (2001) report a case of neurosyphilis mimicking the neuroimaging characteristics of herpes encephalitis. Cautionary tales for differential diagnosis have been reported by physicians for a range of uncommon manifestations, such as osteitis and hepatitis in early stage infection (Gurland et al. 2001; Noto et al. 2008), and for unique and novel forms as well as anomalous degrees of severity in the cutaneous eruptions characteristic of secondary stage infection (Green and Heilman 1985). According to Dar and Raza (2008) and others, there is an increased need for awareness on the part of physicians and researchers to recognize novel and variable forms of syphilis infection.

Owing to its long and destructive presence in Western societies (Quétel 1990), there is a vast body of literature on its immunology, which has been summarized in a regular series of reviews (Cannefax et al. 1967; Chesney 1926; Lukehart 1992; Norris 1988; Radolf and Lukehart 2006; Sell and Norris 1983; Wigfield 1965). However, even though *Treponema pallidum* subsp. *pallidum* was one of the first infectious agents to be associated with a human syndrome (Schaudinn and Hoffman 1905), efforts to elucidate its molecular mechanisms for virulence have been greatly stymied by certain characteristics of the organism (LaFond and Lukehart 2006). *T. pallidum*, for example, cannot survive or multiply outside of a mammalian host (Norris and Edmondson 1986). It has limited metabolic capacities, an unusually slow replication rate (Cumberland and Turner 1949; Magnuson et al. 1948), and is genetically intractable. There are several

animal models, but all manifest anomalous secondary stage infection and do not develop the tertiary stage (Baker-Zander and Sell 1980; Sell et al. 1980), which are those associated with the highest morbidity in humans, and ethical concerns bar human experimentation. Consequently, while researchers have been successful in uncovering some of the secrets of *T. pallidum's* biology and pathogenesis, much about syphilis' greatest mystery—how the spirochete causes the protean manifestations of the disease—remains to be discovered (LaFond and Lukehart 2006).

This paper attempts to use archaeologically derived human skeletal remains and clinical evidence from pre-antibiotic era surveys of syphilis to address one aspect of this enduring mystery. Given the importance that systematic variations in the manifestations of syphilis could have for both individual cases of the disease and public health, it is important to determine whether the manifestations of syphilis vary by sex and if so, to what degree. This paper addresses the question of whether biological sex had an effect on morbidity from syphilis. In other words, was either sex at a higher risk of developing different types of manifestations, and having more severe manifestations, or were males and females at equal risk? This question is investigated using two data sets: autopsy data and clinical studies from three large-scale published studies of untreated syphilis undertaken in the pre-antibiotic era (see Table 3) and a skeletal sample of cases of archaeologically derived syphilis from early modern England (c. 1600-1864). Archaeologically derived skeletal samples of syphilis have yet to be analyzed for sex-based differences in the published literature. Likewise, while the original autopsy series and clinical studies reported differences in the frequencies of infection stages and

manifestations between the sexes, whether these were significant was not reported nor were interpretations of the findings attempted.

Background

Pathophysiology of syphilis infection

Syphilis is a multistage disease with protean manifestations (Peeling and Hook 2006), though very little is known about how the spirochete produces them. In the absence of cytotoxins and other known virulence factors, it is probable that both systemic and localized inflammation and the ensuing adaptive immune response to *T. pallidum* cause the disease's characteristic tissue destruction (LaFond and Lukehart 2006; Radolf and Lukehart 2006; Salazar 2002; Stokes et al. 1944; Turner and Hollander 1957b). Cellular infiltrates composed of lymphocytes, macrophages, and plasma cells, accompanied by vasculopathic changes of varying severity, are, according to Sell and Norris (1983) and Lukehart (2004), the *sine qua non* of syphilitic lesions at all stages of the disease.

Primary stage infection is associated with a chancre, which is frequently indurated and ulcerated and occurs at the site of inoculation, and with moderate regional lymphadenopathy. Because the chancre is painless and in females and MSM may be located at an inconspicuous anatomical site, diagnosis is sometimes delayed in these groups until later manifestations occur. The chancre develops approximately three weeks after inoculation; the incubation period ranges from 10 to 90 days (U.S. Department of

Health 1968). Immediately following inoculation, spirochetes disseminate hematogenously throughout the body (spirochetemia). The presence of a pathogen cues inflammatory and immune cells to migrate to the site of infection. This is facilitated by the expression of cell adhesion molecules on capillary endothelial cells; virulent *T. pallidum* induces cultured endothelial cells to express the adhesion molecules ICAM-1, VCAM-1, and E-selectin. These likely incite binding between endothelial cells and lymphocytes and contribute to early stage inflammation (Lee et al. 2003; Riley et al. 1992). During acute infection, low levels of polymorphonuclear lymphocytes (PMNs), which are often the first cells to infiltrate the site of infection (Bos et al. 1980), seem to engage in bacterial clearance. This involves a mild, localized early inflammatory response (Lukehart 2004; McBroom et al. 1999). Early stage inflammation rarely involves the skeleton, but can produce mild, non-diagnostic periosteal reactions (Ehrlich and Kricun 1976a; Hoeprich 1994).

Secondary syphilis, the disseminated stage of the disease, begins approximately three months after initial infection. Cutaneous manifestations predominate but secondary syphilis can involve any organ system, including the CNS, provoking muscle aches, malaise, alopecia, and diffuse non-tender lymphadenopathy. This reflects the widespread dissemination of spirochetes and the intense, systemic inflammatory response underway. This stage also involves condyloma lata, or inflammation of mucous membranes, and most commonly, a disseminated mucocutaneous rash. Hepatitis, gastric and renal involvement, and early manifestations of neurosyphilis occur infrequently (see Baughn and Musher 2005). On the skeleton, it can produce periosteal reactions, as well as osteitis,

which often spontaneously and completely remodels (Hazen 1921; Ortner 2003; Powell and Cook 2005b; but see Rothschild and Rothschild 1995).

A low level inflammatory response continues throughout primary and secondary stage infection. As in many bacterial infections (Reis e Sousa et al. 1999), it is assumed that spirochetes are phagocytized by immature dendritic cells (DCs), or antigen presenting cells, at sites of infection and then transported to lymph cells (Rekart et al. 2003). There, they act as a bridge between innate or cell-mediated and adaptive or humoral immunity by presenting specific treponemal antigens to T lymphocytes, stimulating them to differentiate and migrate to the site of infection (Reis e Sousa et al. 1999). In response to stimulation by either whole spirochetes or specific treponemal lipoproteins, DCs cause lymphocytes to produce an array of inflammatory cytokines, or pro-inflammatory soluble immune factors. T helper 1-cell (T_h1) lymphocytes produce interleukin 2 (IL-2), IL-γ, IFN, and tumor necrosis factor alpha (TNF-α), the latter of which activates multiple components of the immune response (Van Voorhis et al. 1996). T_h2 cells produce IL-6 and IL-10, which is immunosuppressive and may actually serve to attenuate endotoxin-mediated systemic inflammation. Cytokines IL-12, IL-β, and IL-8 are also produced, but T_h1 cytokines predominate, resulting in an environment that promotes macrophage activation and bacterial clearance (Arroll et al. 1999). The treponemal lipoproteins responsible for this, however, are not surface located and are unlikely to be exposed until the spirochetes become degraded. This results in delays in DC maturation and a slower inflammatory response (Bouis et al. 2001) and may allow *T. pallidum* to disperse widely before an active host immune response has been mounted (LaFond and Lukehart 2006).

Adaptive immune responses, indicated by the development of Immunoglobulin M (IgM) and G (IgG) antibodies, also initiate within days of initial infection (Hanff et al. 1983; Lukehart et al. 1980; Muller and Oelerich 1981). IgM production continues even after symptoms have subsided (Baker-Zander et al. 1985; Baker-Zander et al. 1986) and IgG into late latent stage infection. Simultaneously, macrophages (Lukehart et al. 1980), stimulated in part by these antibodies (Baker-Zander et al. 1993; Jepsen et al. 1968; Lukehart and Miller 1978; Sell et al. 1980; Shaffer et al. 1993), and specialized T lymphocytes—both helper ($CD4^+$) T cells and cytolytic ($CD8^+$) T cells (Engelkens et al. 1993; Tosca et al. 1988; Van Voorhis et al. 1996b)—seem to engage in bacterial clearance (Riley et al. 1992). This dramatically reduces the number of detectable *T. pallidum* organisms. These studies suggest a mechanism similar to delayed-type hypersensitivity as the mode of immune clearance (LaFond and Lukehart 2006).

Bacterial clearance results in a resolution of secondary syphilis within approximately three months, leading to asymptomatic latent infection. Latent infection occurs in two stages: the first, early latent syphilis, lasts for approximately a year. During this time, up to 25% of cases may have recurrent secondary manifestations and spirochetemia (Gjestland 1955). This is because small numbers of bacteria often evade clearance. A number of responsible mechanisms have been proposed. Fitzgerald (1992) has famously posited that, as in many chronic infections, the switch from a predominant T_h1, cell-mediated, response to a T_h2, humoral, response (indicated by the predominance of different types of cytokines), is the pivotal event during syphilitic infection that enables the spirochete to become persistent. Arroll et al. (1999) however, found that T_h1 responses could be elicited at least six months after initial infection, in the midst of

latency, which strongly refutes this. Instead, infection is believed to persist either through maintenance of a low number of slowly replicating organisms at isolated sites or, more likely, through *T. pallidum*'s poor antigenicity (Radolf 1997) and capacity for antigenic variation (LaFond and Lukehart 2006). Viable treponemes remain scattered throughout the body, establishing residual foci of inflammation (Rosahn 1947). Over time, improved immunological control eventually results in a reduction of spirochetemia, a dramatic decline in spirochetal burden, and an end to infectiousness. This stage, late latent syphilis, consists of asymptomatic infection of over a year's duration (and in the pre-antibiotic era, often twenty to forty years (Gjestland 1955; Kampmeier 1972)), ceasing only with death, curative therapy or the onset of tertiary infection.

Approximately one third (15 to 40% of cases) of latent cases develop tertiary infection. In these individuals, the very poorly understood host immunological surveillance mechanisms that contain the spirochetes at their foci fail. Unknown factors cause *T. pallidum* to begin dividing at a higher rate, inciting 'recrudescent' infection and an intensified local inflammatory response (Radolf and Lukehart 2006). In tertiary infection, these active foci cause tissue damage throughout various organ systems. Gummata, focal necrotizing lesions that may be caused by exaggerated, delayed hypersensitivity, or a hyper-allergenic response to treponemes or their antigens (Jaffe 1972; Musher and Baughn 1998; Resnick and Niwayama 1995; Salazar et al. 2002), can emerge as early as two years after infection. They affect a variety of tissues, including skin, neurological tissue, muscle, and bone. According to Gjestland (1955), gummata occurred in 15% of untreated cases. Cardiovascular syphilis, or aortitis, occurred in approximately 30% of cases. Lastly, in approximately 6.5% of untreated cases (Gjestland

1955), neurological complications express. These manifest as meningovascular syphilis, often within five to ten years of initial infection, and as general paresis or tabes dorsalis, within two to three decades. The latter can cause Charcot's joints (trophic lesions on ankles, knees, and hips) (Reginato 1993; Resnick 1988; Todd 1926) and optic nerve damage (Simon 1985).

Tertiary stage is also when cases become securely diagnosable in dry bone and thus visible in the archeological record. As in the previous stages, periosteal reactions and osteitis occur, as well as osteomyelitis. These can result in expansion of the diaphyses of long bones. Gummata also affect the skeleton, causing focal lytic pits with sclerotic margins. In all stages, skeletal lesions are characteristically bilateral and systemic and predilect a range of skeletal elements, including long bone shafts, ribs, the sternum, scapulae, the medial portions of the clavicles, the cranium, and the hands and feet. In tertiary infection, excessive periosteal deposition can infrequently cause pseudo-bowing of the tibia (saber shins, boomerang leg) (Hackett 1936). Joint involvement and arthritis have also been documented both clinically and archaeologically (Rost 1942; Sengupta 1985; Yakinci et al. 1995). Cranially, syphilis can cause palatal perforation and rhinomaxillary destruction (gangosa), periosteal reactions on the maxilla (goundou), and osteitis and caries sicca on the cranial vault (Csonka 1953; Hoeprich 1989; Murray et al. 1956; Taneja 1968). Caries sicca involves a sequence of gummatous focal destruction, necrosis, pitting, and excessive sclerosis. Over time, it can produce a grossly thickened vault covered in confluent pits and radially-grooved stellate scars, which can take on a 'worm eaten' appearance (Hackett 1976; Ortner 2003; Steinbock 1976). It is believed to

be diagnostic of syphilis and of treponemal disease in general (Goff 1967; Stokes et al. 1944; Virchow 1858; 1896; Williams 1932).

Sex differences in syphilis

Many clinical and autopsy studies conducted in the pre-antibiotic era document sex differences in the manifestations of syphilis for all three stages (Bruusgaard 1929; Clark and Danbolt 1964). However, while differences are noted in primary stage infection, no information is available on the nature of these differences; Moore (1922) attributes this to the fact that, as mentioned above, primary chancres are often located internally on females. Thus their infection is not diagnosed and documented until it achieves the secondary stage. In contrast, Kemp and Menninger (1936) attribute their finding that only 23.7% of a sample of three hundred and sixty seven female cases of tertiary syphilis gave an unquestionable history of primary or secondary syphilis to the fact that syphilis manifests differently in females than males. The majority of qualitative data on sex differences comes from the observations of a pathologist, Warthin (1928), on hundreds of clinical cases and autopsies. This and other studies suggest four general suites of differences: in the severity and type of manifestations and in the timing and duration of the different stages.

Overall, manifestations of syphilis are reportedly milder in females (Warthin 1928), though the types of lesions manifested by each sex vary. In a re-analysis of clinical data on hundreds of cases of untreated syphilis, Gjestland (1955) found that in general, manifestations were more severe in males than females. Rosahn and Black-

Schaffer (1943a) note that lesions were more common in males than females in their larger autopsy series. Warthin (1928) writes that while secondary cutaneous lesions in females tend to be milder, a greater preponderance of females than males exhibit 'constitutional' symptoms such as toxemia (in the form of fever), osseous, arthritic, myologic (muscular), renal, and hepatic involvement. Males, however, exhibit more alopecia. Warthin also cites Fournier's (1899) finding that 50% of females manifest 'constitutional' symptoms of secondary syphilis while only 25% of men do, as well Stokes's (1934) finding of the same in 63% of females in contrast to 42% of men (actual numbers of cases not provided). Likewise, Warthin (1928) notes that tertiary lesions differ greatly between males and females. Cardiovascular involvement, including severe aortitis and myocarditis, is 'rare' or 'relatively uncommon' in females in comparison to males, in whom it is very common. Stokes (1934) also reports that males with cardiovascular involvement outnumber females by 4:1. In cases of neurological involvement, Warthin (1928) states that tabes and paresis afflict males three to four times as often as females and severe neurosyphilis in females occurs at one-third its frequency in males. Based on clinical surveys of thirty-eight million German citizens, Gärtner (1921) documents a ratio of 3.43:1 in incidence of paresis. Overall, many cases of tertiary syphilis in females are asymptomatic despite histological evidence of active, systemic spirochetes. However, variation exists. Autopsy studies revealed that splenic changes, interstitial pancreatitis (only milder forms), periosteal involvement, and gummata on the adrenal glands are more common in females. In clinical cases, gummata on the rectum are reported as being fifty percent more common in females than males, though they are usually not 'found' until after menopause (actual numbers of cases not provided).

Likewise, in autopsies, lesions of the liver occur 'much more frequently' in females, with severe hepatic lesions, chiefly gummatous hepatitis, occurring up to twenty-five times as often in females as males (actual number of cases not provided), particularly during their post-reproductive period (Warthin 1928).

Age and reproductive status seem to be strongly associated with the severity, duration, and timing of the manifestations of syphilis. For example, Schmidt-Kraepelin (1921) notes an absence of sex differences in neurological involvement in cases of congenital syphilis, the congenitally acquired form of the disease, in pre-pubescent children. This phenomenon is most strongly pronounced in relation to menopause. Overall, manifestations of secondary and tertiary syphilis are either milder in pre-menopausal adult females or infection is latent and asymptomatic until the onset of menopause (Warthin 1928). Warthin writes that in the majority of females, syphilis is latent and asymptomatic during the 'child-bearing period'; infected, reproductive age females may even give a negative Wasserman reaction, an early 20th century antibody test used, with great uncertainty, to detect infection with syphilis. Secondary symptoms, such as cutaneous lesions, may also be very mild or absent in pre-menopausal women but appear after menopause. Intriguingly, he notes that secondary cutaneous lesions in particular may not manifest until after menopause, even in monitored cases of females with infections of a twenty-year duration. Similar findings are reported for tertiary stage infection, as Warthin (1928) notes that tertiary lesions may only manifest after the onset of menopause.

The most pronounced sex difference reported in the manifestations of syphilis is in relation to pregnancy. That pregnancy might have an inhibiting influence on the course

of syphilis, particularly on incidence of neurosyphilis, was first proposed by Moore (1923) and later confirmed by Keidel (1923) and Solomon (1926). Several studies suggest that pregnancy, whether coincident with initial infection or occurring during the course of early infection, has an ameliorative effect on its manifestations. For example, Moore (1923), citing Brown and Pearce (1920), notes that females infected shortly after conception usually did not develop a chancre or secondary infection. Infection acquired late in pregnancy also often elicited a significant delay in the manifestations of primary and secondary stage manifestations. In a large venereal disease clinic population, Kemp and Menninger (1936) found that of females who had no history of pregnancy, 30.6% of cases (sixty-seven of one hundred and forty eight cases) recalled experiencing manifestations of primary or secondary stage infection. In contrast, only 13.5% (twenty out of two hundred and nineteen cases) who had experienced one or more pregnancies after initial infection recalled having no symptoms, independent of other factors. Conception and pregnancy also seemed to incite spontaneous latent infection. For example, Warthin (1928) noted that pregnancy often incited latent infection or milder symptoms in infected females. Moore (1922) also found that latent syphilis was twice as frequent in females as males in a larger venereal disease clinic population; of the total number of infected females (four hundred and seventy cases), 42% were pregnant at the time of admission and examination.

The most profound effect of pregnancy seems to be on the incidence of neurosyphilis. For example, Kemp and Menninger (1936) found that the timing of pregnancy in relation to that of initial infection seemed to be strongly associated with the incidence of neurosyphilis in tertiary disease. In this study, neurosyphilis was diagnosed

based upon both symptoms of neurological involvement and the presence of spirochetes in the CNS. They documented an incidence of 47.2% in a group of female clinic patients who experienced their first pregnancy (whether carried to term or not is not noted) within six months of initial infection (thirty six of one hundred and three total cases). This is in sharp contrast to an incidence of 17.2% in females who became pregnant between six months to three years after infection but less so in comparison to an incidence of 34.3% in females who did not become pregnant until at least three years afterwards. Kemp and Menninger (1936) attribute these findings to the reported frequency with which pregnancy seems to inhibit the progression of primary and secondary syphilis. They argue that suppression of secondary manifestations may interfere with the immune response to the disease, thus enhancing later opportunities for the spirochetes' invasion of the nervous system. Unfortunately, due to the nature and extent of the available clinical and skeletal data, the effects of pregnancy cannot be investigated in this study.

Sex differences in infectious disease

Multiple factors can affect the expression of infectious disease. These include exposure to causal organisms, inoculum size, pathogenic biology, and host age, nutritional status, immune response, and as is increasingly appreciated, sex. Sex has been long recognized as a contributory factor in the incidence and progression of disorders associated with dysregulation of the immune system, such as autoimmune conditions (Olsen and Kovacs 1996), but more recently, it has been recognized that sex may also influence host immune to response to pathogens (Marriott and Huet-Hudson 2006).

Many modern infectious diseases differentially affect one sex (Klein 2000; Roberts et al. 2001). In general, the proportion of individuals infected, the severity of infection, and the risk of mortality are higher in males than females for viral, bacterial, fungal, and parasitic diseases (Acuna-Soto et al. 2000; Blessmann et al. 2002; Brabin and Brabin 1992; Hoff et al. 1979; Jansen et al. 2007; Kirkwood et al. 1983; Klein 2000; Leone et al. 2004; Noymer and Garenne 2000; Oliviera et al. 1981; Owens 2002; Wells 2000). For example, males are more susceptible to most types of respiratory tract infections, are more likely to suffer from severe symptoms, and are at higher risk of mortality from such infections than females at all ages (Falagas et al. 2008). Many bacterial infections, such as *Staphylococcus aureus*, rabies, gonorrhea, meningitis, and pneumonia, are more common in males (Laupland et al. 2003; Zuk and McKean 1996). Males also demonstrate greater susceptibility to some kinds of cancers, including lymphoma and leukemia, various viruses, such as Coxsaackievirus, and macroparasites, such as *Schistosoma mansoni* (Klein 2000; Zuk and McKean 1996). These differences are not limited to humans: in many mammal and bird species helminth loads are higher and infections more severe in males than females (May 2007; Poulin 1996). However, males are not always at a disadvantage with respect to diseases. For example, malaria more severely affects females, particularly pregnant females, even though the incidence of the disease appears similar in both sexes (Roberts et al. 2001). The prevalence of sexually transmitted infections, such as HIV and herpes simplex-virus 2 (HSV-2) is higher among females. Studies using mouse models have also revealed several other diseases that disproportionately affect females (Alexander 1988; Pasche et al. 2005; Roberts et al. 1995).

Sex differences in infectious disease are a consequence of differences in the expression of sex steroid hormones, in anatomy, and in life experiences and the influences of gender (Fish 2008), which can encompass culturally mediated differences in exposure to causal pathogens and access to treatment (Brabin and Brabin 1992). Of these factors, many clinical and laboratory studies have demonstrated that much of this difference might be attributable to sex differences in immunity.

As a general rule, females exhibit more robust cell-mediated and humoral immune responses to antigenic challenges than males. Studies have increasingly linked this to the effects of circulating sex steroid hormones (Brabin and Brabin 1992; Zuk and McKean 1996). Dimorphism in the adaptive immune response, for example, is most apparent at puberty (Grundbacher 1972; Lichtman et al. 1967). Also, macrophages and lymphocytes, the two major cell types involved in responses to bacterial infection, possess classical and non-classical receptors for androgens (Cutolo et al. 1996; Wunderlich et al. 2002), oestrogens (Cutolo et al. 1996; Danel et al. 1983), and progesterone (Piccini et al. 2000). Oestrogens, such as 17β-oestradiol (E2) and oestriol, progesterone, and of the androgens, testosterone, can mediate many of the sex differences in immune response (Bouman et al. 2005). Overall, available data suggests that sentinel cells, such as macrophages, respond more aggressively to bacterial infection in males than females by producing higher levels of cytokines, which are likely to play a key role in the progression of damaging inflammation. However, the body of literature on the immunomodulatory effects of sex steroid hormones is too large to be fully discussed below; the following discussion places emphasis on sex steroids in relation to inflammatory processes.

In general, estrogens seem to enhance both cellular and humoral immunity (Ansar

Ahmed et al. 1999; Grossman 1985; Janele et al. 2006; Klein 2000; Roberts et al. 2001). For example, oestrogen receptors are expressed by several types of immune cells, including those active in innate and adaptive responses to bacterial infection, such as T cells, DCs, and macrophages, which suggests that oestrogens might have a regulatory role in immunocompetence. Treatment with 17β-oestradiol has an anti-inflammatory effect, and can, for example, abrogate onset of multiple sclerosis (MS) in EAE, a mouse model for the disease (Tiwari-Woodruff et al. 2007). Likewise, oestrogen-based hormone replacement therapy reduces circulating levels of cell adhesion molecules, such as ICAM-1, VCAM-1, and E-selectin (Caulin-Glauser et al. 1998; Oger et al. 2001a; Scarabin et al. 1999; van Baal et al. 1999). Females also have higher CD4+ T-cell numbers than males (Amadori et al. 1995). T_{Reg}-cell frequencies within this population of cells undergo profound changes during the ovarian cycle that, as T_{Reg}-cells regulate the size of the peripheral T-cell pool and modulate immune responses to infection, potentially affect immunoregulation (Arruvito et al. 2007; Tang and Bluestone 2008). Oestrogens are also negative regulators of CD4+ T-cell-derived TNF. Oestrogens might also exert a biphasic effect on T_h1 vs. T_h2-cell differentiation: low doses of oestrogen have been associated with T_h1-cell responses and enhanced cell-mediated immunity. High doses promote T_h2-cell and humoral responses (Pernis 2007). Lastly, oestrogens also affect development of B-cells, antibody generating and antigen-presenting cells, by enhancing polyclonal activation of B-cells, which leads to higher serum levels of IgG and IgM (Lamason et al. 2006).

In contrast, the effects of oestrogens on the innate immune responses that are mediated by monocytes and macrophages are generally repressive (Harkonen and

Vaananen 2006). Oestrogens, for example, reduce monocyte and macrophage production of the proinflammatory cytokines IL-1β, IL-6 and TNF *in vitro* (Kramer et al. 2004), producing an anti-inflammatory effect. Schroder et al. (1998) have also reported that female bacterial sepsis patients exhibit lower levels of TNF-α and higher levels of IL-10, which is immunosuppressive and may actually serve to attenuate endotoxin-mediated systemic inflammation. Oestrogens also decrease plasma IL-6 levels and, during the ovarian cycle, low levels are associated with low levels of production of TNF and IL-1β (Bouman et al. 2005). Recent findings also demonstrate that they can regulate DC development; exposure of bone-marrow DC precursors to oestrogens facilitated their development into conventional DCs that secreted pro-inflammatory IL-12 (Siracusa et al. 2008). Oestrogens can further moderate immune responses by affecting microvascular endothelial cells, which actively recruit immune and inflammatory cells to lymphoid and peripheral tissues by expressing adhesion molecules and chemokines (Murphy et al. 2004).

Changes in hormones concentrations owing to the menstrual cycle, pregnancy, menopause, and in modern populations, contraception usage and hormone-replacement therapy, all influence the immune response to pathogens (Fish 2008). For example, hormonal fluctuations during pregnancy affect disease activity in several autoimmune diseases. The potentially biphasic effect of oestrogen on T_h1 vs. T_h2-cell differentiation is exemplified by the hormonal environment during pregnancy, in which increased oestrogen and progesterone levels in the third trimester favor generation of T_h2-cell responses. Among other consequences, a T_h2-cell-type environment contributes to enhanced antibody production which exacerbates systemic lupus erythematosus (Pernis

2007). In multiple sclerosis, recent evidence from EAE models, or mouse models of multiple sclerosis, indicates that the documented decrease in manifestations of the disease is likely associated within an immunoregulatory environment rather than with the suppression of T_h1-cell responses (McClain et al. 2007). Notably, the remission of multiple sclerosis during pregnancy is often followed by a flare of disease activity post-partum, when oestrogen and progesterone levels fall (Houtchens 2007). Potential, similar interactions have yet to be demonstrated or investigated in bacterial diseases.

In females, the menopausal transition is associated with both significant changes in hormonal levels and with increased risk for a variety of health conditions, including several cancer and inflammatory immune disorders (Calaf i Alsina 1997). Growing evidence suggests that changes in hormonal profiles are associated with simultaneous alterations in immune cell populations and functions (Marriott and Huet-Hudson 2006). During peri-menopause, circulating oestrogen levels fluctuate greatly, becoming significantly different near cessation of menstruation. Progesterone levels also decline in late peri-menopause (Burger 1994; Metcalf 1988; Sherman and Korenman 1975; Shideler et al. 1989). Post-menopause, both oestrogen and progesterone drop drastically, the former being undetectable in plasma (Rannevik et al. 1995). The primary effect of this sharp decline in oestrogen seems to be a rise in inflammatory markers (Karim et al. 2010). For example, in a rodent model of surgically induced menopause, ovariectomized rats demonstrate reduced adaptive immune responsiveness in the form of reduced lymphocyte chemotaxis, or movement, mitogen-induced T cell proliferation responses, and IL-2 production than intact females (De la Fuente et al. 2004). This has correlates in humans: late menopausal females and those with surgically induced menopause exhibit

reduced numbers of B cells and serum levels of T helper cell–derived cytokines including IL-4 (Kamada et al. 2000; Kumru et al. 2004). Reductions in adaptive immunity may also explain some morbidity patterns among females, such as that postmenopausal females display a higher incidence of sepsis (Beery 2003; Porter et al. 2001). Studies of coronary heart disease have also revealed differences in inflammatory responses with menopause: a cross-sectional study demonstrated that circulating inflammatory markers, including sICAM, VCAM, and E- and P-selectins, were significantly higher in postmenopausal women not taking hormone therapy compared with premenopausal women, controlling for age and body mass index (Oger et al. 2001). Importantly, these effects can be reversed with hormone replacement therapy in age matched females, strongly suggesting that impaired adaptive immune function can be attributed to hormonal changes rather than to the effects of aging (Goudev et al. 2002; Porter et al. 2001). However, the effects of menopause on many aspects of immune response remain largely unexplored, such as the effect of menopause on host responses to bacterial infection (Marriott and Huet-Hudson 2006) and the effects of androgens on inflammation in post-menopausal females (Karim et al. 2010).

In contrast, androgens, such as testosterone, largely suppress immune function (Ansar Ahmed et al. 1999; Grossman 1985; Janele et al. 2006; Klein 2000; Roberts et al. 2001). For example, the greater incidence of autoimmune conditions in females and androgen- deficient males has been attributed to the immunosuppressive effects of androgens compared with estrogens (Cutolo and Wilder 2000). Several case reports and small clinical trials of testosterone therapy have demonstrated improved clinical status and levels of inflammation in several autoimmune diseases (Cutolo et al. 1991; Olsen and

Kovacs 1995). Rodent models of experimentally induced inflammatory disease have also reported a beneficial response with androgen therapy (Dalal et al. 1997; Kimura et al. 1998). While the mechanisms remain uncertain, testosterone suppresses pro-inflammatory cytokines and may up-regulate anti-inflammatory cytokines. Studies have demonstrated that testosterone incubated in cell culture attenuates production of inflammatory cytokines such as TNF, IL-1, and IL-6 in human macrophages among other cells (D'Agostino et al. 1999). TNF reduction leads to decreased T- and B-cell proliferation and decreased immunoglobulin and cytokine production and limited lymphocyte proliferation (Olsen and Kovacs 1996). However, some evidence on the effects of testosterone are contradictory and condition dependent. For example, Liva and Voskuhl (2001) and Bebo et al. (1999) found that anti-inflammatory cytokines such as IL-10 are stimulated in the presence of testosterone, while Schroder et al. (1998) and Blackwell and Christman (1996) found that male sepsis patients exhibited lower levels IL-10 than age- and disease-severity-matched female patients, which may promote an inflammatory response in males. Bacterial sepsis in males is also associated with higher levels of IL-1β, IL-6, and TNF-α, which, as discussed above, are potent inflammatory mediators and are positively correlated with a worse prognosis (Schroder et al. 1998). Although total counts of lymphocytes are similar in males and females (Bouman et al. 2004; Giltay et al. 2000), the percentage of T lymphocytes is lower in males than females. This may be due to higher testosterone concentrations in males, as this hormone may increase apoptosis in T cells (Giltay et al. 2000). Testosterone decreases the expression of macrophage and monocyte Toll-like receptor 4 (TLR4), which is involved in activating the innate immune system in response to pathogen challenge. This decrease

in TLR4 expression suggests a potential underlying mechanism for the immunosuppressive effects of testosterone (Rettew et al. 2008).

Nevertheless, Marriot and Huet-Hudson (2006) and others emphasize that attributing definitive, immunomodulatory roles for sex steroids has been complicated by the apparent dose dependency of their effects. For example, low doses of oestrogen enhance immune functions by elevating antibody production but high concentrations have been shown to result in thymic involution and suppression of mixed lymphocyte proliferation responses (Screpanti et al. 1982; Sorachi et al. 1993). Oestrogens may have a dose dependent effects on macrophages (Cutolo et al. 1995): low doses of oestrogen have been shown to augment production of TNF-α and IL-6 by macrophages (Chao et al. 1995; Zuckerman et al. 1996) while high concentrations decrease TNF-α production (Salem et al. 2000). Similar mechanisms may be at work in the effects of testosterone. Overall, as this suggests, it is likely that sex differences in microbial susceptibility result from a more complex interplay between sex steroid hormones and immune cells than the available research suggests (Marriott and Huet-Hudson 2006).

Problematically, issues of dose dependency remain poorly understood. Although it is recognized that sex differences predispose susceptibility to many autoimmune diseases, with few exceptions, sex dependent differences in immune responses to infectious pathogens have been disregarded in the published literature. According to Fish (2008) very few investigations have explored sex differences in infectious diseases in humans; most have been carried out in mice or rats. Data from rodent studies have, however, provided some insights into the mechanisms that contribute to sex differences in disease severity. For example, ovarectomized female mice have been found to be less

resistant to bacterial infection compared to control females (Leone et al. 2004), and gonadectomized male mice display higher immune response and resistance to disease in comparison to male controls (Klein 2000). Female mice have also been shown to mount more vigorous T-cell responses to exogenous antigens than males (Weinstein et al. 1984), though this has not been replicated in humans. Additionally, female and hypogonadal male mice have higher CD4:CD8 T cell ratios than normal males due to having relatively lower numbers of CD8+ lymphocytes (Bizzarro et al. 1987). Animal models have also clearly demonstrated that sex steroid hormones also affect behaviors, such as aggression and dispersal, which can play a role in risk of exposure to and spread of infectious disease (Klein 2000). Sexual dimorphism may also play a role in sex differences in disease patterns, as the larger sex potentially provides more resources or larger 'targets' for pathogens and parasites (May 2007).

Sex differences in archaeological skeletal samples

While sex differences are evident in infectious disease among modern populations, can the same be detected in the archaeological record? Unfortunately, not all osteologists record prevalence by sex (Roberts and Cox 2003b), but sex differences in skeletal indicators of disease have nevertheless been found in many skeletal samples. In the majority, lesion frequencies are consistently higher in males than females (Jaffe 1972; Stini 1985; Stinson 1985). Several researchers have reported sex differences in the frequency or severity of periosteal lesions in many skeletal samples throughout the world. As reviewed in DeWitte (2009), Ortner (1998) and Larsen (1998) reported higher

frequencies of periosteal reactions in male skeletons compared to female skeletons in prehistoric Native American samples. Cassidy (1984) reported a higher frequency among males at a Mississippian site, though the difference was not statistically significant. Likewise, frequencies in males twice that in females have been documented in an early medieval Croatian sample (2008) and two late medieval British samples (Hacking and Wakeley ND; Stroud and Kemp 1993). In contrast, Larsen (1997) reported higher frequencies or greater severities in females in comparison to males in the several ples from the prehistoric Southwestern U.S. Šlaus (2000) likewise found higher frequencies in females at a late medieval Croatian site, though the latter was not significant. However, periosteal reactions can be caused by a variety of conditions, including trauma, growth, inflammation, and infectious processes (Adler 2000; Ragsdale 1993; Ragsdale et al. 1981; Richardson 2001), so these results do not unambiguously indicate higher morbidity from infectious disease among males in these samples, as implied by Ortner (Ortner 1998).

Ambiguous patterns of sex differences have been found for a variety of other conditions. In an investigation of sex differences in maxillary sinusitis in medieval English samples, Roberts et al. (1998) only found a significant difference—higher frequencies in females—at Wharram Percy. A more recent review of cases from North American, English, and Nubian samples yielded a consistently higher frequency in females than males (Roberts 2007). As living in housing without effective chimneys would exacerbate this condition and females presumably spend more time indoors than males, this may have a gendered behavioral component. Grauer et al. (1998) found no significant sex differences in frequencies of periosteal lesions, linear enamel hypoplasia,

and other pathological lesions in a sample from a 19th c. Chicago poorhouse. DeWitte (2009) failed to find any significant sex based differences in mortality attributed to the 14th c. Black Death in an English skeletal sample, despite historical evidence indicating that males were disproportionately more susceptible to the plague. Likewise, Buikstra and Cook (1981) and Powell (1988b) did not find a sex difference in frequencies of tuberculosis lesions in several North American samples, though Powell (1991) documented higher frequencies in females at Irene Mound. In contrast, Djuric-Srejic and Roberts (2001) found an uncorrected prevalence of infectious disease lesions three times higher in males than females in several later medieval Serbian samples, though this was insignificant. Yaws, a non-venereal treponemal disease (caused by *Treponema pallidum* subsp. *pertenue*), which is believed to have a pathophysiology very similar to that of syphilis (Antal et al. 2002; Centurion-Lara et al. 2006; Musher 1992; Schmid 1989) also produces sex differences in skeletal lesions. For example, two thirds of the cases of yaws documented by Buckley and Tales (2003) in a site from the southwest Pacific Islands were female.

Sex differences have also been found in syphilis in several archaeological skeletal samples. Djuric-Srejic and Roberts (2001) found a consistently higher uncorrected prevalence of syphilitic lesions in male than female skeletons in several later medieval Serbian samples, though this was insignificant. Likewise, while results varied, Suzuki (1984a) found frequencies of syphilitic lesions in males two and three times higher in males than females at several sites in 17th to 19th century Japan, though none were significant. Likewise, in England, higher frequencies of syphilitic lesions were

documented in female than male skeletons at several post-medieval sites, though results varied (WORD database 2010).

Overall, however, in comparison to the number of skeletal cases of other major infectious diseases, such as tuberculosis and leprosy, there are few reports of cases of syphilis in the archaeological record and even fewer that report sex differences between cases. This is true even for time periods and regions where syphilis was undoubtedly endemic, such as 16th to 19th century England, Spain, Japan, Russia, Italy, the modern day Czech Republic, Denmark, and Portugal (Buzhilova 1999; Codinha 2002; Fornaciari et al. 1989a; Horáčková and Vargová 2001; Malgosa et al. 1996a; Miles and Connell 2006; Miles et al. 2008; Rasmussen et al. 2008; Roberts and Cox 2003a; Suzuki 1984b; WORD database 2010). When differences are recorded, they are primarily those of prevalence or frequency of cases (e.g., Pietrusewsky et al. 1997; Rothschild and Heathcote 1993) rather than any in the type or severity of involvement or duration of disease episodes (but see Buckley and Tayles 2003). Whether this constitutes evidence of absence or merely absence of evidence is unknown.

This dearth is likely attributable to two factors. First, among the few infectious diseases that generate distinctive skeletal lesions (Ortner 2003; Roberts and Manchester 1999), syphilis does so very infrequently and with great variability (i.e., low sensitivity). The most commonly cited estimate is between 1.5% and 20% of cases might exhibit skeletal involvement (Resnick and Niwayama 1995: 2496). In a survey of two thousand cases of syphilis in Norway extending from 1890 to 1920, Gjestland (1955) found that approximately 1% of cases showed bone lesions. Applied, the combination of these figures would result in the frequency of syphilitic bone lesions in about 1 in 1,000

Europeans in the pre-antibiotic era (Hackett 1976: 114). Consequently, Ortner (2003) warns that paleoepidemiological reconstructions of syphilis should be undertaken with extreme caution (if at all). Second, syphilitic lesions are often non-specific. Establishing the specificity of the variety of associated lesions to syphilis has been historically problematic (Powell and Cook 2005b). The only published study to rigorously evaluate this specificity, Hackett (1976), found that caries sicca and osseous expansions and nodes with superficial cavitations on long bones (e.g., gummatous osteoperiostitis) are highly specific, with variations on the latter being only suggestive of the disease (i.e., 'on trial'). Despite their usage as diagnostic indicators (e.g., Rothschild and Rothschild 1995; Steinbock 1976; Waldron 2009), other lesions, such as systemic periosteal reactions or tibial pseudo-bowing are non-specific and thus only consistent with infection (Hackett 1976b: 79-93; Powell and Cook 2005b; Webb 1995; Weston 2008). More recent studies have asserted that microscopic indicators are useful in diagnosing syphilis (Schultz 1994; 2001b; 2003) but these structures have also been reported in non-syphilitic lesions (Blondiaux et al. 2002; Weston 2009). Additionally, in geographical and temporal contexts where both syphilis and another treponematosis, such as yaws or bejel (endemic syphilis), might have been present, it can be impossible to differentiate between them in the skeleton as the syndromes manifest with very similar lesions (Anderson et al. 1986; Hackett 1976b; Ortner 2003; Ortner and Putschar 1981; Steinbock 1976b).

This study examines the relationship between manifestations of syphilis and biological sex. As any association between sex and the manifestations of syphilis indicates differences among individuals in susceptibility to the disease, this addresses the issue of heterogeneity of frailty (age-adjusted relative risk of death)(Wood et al. 1992).

This is the observation that individuals may vary dramatically in their susceptibility to illness and thus mortality (Wright and Yoder 2003). Evidence of differential susceptibility linked to sex will be examined in two discrete data sets. The first is a re-analysis of primary data from several 19th and early 20th century clinical surveys and autopsy series of untreated syphilis in Europe and the United States. Much of the data from these studies has not been re-analyzed since its initial publication and to the best of the author's knowledge, has yet to be analyzed comparatively. The second is a skeletal sample of clinically and archaeologically derived cases of syphilis from late medieval and early modern England (c. 1600-1864). As indicated above, the focus of the current study does not lend itself to an analysis of prevalence, as conducted in those discussed above which report sex differences in archaeological skeletal samples. One cannot compare the prevalence of lesions in males and females to investigate sex patterns of morbidity in syphilis. Instead, this analysis investigates evidence for sex differences in the type of syphilitic manifestations, their severity, and duration of disease episodes evident in both soft tissue (clinical and autopsy studies) and on the skeleton.

Materials

Clinical and autopsy studies

See Chapter Two for discussion of the clinical and autopsy data sets.

Skeletal sample

See Chapter Two for discussion of the skeletal data set.

Integration and comparison of these two types of data allows a more comprehensive evaluation of sex differences in the manifestations of syphilis than would be enabled through separate analysis. For example, skeletal data is not amenable to studying primary and secondary stage syphilis but these manifestations are evident in clinical data. Most importantly, the use of different diagnostic criteria and data collection techniques may act to limit selection biases in each data type. Subtle skeletal lesions, for example, are often difficult to detect through radiography and autopsies. They are thus likely to be both systematically undercounted (Walker et al. 1997; Weston 2008) and biased towards more severe lesions (Ortner 1991; Powell 1988a). However, they are easily recognized in dry bone (Powell 1988a). As mentioned above, use of rigorous diagnostic criteria for skeletal cases of syphilis greatly reduces the number of cases available for study, as many cases of infection are unlikely to manifest suggestive or specific lesions. This creates a selection bias towards more severe outcomes but limits the number of false positive cases. In contrast, the use of diagnostic criteria in autopsy and clinical studies with low specificity likely introduced many false positive cases into these data sets. For example, positive Wasserman reactions can be triggered by antibodies for infections other than syphilis, such as tuberculosis, and negative reactions in infected individuals (Gilbert 1930). Likewise, the protean manifestations of syphilis may have created diagnostic confusion that generated both false positive and negative cases.

Overall, these differences are expected to elucidate differing, complementary aspects of any sex-based differences evident in the manifestations of syphilis.

Methods

Skeletal data collection and clinical and autopsy series data collection

See Chapter Two for discussion of diagnostic criteria and methods of skeletal data collection and data collection from the clinical and autopsy series.

Some of the available information on the stages and manifestations of syphilis from the clinical studies and autopsy series was not integrated into the analysis, such as information on primary stage infection and specific organ involvement (e.g., gummata of the lymph nodes, ocular involvement). Primary stage data was excluded over concerns that delayed medical diagnosis or patient recognition of primary infection in females might bias the existing data. As each data set was independently analyzed for sex-based differences in the original publications, data on specific organ involvement was only included if found in more than one data set, allowing comparison.

Analysis

Statistical analyses were run using STATA 11.0® and SPSS 17.0®. To evaluate **H_2a** and **H_2b,** logistic regressions were run using STATA 11.0® to assess any significant variation in manifestations of syphilis evident in the skeletal sample (e.g., lesion type, lesion frequency) by sex or age as well as sex and age. Sex was scored as binomial data (male (M), female (F), or intermediate (?) with intermediate individuals excluded from

the analysis). Age was also scored as binomial data to incorporate reproductive stage (>17 yrs; 18-45 yrs; >46 yrs, with those >17 excluded from analysis). To evaluate **H_2b,** chi-square tests were run using SPSS 17.0® to assess any significant variation between frequencies of the manifestations of syphilis (e.g., involvement type, lesion type) and sex in the clinical and autopsy samples.

Results

Results indicate no significant variation between binomial sex (M/F) and likelihood of manifesting gummatous involvement on the skull (p=.365; odds ratio = 2.4). In contrast, there was a significant relationship between binomial age, i.e., being of or older than reproductive age, and likelihood of manifesting gummata on the skeleton, with older individuals (>46 yrs.) significantly more likely than younger individuals (18-45 yrs.) to manifest gummata (p=.041; odds ratio = 10.154). Older individuals are also highly significantly more likely to exhibit more than one gummatous lesion on the skeleton than younger, reproductive age individuals (p=.002; odds ratio = 36.0). In contrast, no significant variation was found between binomial sex and evidence of gummatous involvement on the skull, presence of gummata on the skeleton, or of more than one gumma. An insufficient sample subset size prevented assessment of variation between manifestations of syphilis by age between males and females. Controlling for age, there is also no significant variation between the manifestations of syphilis by sex (see Tables 20 to 28).

Analysis of the clinical study and autopsy series data revealed that frequencies of secondary stage infection did not vary significantly by sex in Turner's sample, but did at a high level of significance in Gjestland's ($p=.000$; $p<.01$). Relapsing or recurrent secondary infection highly significantly covaried in Turner's data ($p=.000$) but not Gjestland's. Frequencies of cutaneous lesions also covaried by sex in Turner's data at high significance ($p=.000$), but not Gjestland's. The same was also true for frequencies of tertiary stage disease, which significantly covaried in Turner's data ($p=.000$) but not Gjestland's. In contrast, frequencies of skeletal involvement (undefined) in tertiary disease were significantly related to sex in both Turner's ($p=.012$; $p<.05$) and Gjestland's data ($p=.015$) as were frequencies of cardiovascular involvement ($p=.000$ and $p=.000$; $p<.01$), which were highly significant. Central nervous system involvement highly significantly covaried with sex in Turner ($p=.000$) and Gjestland's data ($p=.000$) but not Rosahn and Black-Schaffer's data set (see Table 36).

Discussion

Results of analysis of the two types of data sets suggest two different patterns in the manifestations of syphilis, neither of which are clearly congruent with significant sex-based differences in the pathophysiology of the disease. In other words, neither of the hypotheses proposed for this analysis—first, that sex is associated with differences in the manifestations and syphilis, and second, that sex and age (reproductive status) are associated with differences in the manifestations and syphilis—are unambiguously supported by the data. This ambiguity is congruent with the few studies that have reported sex differences in syphilis within archaeologically derived skeletal samples, but

not with the more clear-cut reports of sex-based differences in the disease evident in the clinical literature.

For example, assessment of the skeletal data set demonstrated no systematic, significant relationships between skeletally assigned sex and the presence and prevalence of gummata. This result is unlikely to be due to potential biases in the sex designations of skeletons (see Walker 1995; Walrath et al. 2004) and differences in the numbers of males and females in the sample were accommodated statistically. Errors in skeletal recording are equally unlikely as extremely conservative criteria were employed in assigning measures of infection duration and tempo (see Table 12). Instead these results suggest that delayed hypersensitivity to spirochetes or to treponemal antigens—the presumed cause of gummata (Salazar et al. 2002)—is not influenced by biological sex. This finding is congruent with clinical literature on the subject, which suggests that delayed-type hypersensitivity is substantially modified by age, immunological status, and overall health (see McDade 2005). Thus, this result provides independent, additional support for the findings made in Chapter Five, further indicating that overall health throughout the life-course may have a powerful modulatory effect on the pathophysiology of syphilis.

The results on skeletal involvement in syphilis in this analysis seem to present a minor conundrum; while the skeletal sample exhibited no variation in ossesous lesions that could be attributed to sex, the contrary was found in the clinical sample. Both Gjestland's and Turner's data demonstrate significant relationships between skeletal involvement and sex. (Problematically, as 'skeletal involvement' was left undefined by these authors, whether it implies gummatous involvement, and thus variation in the ability to mount a delayed-type hypersensitive reaction, or a more general inflammatory

process, cannot be discerned). However, these results are not systematic; males present significantly more involvement than females in the former and females dominate in the latter. This is puzzling, as subtle skeletal lesions are difficult to detect at autopsy and via radiography and are likely to be undercounted (Walker et al. 1997; Weston 2008) and when found, biased towards more severe lesions (Ortner 1991; Powell 1988a), though they are easily recognized in dry bone (Powell 1988a). The stringent diagnostic criteria employed here, however, also limit inclusion of mild cases in the skeletal sample. As such, the clinical findings may instead be due to Turner, Gjestland and Boeck's diagnostic criteria. In both data sets, skeletal involvement, which is not defined, was diagnosed based on patient-reported bone pain (Gjestland 1955; Turner 1930), which often—but not always—coincides with actual skeletal involvement(Hansen et al. 1984; Kumar et al. 1989; Rademacher and Radolf 1996) (radiographs were employed by Gjestland in the follow up sample in only a minority of cases). This, as well as the opposing relationship with sex found in these studies suggests that skeletal involvement does not vary by sex in syphilis, though potentially more subjective reports of bone pain might.

Similarly, many of the other disparate findings between the two studies in re-analysis of the data are likely due to differences in study design and diagnostic criteria rather than being indicative of sex-based differences in the manifestations of syphilis. For example, results indicate sex-based differences in the frequency of secondary disease and recurrent infections in Gjestland's but not Turner's data and vice versa for recurrent secondary infection, cutaneous secondary lesions, and frequency of tertiary disease. Sex-based differences in the frequencies of secondary stage infection, recurrent secondary

infection, and tertiary disease would be in support of **H_2a**, that syphilis manifests different between males and females, but not ambiguously, as they are not systematic. The discrepancies may be due the clinical samples employed in each study: Turner's—but not Gjestland's—sample was drawn from an outpatient clinic population. Patients provided medical histories and were seen by physicians intermittently but were not subject to constant observation. These disparities could also be caused by the age distribution of Turner's sample—if it included a small proportion of reproductive age or pregnant females, who are reported to display milder cases of secondary disease (Warthin 1928). However, Turner only notes that his sample was comprised of individuals over twelve years of age. Uniquely, Boeck hospitalized all patients presenting with secondary syphilis until their symptoms disappeared, which required between one and twelve months, with an average of 3.6 months. Therefore, Gjestland's data may represent a much more accurate picture of early stage syphilis. The disparity for tertiary disease is less easily explained. It may also be attributable to differences in diagnostic criteria. Boeck's sample was diagnosed based only on clinical manifestations as darkfield and serological tests were unavailable in 1910, which may have introduced false positives, though retrospective examination of these patients on two separate occasions ante mortem and analysis of medical records postmortem makes this highly unlikely (Clark and Danbolt 1964). In contrast, Turner's sample was diagnosed based on a positive Wasserman reaction, clinical lesions, or in reproductive age women with a negative Wasserman, birth of syphilitic children. Given the great potential for both false positive and negative reactions in Wasserman tests (Gilbert 1930), the intermittent nature of Turner's data collection, and syphilis' capacity for causing a diverse range of symptoms,

this sample likely includes a great number of patients who were not actually infected with the disease. This is reaffirmed by evidence of a strong selection bias for severe outcomes in Boeck's (Gjestland 1955; Harrison 1941; Sowder 1940) and even Gjestland's data. Despite Gjestland's attempts at removing the original biases, 80.6% of female patients and 83.8% of male patients in Gjestland's sample, for example, exhibited tertiary syphilis, though most studies of the incidence of syphilis report that only 15 to 40% of cases progress to tertiary disease. In contrast to the sample for secondary stage disease, this may be due to a self-selecting tertiary sample. Gjestland's sample of tertiary syphilitics represent those who returned to the hospital for unrelated health conditions, symptoms of syphilis, or who responded to his entreaties for follow up care, suggesting that this sample was characterized by disproportionately high morbidity. Consequently, while sex-based differences may be evident in the frequency of secondary stage infection and recurrent infection—and thus the effectiveness of early stage bacterial clearance—this finding is highly tentative. No conclusions can be drawn on existence of any like differences in the frequency of tertiary infection.

In contrast, congruent findings on sex-based differences in cardiovascular and neurological involvement may indicate sex-based differences in the disease. Intriguingly, these findings are congruent with the expectation that females would manifest lower frequencies of organ system involvement that males. Both Gjestland and Turner's data show systematic, significant relationships between sex and cardiovascular involvement, with 13.6% of males and 8.2% of females in Gjestland's data and 8.4% of males and 4.6% of females in Turner's expressing involvement. Both Turner and Boeck and Gjestland employed roentograms and clinical evidence in making this diagnosis. These

findings corroborate those of several early 20th century physicians on cardiovascular involvement in syphilis (Stokes 1934; Warthin 1928), though not to the degree that they reported. Frequencies of neurological involvement also showed significant and disproportionate distribution between the sexes, with 15.7% of males and 7.2% in Turner's data and 8.3% of males and 3.3% of females in Gjestland's showing involvement. Rosahn and Black-Schaffer's data did not demonstrate a significant difference, but the trend was for more involvement in males (47%) vs. females (31.6%). As both cardiovascular and neurological involvement, like the other aspects of tertiary morbidity, involve inflammation, these sex-based differences may correspond to the generally anti-inflammatory effects of oestrogens and to the findings of several researchers that androgens may exert a pro-inflammatory effect in the face of bacterial infection (Blackwell and Christman 1996; Schroder et al. 1998). On the contrary, as other studies have produced contradictory results on the anti-inflammatory effects of these hormones and as testosterone seems to exert a protective influence on cardiovascular health (Cavasin et al. 2005; Malkin et al. 2003), the significant differences in cardiovascular involvement may be attributable to the consistent, well-documented sex-based disparities in cardiovascular disease (Lerner and Kannel 1986; Wenger et al. 1993). However, given that the same inflammatory processes are at work, sex-based differences in neurological involvement indicate that an underlying process influenced by hormones may be responsible. Intriguingly, neither Turner or Gjestland's data corroborate the findings of several early 20th century physicians that neurological involvement was more common in males than females (Gärtner 1921; Warthin 1928). This may be a product of the age and reproductive status-distributions of these samples—if, as raised above for

Turner, both included significantly lower numbers of reproductive age females and pregnant females than post-menopausal females. Problematically, as Gjestland also does not include age data in the descriptions of lesion frequencies, this possibility cannot be assessed. Nonetheless, as cardiovascular and neurological involvement are responsible for the majority of mortality directly attributable to syphilis (see Singh and Romanowski 1999), these differences should be considered in analyses of the heterogeneity of frailty in skeletal studies of syphilis and potentially, its related treponemal variants, endemic syphilis and yaws.

Unfortunately, this study must leave the question of the effects of reproductive age and menopause on the manifestations of syphilis and the duration and timing of its stages un-assessed. Likewise, the effects of pregnancy cannot be assessed as information on pregnancy was only infrequently addressed by Gjestland and in a non-standardized manner. However, age-based differences in the manifestations of syphilis were noted in the skeletal sample: adults over the age of forty six years were significantly likely to manifest gummata on the skeleton and to manifest more than one gumma. This finding may be due to well-documented difficulties in aging older skeletons (see Boldsen et al. 2002), but as sex is not significantly related to this finding and thus not menopausal age, i.e., the specific age associated with this significant relationship, this potential bias has little effect here. Instead, it may be attributable to the deleterious but still poorly understood effects of aging on the immune system (Castle 2000; Kovaiou et al. 2007). Future analyses might be fruitfully directed at investigating age-based differences in syphilis and the other treponematoses in archaeologically derived skeletal material.

Any analysis of the severity of pre-modern syphilis must also take the effects of treatment into consideration. As discussed in Chapter Six, many of the skeletons included in this study do bear trace element evidence of therapeutic exposure to mercury. Likewise, an unknown portion of the individuals in the clinical and autopsy sample received treatment with a variety of substances. While it is clear that non-mercury therapies, such as potassium bromide, had little to no discernable effect on infection until the invention of Salvarsan (Oriel 1994), there is ongoing debate as to the efficacy of mercury treatments (Goldwater 1972). Mercury has spirilocidal, anti-mitotic, and anti-inflammatory effects, and can clear cutaneous lesions of spirochaetes (Fabricius 1994; Goldwater 1972; Holmes 1984; Keogh 1913; Lees 1937; Osler and Macrae 1920). O'Shea (1990) has even speculated that treatments may have ameliorated the symptoms of infection during tertiary stage infection, but there are no *in vitro* studies to support this. Instead it is likely that the recurrent nature of infection and long latent period may have confused clinicians. While Ortner (2003) and others have speculated that high doses of mercury could exacerbate the severity of syphilitic lesions, analyses comparing trace element concentrations of mercury to the severity of syphilitic lesions have found no support for this assertion (Tucker 2007). Consequently, it is strongly argued that none of the differences in the manifestations of syphilis detected here are attributable to treatment.

Chapter Five: Overall Health and the Pathophysiology of Tertiary Syphilis

Introduction

Syphilis has been a persistent focus and stimulus of research in paleopathology since the field's inception in the 18th century (Meyer et al. 2002). During this time, the bulk of studies have focused on answering one of the greatest historico-scientific questions of all time: the origins and antiquity of syphilis. Hundreds of these have been devoted to documenting the global geographical and temporal distribution of syphilis and its related variants (see Baker and Armelagos 1988; Dutour et al. 1994; Harper et al. Accepted; Hutchinson and Richman 2005; Meyer et al. 2002; Powell and Cook 2005a). However, the result of this enterprise is that many other questions about the disease remain relatively unaddressed.

Among these is one of the disease's other great mysteries: how the causal spirochete, *Treponema pallidum* subspecies *pallidum*, causes the protean manifestations of syphilis. Syphilis is notorious for its great variability, for its multi-stage progression, and for producing an unpredictable range of symptoms (Bruusgaard 1929; Peeling and Hook 2006). For example, only 16 to 30% of individuals who have sexual contact with an infected person become infected (Moore et al. 1963; Schroeter et al. 1971), though actual transmission rates are presumably much higher (Alexander and Schoch 1949; Garnett et al. 1997). While the classic sign of primary infection is the chancre, as many as 60% of patients do not recall having a lesion of any sort (see Singh and Romanowski 1999). The secondary stage can be very subtle, most commonly featuring mild rashes and oral lesions, but potentially more severe manifestations also occur, such as deafness,

meningitis, which occurs in 8 to 40% of patients, jaundice in 12%, and most commonly, proteinuria, which can lead to kidney failure (see Baughn and Musher 2005). Latent or asymptomatic infection follows the cessation of these symptoms, and can last anywhere from one to thirty years; 25% of patients relapse into secondary infection during the first few years (Fournier 1899; Gjestland 1955). Less than a third of patients progress to tertiary stage, which can have an unfolding incubation period of nearly half a century (Clark and Danbolt 1964). Of these, only a few experience gummata, destructive, disfiguring tumors which can affect any organ (Gjestland 1955). Nearly half however, suffer nervous and cardiovascular involvement, leading to aortic aneurysms (symptomatic in 5-10% of patients) and neurosyphilis, the most feared syndrome, which is as likely to be asymptomatic as it is to cause excruciating pain and neurological impairment in tabes dorsalis and lead to dementia and psychosis in general paresis of the insane (Merritt et al. 1946).

During the 19th and 20th centuries, a large and vigorous area of research on syphilis was devoted to investigating variation in its symptoms and manifestations, particularly that related to the 'constitution' of patients (Fleming and Moore 1941). Many hypotheses were put forth in the clinical literature, focusing on immunity and susceptibility to re-infection (Magnuson et al. 1956; Magnuson et al. 1951), the underlying causes of relapsing infection (Chesney 1926; Moore 1941; Thomas 1956), and factors responsible for the onset of tertiary disease (Turner and Hollander 1957), and to a more limited extent, those responsible for variation within tertiary infection.

Investigations of this subject slowed to a halt[6] following the advent of antibiotics (Oriel 1994), leaving many of the persistent questions about its pathogenesis unanswered and largely unanswerable (Thomas 1956). *T. pallidum* is notoriously impossible to culture (Cumberland and Turner 1949; Magnuson et al. 1948; Norris and Edmondson 1986), the few animal models do not manifest tertiary stage infection (Baker-Zander and Sell 1980; Sell et al. 1980), and ethical concerns bar human experimentation. As a result, much about its virulence mechanisms remain to be discovered.

Despite these complications, the growing rise in the global incidence of syphilis and the largely unchecked progression of the HIV/AIDS pandemic have kept this question germane to contemporary research (Radolf and Lukehart 2006). Importantly, even with modern diagnostic capabilities, variation in the manifestations of syphilis, particularly the presentation of mild or uncommon symptoms, can interfere with recognition, diagnosis and thus treatment of cases (see Bash et al. 2001; Gurland et al. 2001; Meier and Mollet 1986; Noto et al. 2008; Wang et al. 1991). This is especially true for patients co-infected with other diseases that can impair immune responses, such HIV/AIDS and tuberculosis (Brightbill et al. 1995; Harris et al. 1997). The consequences of undiagnosed, untreated infection include morbidity from tertiary infection and synergy with HIV/AIDS. Syphilis remains a substantial source of adult morbidity. The heaviest burden is in the developing world and Eastern Europe, though cases are on the rise in some sub-populations in the United States, United Kingdom, and Western Europe (CDC 2007). Recognition that infection with syphilis increases transmission and acquisition of HIV/ AIDS and exacerbates morbidity (Buchacz et al. 2004; Greenblatt et al. 1988;

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[6] With notable exceptions, such the Tuskegee Study of Untreated Syphilis (1932-1972) of untreated syphilis in adult African American males.

Stamm et al. 1988) makes attention to variation in the manifestation of syphilis an especially pressing public health concern (Dar and Raza 2008; Karp et al. 2009; Radolf and Lukehart 2006).

This study aims to circumvent some of these constraints by investigating relationships between skeletal indicators of overall health and the pathogenesis of tertiary syphilis in human skeletal remains from post-medieval England (c. 1600-1864 AD). Skeletal evidence can only be used to examine tertiary syphilis; though syphilis is one of the few infectious diseases to manifest on bone, it only generates diagnostic lesions in the tertiary stage (Ortner 2003). This study specifically investigates associations between indicators of overall health and the presence of tertiary infection, and within individuals with tertiary infection, the extent of tertiary manifestations and the type of syphilitic lesions expressed. The indicators of overall health include periodontal disease, dental caries, and linear enamel hypoplasias. This is because the former two are the most common oral pathologies in modern populations (Rose and Vieira 2008), and there is therefore a huge body of literature about their associations with general health. LEH have been subject to intensive bioarchaeological study for several decades and there is also a large body of literature on their significance for past health.

Background

Pathophysiology of untreated syphilis

Very little is known about how *T. pallidum* produces the disease's protean manifestations. In the absence of cytotoxins and other known virulence factors, it is probable that both systemic and localized inflammation cause syphilis' characteristic tissue destruction (LaFond and Lukehart 2006).

Primary stage infection, which is associated with a chancre and regional lymphadenopathy, occurs approximately three weeks after inoculation. Treponemal spirochetes disseminate systemically, inducing a mild, localized inflammatory response and bacterial clearance (Lukehart 2004; McBroom et al. 1999). Secondary stage ensues approximately three months later, inducing an array of localized and systemic symptoms, including those mentioned above. Both stages can also produce periosteal reactions and osteitis, but these are not specific to the disease and often completely remodel (Hazen 1921; Ortner 2003). The continued presence of spirochetes in secondary infection induces production of inflammatory factors, including T lymphocytes, pro-inflammatory cytokines, and antibodies (Hanff et al. 1983; Lukehart et al. 1980; Muller and Oelerich 1981), as well as macrophages, which engage in bacterial clearance (Riley et al. 1992). Studies suggest a mechanism similar to delayed-type hypersensitivity, a hyper-allergenic response, as the mode of clearance (LaFond and Lukehart 2006). Latent, asymptomatic infection ensues, with its variable time frame and capacity for recurrent symptoms, enabled by persistent, scattered pockets of slowly replicating bacteria (Rosahn 1947). Turner and Hollander (1957) proposed that *T. pallidum* persisted in the body by

maintaining numbers below the critical antigenic mass need to provoke a host immune response. Instead, its persistence is more likely due to *T. pallidum*'s poor antigenicity (Radolf 1997) and capacity for antigenic variation (LaFond and Lukehart 2006). After approximately one year, improved immunological control leads to wholly asymptomatic infection (late latent) that without treatment can last for years to decades (Gjestland 1955; Kampmeier 1972).

Between 15 to 40% of latent patients develop tertiary infection. In these individuals, the very poorly understood host immunological surveillance mechanisms that contained the spirochetes at their foci fail. Unknown factors cause *T. pallidum* to begin replicating at a higher rate, inciting recrudescent infection and intensified, destructive inflammation (Radolf and Lukehart 2006). As mentioned above, gummata, focal necrotizing lesions, can form in skin, muscle, bone, and neurological tissues. From observations of endemic syphilis, a related, non-venereal variant, Grin (1953) concluded that many were due to persistent 'skin sensitivity' and super- or re-infection, though this has been rejected. Likewise, Buckley and Dias (2002) have dispelled the proposal (see Keyes 1908; Steinbock 1976) that localized trauma to bones closely underlying the epidermis could release sequestered spirochetes and cause gummata Instead, gummata may be caused by exaggerated, delayed type hypersensitivity exaggerated, delayed hypersensitivity—a hyper-allergenic response to spirochetes or their antigens (Salazar et al. 2002). Tertiary syphilis rarely manifests on the skeleton, in 0.5 to 10% of patients (Resnick and Niwayama 1995). When it does, in addition to gummata it produces osteitis, osteomyelitis, and periosteal reactions, which in excess can pseudo-bowing of the tibia (saber shins, boomerang leg), and less commonly, the radius and ulna (Hackett 1936).

Joint involvement also occurs, including Charcot's joints and arthritis (Reginato 1993; Resnick 1988). On the crania, syphilis can cause palatal perforation and rhinomaxillary destruction (gangosa), periosteal reactions on the maxilla (goundou), and caries sicca, or gummata, necrosis, pitting, and excessive sclerosis, on the vault (Ortner 2003).

Overall health and tertiary syphilis

Very few studies have explored the possibility of a relationship between overall health and the pathophysiology of tertiary disease. Most findings are indirect. For example, the Oslo study of untreated syphilis (c.1891-1927) did not address the effects of overall health but re-analysis of the data has shown that syphilis produced an excess of mortality not directly attributable to the disease itself (Gjestland 1955). Similarly, results of the Tuskegee study of untreated syphilis (1932-1972), whose emphasis was on racial differences in syphilis, revealed that untreated syphilitic patients have significantly higher morbidity and mortality than uninfected control individuals during adulthood (Olansky et al. 1956; Pesare et al. 1950). Findings from the Yale Autopsy study (1917-1941) confirmed significant reductions in longevity among patients in the absence of any evidence of co-morbidity (Rosahn and Black-Schaffer 1943b). This and other studies have shown that only 20 to 30% of this mortality can be attributed to the disease itself, mainly from cardiovascular involvement (Rockwell et al. 1964; Rosahn and Black-Schaffer 1943b). These findings seem to indicate destructive synergistic relationship between syphilis and other sources of morbidity, such as co-existing conditions. In modern populations, several studies have examined the effects of co-infection with

HIV/AIDS on syphilis. Results are diverse, contradictory, and controversial (Lynn and Lightman 2004). In general, co-infected individuals usually have a more aggressive, malignant course, with atypical manifestations (see Karp et al. 2009; Lynn and Lightman 2004; Singh and Romanowski 1999). Immunocompromised hosts, especially HIV patients, also often require prolonged antibiotic therapy for full bacterial clearance and prevention of neurosyphilis (Mandell et al. 2005; Marra et al. 2004). However, it is unclear whether this dynamic is specific to a synergy with HIV/AIDs or only severe immunosuppression.

Historical and anecdotal evidence also suggests that a possible synergistic relationship exists between overall health and syphilis. For example, Mandell et al. (2005) very briefly noted that secondary and tertiary stage disease in syphilis and in a non-venereal variant, yaws, was exacerbated by poor overall health in modern populations. For those in the past, Carmichael (1814) noted that lesions attributed to the disease were often significantly worse in less healthy individuals in 18th century urban London. Arrizabalaga et al. (1997) found that chroniclers and physicians writing in late 15th and early 16th century Italy, reported that the infection was often 'curable' among their peers and high status patients but the same optimism was not found in reports of lower status patients. These sufferers may have received inferior care, become co-infected, died of other complications, and, though not mentioned by the authors, consumed an inadequate diet. Miles et al. (2008) speculate that the very low frequencies of syphilitic lesions found in high status cemetery samples in London, such as St. Marylebone, may be due to upper status individuals surviving longer without developing tertiary symptoms due to having uncompromised immune systems.

A survey of the published literature shows that no studies have examined any potential relationships between syphilitic skeletal involvement and overall health. Skeletal manifestations are often mentioned in modern cases and reports of patients co-infected with syphilis and HIV/ AIDS frequently mention findings of osteitis, osteomyelitis, periosteal reactions, and gummata (e.g., Lynn and Lightman 2004; Rademacher and Radolf 1996). However, because syphilitic skeletal involvement is already rare, no differences in frequency or severity of skeletal manifestations between cases have been noted.

Overall health, immune responses and inflammation

A large body of research exists on the relationship between overall health, immune function, and chronic infectious disease. Research in biodemography and life-course epidemiology has demonstrated that early-life exposure to infection and inflammation in modern populations has significant effects on the development of chronic disease and inflammatory responses in later life. However, the underlying biological pathways remain poorly understood (Dowd et al. 2009). Early exposure to infections during critical periods is thought to predispose individuals to chronic disease, in part through the reallocation of energy away from development needed for immune and inflammatory responses (McDade 2005). Differential pathogen burdens during early life may also play a role, as infections elicit an inflammatory response from the innate immune system and chronic infections may elicit a persistent pro-inflammatory response. (Eskandari and Sternberg 2002; Kiecolt-Glaser et al. 2002; Segerstrom and Miller 2004).

Malnutrition at early age—both in utero and during infancy and early childhood—is also hypothesized to influence later life morbidity and mortality, especially from chronic disease (e.g., the Developmental Origins of Health and Disease Hypothesis or Barker Hypothesis) (de Boo and Harding 2006; McMillen and Robinson 2005; Riley 2001). Infection and inflammation may also play a role in this dynamic (Finch and Crimmins 2004), as several studies have demonstrated that maternal exposure to pathogens can also affect early life growth and health and later life morbidity and mortality (Bengtsson and Lindström 2003; Elo and Preston 1992; Riley 2001).

Following development, additional aspects of overall health can have a detrimental effect on the immune system including malnutrition and psychosocial stress. Malnutrition can have a strongly negative effect on immune structure and function. Overall, studies have demonstrated that cell-mediated immunity is particularly sensitive to macro-nutrient deficiencies, resulting in reduced circulating levels of T lymphocytes and suppressed delayed-type hypersensitivity, though humoral immunity is relatively buffered (Lunn 1991). Psychosocial stress also seems to impact the immune system, but through a variety of pathways. Multiple studies have found that stressors, especially when associated with low socioeconomic status in modern populations, downregulate various aspects of the cellular immune response, which increases susceptibility to infection, and can also prolong infection (Glaser and Kiecolt-Glaser 2005). Chronic and even short term stressors can reduce lymphocyte proliferation and increase pro-inflammatory cytokine production (Evans et al. 2000; Segerstrom and Miller 2004). Stressors as well as depression can also sensitize the inflammatory response, thereby producing heightened responsiveness to subsequent stressful events, as well as to antigen challenge (Glaser et

al. 2003; Johnson 2002; Penninx et al. 2003; Zhou et al. 1993). These stress related changes have been linked to certain cancers, chronic conditions, frailty, and various age-related diseases (Harris 1999). These impacts are likely to be heightened in early life and older adulthood (Coe and Lubach 2003; Kiecolt-Glaser et al. 1996; Kiecolt-Glaser et al. 1998). Thus, adaptive responses to short-term infections can become maladaptive in the long term with the potential of being further exacerbated by stressors in later life.

Indicators of Overall Health

Studies of oral health in both modern populations and archaeologically derived skeletal samples suggest that dental caries, periodontitis, and linear enamel hypoplasias are associated with increased risk of systemic diseases and with increased mortality. For the former two pathologies, this may be due to a spread or oral infection to systemic infection, a common risk factor, or chronic inflammation initiated by an oral pathology. For the latter it may be due to lifelong exposure to stressors, or, for all three, an underlying problem with the immune system or a possible combination of factors.

Linear enamel hypoplasias (LEH) are characterized as horizontal lines of deficiencies in the amount or thickness of enamel on the buccal surface of teeth (Goodman and Rose 1990). They can be caused by a number of factors but are most likely to be caused by systemic physiological stress, such as systemic disease, neonatal disturbances, and nutritional deprivation (Hillson 1996). As it is not possible to determine the specific cause of LEH in archaeological skeletal samples they serve as non-specific indicators of physiological stress (Goodman and Rose 1990; Pindborg 1982). Several

studies have demonstrated a clear link between markedly reduced longevity and frequencies of hypoplasias, both those formed during uterine development (Armelagos et al. 2009; Cook and Buikstra 1979) and the post-natal developmental period (Blakey and Armelagos 1985; Boldsen 2007; Goodman and Armelagos 1988). This suggests that, rather than benign indicators of growth arrest, LEH represent stress-induced growth disruptions with long-term health effects (Duray 1996). There are several possible explanations for this association (Goodman and Armelagos 1988), none of which are unambiguously supported by available data (Armelagos et al. 2009; Boldsen 2007). Individuals with defects and increased frailty (age standardized relative risk of death) may have a pre-existing inherent susceptibility to biological insults, independent of early life conditions (Rothman and Greenlander 1998). Alternatively, the association may indicate differential, life-long patterns of social, cultural, and behavioral exposure to stressors, in that individuals with defects experienced high levels of both early and later life stress. Lastly, earlier mortality of affected individuals may be due to 'biological damage' to the immune system during prenatal or postnatal development, resulting in both defects and greater susceptibility to insults in later life (Armelagos et al. 2009; Duray 1996).

Dental caries is characterized by localized demineralization of hard tissues of teeth (enamel, dentine, and cementum) by weak organic acids produced by bacterial fermentation of dietary carbohydrates (Larsen 1997; Selwitz et al. 2007). Carious lesions form when oral bacteria, contained in an oral biofilm (dental plaque), remain on the surface of the tooth for an extended period of time. Eventually this causes subsurface demineralization, which can progress to cavity formation (Selwitz et al. 2007). Several

studies have found an association between dental caries and general health status (Acs et al. 1999; Joshipura et al. 2003; Misra et al. 2007; Ylostalo et al. 2006) and infection can also spread from caries to other tissues (Ngoenwiwatkul and Leela-Adisorn 2009). Caries can also lead to a systemic inflammatory response, that may, for example, increase the risk of coronary heart disease (Joshipura et al. 2006). Caries may also be the result of the body's inability to control the proliferation of cariogenic oral bacteria and thus may reflect general inadequacies of the body's immune response (Acs et al. 1999). Studies have also shown a link in modern populations between caries, reduced growth and development, and nutritional inadequacy, which can in turn lead to impaired immune response. This may be due to dental pain from carious teeth interfering with eating (Acs et al. 1999) or with sleep, which can adversely affect growth through associated stress (Sheiham 2006), or from consumption of cariogenic, low nutrient quality foods (Miller et al. 1982).

Periodontitis (periodontal disease) is caused by a chronic oral bacterial infection that causes inflammation and gradual destruction of the gingiva, periodontal ligaments, root cementum, and alveolar bone and the gradual destruction of periodontal tissues and alveolar bone (Irfan et al. 2001). Periodontitis can be caused by a variety of pathogenic infectious agents found in biofilms, including *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis*, and *Treponema denticola* and various herpes viruses (Li et al. 2000; van Winkelhoff and Slots 1999). In skeletal material, periodontitis can be identified by the loss of alveolar bone, which exposes the underlying trabecular bone, producing porosity or causing the alveolar crest (AC) to recede relative to the cemento-enamel junction (CEJ) of the associated tooth (Larsen 1997). Many studies of periodontitis in

modern populations have shown that it is associated with a greatly increased frailty or risk of all-cause mortality (DeStefano et al. 1993). DeWitte and Bekvalac (2010) have demonstrated that this same association between periodontitis and increased mortality also existed for past populations. The condition has also been shown to be a risk factor for multiple systemic diseases in modern populations, including cardiovascular diseases, respiratory infections, certain types of cancer, Alzheimer's disease, diabetes mellitus, renal disease, necrotizing fasciitis, osteoporosis, and rheumatoid arthritis (see Williams et al. 2008). Very early proponents of this linkage also included syphilis in the list of systemic disease associated with oral infection (Hunter 1900; Mayo 1922), but this dynamic seems to have gone uninvestigated since. The observed associations between cancer and periodontitis might also reflect the presence of an impaired immune system that is unable to clear an infection or monitor and control tumor growth (Michaud et al. 2008). Studies of these linkages have also led some to suggest that periodontitis may cause these conditions, specifically cardiovascular disease (Beck and Offenbacher 2005), by causing chronic systemic infection or inflammation. The pathogens that cause periodontitis, or components of those pathogens such as endotoxins or antigens, can enter the bloodstream through pockets of ulcerated gingival tissue (Amabile et al. 2008) and the body then responds to these through production of proinflammatory cytokines (Loos 2005; Spahr et al. 2006). As such, it may be possible that these cytokines could exacerbate existing inflammation from syphilis.

This study examines the relationship between expression of tertiary stage syphilis and its manifestations and indicators of overall health: periodontitis, linear enamel hypoplasias, and dental caries. As any association between these indicators and any

expression and manifestations of syphilis indicates differences among individuals in susceptibility to the disease, this addresses the issue of heterogeneity of frailty (Wood et al. 1992). This is the observation that individuals may vary dramatically in their susceptibility to illness and thus mortality (Wright and Yoder 2003). Multiple studies have demonstrated that periodontitis, linear enamel hypoplasias, and dental caries are strongly informative about frailty in past populations and should thus be indicative of the differential susceptibility of past individuals to syphilis.

Materials and Methods

Data was derived from two data sets and two skeletal samples. Skeletal data on the manifestations of syphilis was collected by the first author from skeletons from two post-medieval skeletal samples from London, New London Bridge / St. Thomas Hospital (NLB91) (N=17) and Lower St. Bride's/ Farringdon Street (FAO90) (N=7). Both are held by the Centre for Human Bioarchaeology at the Museum of London and have been fully inventoried by staff osteologists. Therefore, to limit inter-observer error, data on oral pathologies from all adult (>18 yrs) skeletons (N=160), both those with and without diagnostic skeletal evidence of syphilis) recovered from these sites was derived from the Museum of London's WORD database (2010).

Skeletal samples

The St. Bride's Lower Churchyard, Farringdon Street (FAO90), represents one of two components of the burial ground for the parish of St. Bride's, London. The lower

cemetery accommodated overflow from the overcrowded Fleet Street churchyard and vault. Individuals buried therein were poor and lower status servants, infants, residents of the nearby Bridewell workhouse and Fleet prison, vagrants, and visitors from other parishes. A burial ground was opened on the site in 1610, but the excavated and analyzed burials all date to the late 18 to 19th century (AD 1770-1849). The west end of the site contained a brick burial vault, which contained 47 burials in coffins and 75 individuals piled at the end of vault. Excavations of the site in 1991-92 yielded a total of 606 skeletons, of which 544 were analyzed (Miles and Conheeney 2005). This yielded 8 skeletons with lesions suggestive of or specific to syphilis; one lacked dentition and was thus excluded from the analysis.

The New London Bridge/ St Thomas' Hospital sample represents a small portion of a large, post-medieval cemetery associated with St. Thomas Hospital. The sample was excavated in 1991 from a small area (6m x 3m) of the New London Bridge House site, Southwark (NLB91). The excavation revealed at least three burial trenches identified as mass graves associated with the Hospital that are believed to be either pauper or epidemic graves. The 227 articulated individuals recovered were found beneath a presumed charnel pit and dated to the 17th century based on pottery; St. Thomas was one of only three hospitals to survive the dissolution of the monasteries in 1538. Of the 193 analyzed, 24 had lesions attributable to syphilis, of which seventeen were suggestive or specific. The prevalence of non-specific periosteal lesions was also very high (35.2%) and may in some instances have been a precursor to specific infection. The high prevalence is attributed to the cemetery representing a hospital population for an institution that provided care to patients with syphilis throughout the early modern period (Jones 1991).

Oral pathology

For this study, linear enamel hypoplasia was diagnosed following Hillson (1996) and scored as present following Powers (2008) if it could be clearly felt with a fingernail or if a tooth presented with clear brown ridges on the enamel surface. Following Goodman et al.'s (1980) 'best teeth' method, LEH was scored only for the maxillary and mandibular incisors and canines. Periodontitis was scored as present if the distance between the CEJ and AC was greater than 2 mm. Alveolar bone surrounding each tooth was scored individually but the analysis incorporated pooled mandibular scores and pooled maxillary scores to assess the condition at a broader scale. Use of this criterion is potentially problematic, as non-pathological processes such as continued eruption of teeth during adulthood, can increase the distance beyond 2 mm (see Hillson 1996). This can potentially lead to overestimation of the prevalence of periodontitis. While scoring alveolar porosity can help to correct for this, it was not employed as a diagnostic criterion for skeletal material recorded in the WORD database (Powers 2008) and was thus not available for inclusion here. The potential effects of this bias on this analysis are presented in the Discussion section. Dental caries presence was assessed for the premolars and molars; carious lesions were scored as present if destruction of enamel or dentine was visible to the naked eye. Though data on level of severity have been collected, the following analysis incorporated data only on the presence or absence of caries.

Skeletal data collection

Individuals included in the sample group exhibited gross skeletal lesions *highly suggestive* of or *specific* to syphilis, following Hackett (1976) and Powell and Cook (2005a), supplemented by Ortner (2003) and Steinbock (1976), and Aufderheide and Rodrìguez-Martìn (1998b). Because of syphilis' protean manifestations, establishing the specificity of various lesions to the disease has been historically problematic. Hackett (1976), which compared skeletons of clinically diagnosed cases of syphilis, cases of other pathological conditions, and healthy controls were, is the only published study wherein the specificity of various skeletal lesions to treponemal disease was rigorously tested. Hackett found two diagnostic markers: caries sicca, and osseous expansions and nodes with superficial cavitations on long bones. Variations upon these—both rugose and finely striated nodes and expansions, and coarsely striated and pitted expansions on long bones—are not diagnostic but instead strongly suggestive of treponemal disease. Following Hackett and Powell and Cook (2005a). These stringent criteria, wile excluding consistent cases, avoid inclusion and analysis of false positives for infection.

Analysis

Statistical analyses were run using STATA 11.0® and Microsoft Excel 2008®. Frequencies of periodontitis, dental caries, and LEH were generated using Excel. To evaluate $\mathbf{H_3a}$, logistic regressions were run using STATA to assess any significant variation in the presence of tertiary syphilis and of LEH, periodontitis, or dental caries in the skeletal sample from NLB. To evaluate $\mathbf{H_3b}$, logistic regressions were also run to

assess any significant variation between presence of gummata and of LEH, periodontitis, or dental caries in the sub-sample of skeletons with evidence of tertiary syphilis from NLB and FAO. As absolute number of gummata present in the sub-sample with evidence of syphilis was not assessed.

Results

Analysis demonstrated a significant relationship between presence of tertiary syphilis and presence of periodontitis ($p=.04$; $p<.05$) and between presence of tertiary syphilis and LEH ($p=.03$; $p<.05$), but not between presence of tertiary syphilis and dental caries in the NLB skeletal sample. A significant relationship was also found between presence of syphilis and presence of both LEH and periodontitis ($p=.021$; $p<.05$). In the combined sub-samples of skeletons with evidence of tertiary syphilis from NLB and FAO, no significant covariance was found between presence of gummata and presence of LEH, caries, or periodontitis.

Discussion

The results support the first hypothesis—that the pathophysiology of the stages of syphilis varies in relation to overall health, specifically oral health, but not the second, that the manifestations of tertiary syphilis vary in relation to overall health. The former, particularly the findings indicating a significant relationship between the presence of LEH and the presence of syphilis suggest that early life experiences may play a critical role in creating differential susceptibility to the progression of syphilis in later life. Specifically, these suggest that early life exposure to stressors sufficient to cause

physiological disruption (and temporarily arrest growth) results in life long impairment of the immune surveillance mechanisms presumed to be responsible for checking the progression of latent syphilis into recrudescent tertiary disease. The exact mechanisms responsible remain unknown however, meaning that this dynamic cannot be more clearly interpreted. The relationship between LEH and indicators of health and stress in skeletal samples has only been evaluated in relation to mortality levels in the published literature; a survey of the published literature shows that potential associations between LEH and chronic infectious disease remain yet uninvestigated. As discussed above, dozens of studies have established a strong association between presence of LEH and increased frailty, though the underlying linkage remains unknown. Results of this study do not greatly clarify this ambiguity. As onset of tertiary disease is linked to the failure of immunological regulation however, this study does lend support to the hypothesis that individuals with LEH suffered 'biological damage' to the immune system during prenatal or postnatal development, leaving them with both defects and a greater susceptibility to insults in later life (Armelagos et al. 2009; Duray 1996).

However, results may also be congruent with the alternative explanation, that the association is due to differential, life-long patterns of social, cultural, and behavioral exposure to stressors, in that individuals with defects experienced high levels of both early and later life stress. There is significant evidence to suggest that there may have been a dialectical relationship between overall health and syphilis. Syphilis had a well-documented impoverishing effect in early modern England. In part, this was caused by the high price of treatments for the disease (Porter 1989). While mercury, the predominant contemporary therapy was supplied to many impoverished sufferers in

public institutions in London for free throughout the 16th and 17th centuries, many sought private and thus more costly treatment (Siena 2001; Siena 2004). Non-mercurial 'vegetable cures' were also frequently very costly (McAllister 1996). As syphilis is often recurrent and can manifest for decades, costly treatments may thus have been necessary throughout adulthood, driving many individuals into poverty. Syphilis was also highly stigmatized; infection seems to have commonly resulted in social ostracism and lost employment for individuals of all social strata (Siena 2004). Consequent malnutrition and psychosocial stress may have exacerbated both the infection and individuals' overall health, potentially making them more likely to manifest tertiary stage disease. The particular skeletal samples employed for this analysis, however, may be able to shed only limited light on the explanatory potential of this hypothesis. This is because the New London Bridge/ St Thomas Hospital (NLB) site likely represents a segment of the population of London with comparatively low levels of overall health. St Thomas Hospital served as one of the primary sources of health care for impoverished, chronically ill, and lower status residents of London (Siena 2004; Watson 1972). Frequencies of oral pathology from the site are elevated in comparison to those of other post-medieval skeletal samples from London. For the whole dentition, 74.6% of adults exhibit dental caries, 60.3% LEH, and 77.8% periodontitis. Higher status samples, like St.Bride's Crypt, exhibit LEH in 0.56% of whole dentitions, periodontitis in 52.24% and caries in 1.69% (Harvey 1968). Lower status samples, such as Cross Bones, exhibit caries in 25.93% of dentitions (Brickley et al. 1999), and skeletons from the Newcastle Infirmary site, another hospital cemetery, manifest caries in 10.11% of teeth and periodontitis in 17.27% of teeth (Boulter et al. 1998). Similar levels of oral pathologies

also exist between males and females, which is also congruent with findings in other contemporary samples (WORD database 2010). Overall levels of pathology are equally anomalous: NLB skeletons show elevated levels of systemic, non-specific stress and infection (i.e., periosteal reactions), as well as specific infections, such as tuberculosis, in comparison to other contemporary samples (WORD database 2010). Consequently, it is not currently possible to examine whether major differences in life long exposure to stressors related to socioeconomic status or other factors play a great role in this dynamic as all of the individuals in the sample can be assumed to have been chronically stressed throughout the life course.

Much like DeWitte and Bekvalac's (2010) finding that periodontitis is associated with increased frailty in skeletal samples, results here suggest that it can also be associated with susceptibility to chronic infectious disease. Among other possibilities, DeWitte and Bekvalac proposed that periodontitis might have caused systemic chronic inflammation or infection, which subsequently influenced the development or severity of other life-threatening conditions. While severity cannot be currently assessed, this dynamic may be responsible for the association between periodontitis and syphilis. This finding is, however, complicated by the fact that the methodology employed for recording periodontitis may systematically overestimate prevalence of the condition in a given sample (Clarke and Hirsch 1991; Costa 1982; Varrela et al. 1995). As such, this association may be inflated. Future statistical tests will be required to assess the extent of any possible bias, following DeWitte and Bekvalac (2010). As the tissue destruction associated with syphilis is presumed to be a product of both systemic and localized inflammation, the inflammation associated with periodontitis, which some scholars have

speculated might either cause or exacerbate other inflammatory conditions, such as cardiovascular disease, could also exacerbate the manifestations of syphilis. The current small size of the sub-sample of skeletons with tertiary syphilis prohibits assessment of this dynamic. However, future investigations will incorporate additional pathological skeletons from the study's overall skeletal sample to assess whether presence of periostitis is also linked to variation in presence of lytic activity or periosteal deposition on the skeleton.

The absence of a significant relationship between the presence of LEH and that of gummata, however, suggests that the same effect does not operate on individuals' capacity for exaggerated, delayed type hypersensitivity, the mechanism presumed to be responsible for the formation of these lesions. A lack of association was also found between the presence of gummata and of dental caries or periodontitis. A search of the published clinical literature demonstrates that associations between these health indicators and delayed type hypersensitivity may have yet to be conducted. However, clinical studies using animal models have demonstrated that delayed type hypersensitivity is suppressed in malnourished individuals (see McDade 2005). As malnutrition has been associated with dental caries in living human populations, though again the underlying linkage remains unknown, the absence of covariation between dental caries and gummata also supports this interpretation. Combined, this suggests that overall poor health may not make individuals more susceptible to gummata. In turn, this lends limited support to one aspect of the osteological paradox: Ortner's (1991) contention that skeletons with few pathologies may actually represent the most unhealthy individuals. However, while individuals with indicators of poor overall health may be no more likely than those with

fewer of these indicators to manifest the most destructive of syphilis' manifestations, they are still more likely to manifest the tertiary stage of the disease itself.

Overall, these results suggest that early life stressors and nutrition may synergistically combine with exposure to inflammation to affect health in later life. Specifically, associations between presence of syphilis, LEH, and periodontitis suggest that early life exposure to stressors may combine synergistically with elevated inflammatory responses and a compromised immune response in later life. Compromised immune function, for example, could be the result of suboptimal nutritional status. Documentary evidence suggests that typical diets in early modern England may have been nutritionally deficient, particularly in regards to protein and other macronutrients (Albala 2003; Atkins et al. 2007; Roberts and Cox 2003c). However, given the contemporary potential for social mobility, especially downwards (Porter 1995); high degrees of geographical mobility, especially from rural to urban areas (Wrigley 1987; Wrigley et al. 1997; Wrigley and Schofield 1981), and the heterogeneity of diet between these two locales, as well as the heterogeneity of dietary resources demonstrated by many isotopic dietary reconstructions of English skeletal samples (Albala 2003; Barrett et al. 2004; Mays 1997; Müldner and Richards 2007), no direct relationship between diet and immunocompetence can be assumed or inferred here. Alternately, periodontitis might be caused by poor immune functioning; studies have shown that in modern populations, development of caries might reflect the immune system's inability to control the proliferation of cariogenic oral bacteria (Acs et al. 1999). Likewise, in individuals with compromised immune systems (e.g., HIV infection or cancer treatments) the severity of periodontitis increases. Some scholars have further hypothesized the existence of a

hyperinflammatory trait causing some individuals to exhibit an abnormally high inflammatory responses to pathogens (Beck et al. 1996) or the presence of genetic polymorphisms for genes involved in the inflammatory process of periodontal disease and other linked inflammatory disorders, such as Alzheimer's disease (Watts et al. 2008). Periodontitis may also be tied to contemporary population-level exposure to infection and experiences of inflammatory processes. Crimmins and Finch (2006; 2004) have hypothesized that the demographic transition of long-term declines in mortality beginning before 1800 in many areas of Europe may have been caused by a reduction in life time exposure to infectious disease and other sources of inflammation, leaving individuals less likely to die of inflammatory chronic conditions, such as cardiovascular disease, later in life. As the New London Bridge sample is dated to the 17th century and comprises individuals of very low social status and with very poor overall health, they may have been exposed to high levels of infectious disease—which is supported by the sample's high levels of LEH and other pathologies—and consequently have manifested an elevated inflammatory response to any insult.

Significance

According to DeWitte and Bekvalac (2010), if, as clinical studies suggest, it is reasonable to suspect that the associations between oral health and systemic diseases in modern populations are at least partly determined by variation in genes influencing the immune system or by infection with diseases that affect immune responses, such mechanisms could also have been at work in past populations. In the skeletal samples,

there might have been some individuals who were genetically predisposed to developing periodontitis, LEH, tertiary syphilis, and other diseases, or who had immune systems weakened by disease and were thus more highly susceptible to oral pathologies and other causes of morbidity. As their results suggest that periodontitis is associated with elevated risks of death in past populations, it might also have been associated with other systemic diseases in the past. Results of this study further confirm this finding. As discussed above, syphilis has not been associated with periodontitis in modern populations. Indeed, given that in industrialized nations, such as England, the prevalence of degenerative diseases has increased over the few centuries, gradually replacing infectious diseases as the common causes of death (Armelagos 2009; Gage 2005), if periodontitis was in fact associated with systemic diseases, these would have been primarily infectious (DeWitte and Bekvalac 2010). Results of this study support this, suggesting that a linkage exists between the processes associated with formation of periodontitis and those associated with progression of a chronic infectious disease. Overall, they further indicate that individuals with lower overall health, specifically those with a life-long trajectory of exposure to stressors and inflammatory processes, also manifest increased susceptibility to a major chronic, infectious disease. Further study might be fruitfully devoted to determining whether such an association also exists between these indicators and other non-inflammatory and inflammatory conditions evident on the skeleton.

Chapter Six: Mercury in the Midst of Mars and Venus: Treatment of Acquired Syphilis with Mercury in 17th to 19th century England

The Unfortunate Rake

As I was a-walking down by St. James' Hospital,
I was a-walking down by there one day,
What should I spy but one of my comrades
All wrapped up in flannel though warm was the day.

I asked him what ailed him, I asked him what failed him,
I asked him the cause of all his complaint.
"It's all on account of some handsome young woman,
'Tis she that has caused me to weep and lament.

"And had she but told me before she disordered me,
Had she but told me of it in time,
I might have got pills and salts of white mercury,
But now I'm cut down in the height of my prime.

"Get six young soldiers to carry my coffin,
Six young girls to sing me a song,
And each of them carry a bunch of green laurel

So they don't smell me as they bear me along.

"Don't muffle your drums and play your fifes merrily,
Play a quick march as you carry me along,
And fire your bright muskets all over my coffin,
Saying: There goes an unfortunate lad to his home."

18th century English Folk Song.[7]

Introduction

Syphilis was a significant, though still underestimated, public health problem in early modern England (Siena 2004). Various lines of evidence, including chronicler's reports, physicians', hospital records, and military records, suggest that rates of infection were extremely high in 17th and 18th century London and, presumably, other urban centers (Trumbauch 1998). These records also suggest that a large number of sufferers actively pursued medical treatment for their infection. Ads for 'pox' cures literally dominated early modern medical advertising. For example, more than half of the collection of medical advertisements held by the British Library, which date to approximately 1660 to 1715 AD, are for pox treatments (Siena 2001). Records of London's Royal Hospitals, St Thomas and St Bartholomew's, which were the city's two public hospitals, also reveal

[7] Smithsonian Center for Folklife and Cultural Heritage, Washington DC.
Audio clip: www.folkways.si.edu/albumdetails.aspx?itemid=2229

that the pox was the single most common disease treated at both institutions. In most years in the 17th century, venereal disease patients represented roughly a fifth to a quarter of patients treated at St. Bartholomew's and in some years, nearly one third. Similarly, records from St. Thomas, the cemetery of which yielded many of the skeletons included in this study, indicate that more than 28% of patients entering the hospital between 1773 and 1776 entered the venereal wards (Siena 2004). As Renaissance disease concepts grouped multiple conditions, including syphilis and gonorrhea, under the umbrella of 'the pox,' 'lues venerea,''venereal disease', or most commonly, 'the pox,' it is incorrect to assume that all of these patients were syphilitics (Siena 2005b). Nonetheless, the records suggest widespread or infection or at the very least, widespread diagnosis (Siena 2004).

Scholarship on the history of medicine and sexuality paints a complex picture of treatment options for syphilis in early modern England. Recent work has suggested that up until the mid 18th century, publicly funded institutional care options were nonexistent, making treatment predominantly available only to middling and high status sufferers through a private, fee-based medical marketplace (Allen 2000; Bynum 1987; Williams 1996). Instead through recent scholarship Siena (2004) has shown that institutional care for the pox became available in the mid 16th century in London. The city, Siena found, was characterized by a two-tiered medical system with radically different treatment opportunities: individuals who could afford to do so participated in the private, fee-based medical marketplace. Those who could not received care and treatment through public institutions.

Mercury, especially in high doses (i.e., salivation) remained the dominant treatment of the period (Goldwater 1972). However, it may have been progressively

rejected by higher status sufferers in favor of gentler, vegetable-based cures, such as guaiac, which were mostly out of the reach of the poor. Complicating this though, the well-documented impoverishing effect of 'the pox' may have placed some individuals in both spheres. Syphilis is often a lifelong, recurrent chronic infection, thus requiring treatment off and on for decades in some cases. These progressive expenses may have gradually downgraded sufferers from the pleasantries of guaiac to the horrors of mercury over the course of their lives (Siena 2004). Gender also played a determining role in treatment opportunities. For example, while middle and upper class women were serviced by a specialized subset of women healers who fulfilled women's need for discretion and specialized knowledge of the female body and physiology (Siena 2001), poorer women had comparatively fewer opportunities for treatment throughout the majority of the period. At least for the poor, the stigma associated with the disease meant that treatment was also often highly dependent on whether sufferers were perceived as having been infected 'innocently' or through illicit sex; though it may have been primarily a byproduct of class differences in treatment preferences, records suggest that poor sufferers may have been given toxically high doses of mercury as a punitive social shaming device (Temkin 1977).

While these ideologies are evident in documentary evidence of the time, actual practice is harder to decipher (Churchill 2005). As such, this study examines physical evidence for mercury treatment in several urban skeletal samples from early modern London. In doing so, this attempts to reconstruct a patient-centered history of illness-experiences (eg. Duden 199; Porter 1985a; 1985b). As these samples also represent a range of socioeconomic strata, this approach circumvents standard limitations produced

by the traditional use of documentary evidence; the surviving source material is biased towards elite patients. The use of institutional records to examine experiences of the poor also inserts a lens of hospital officials, doctors, and churchwardens into the material (Siena 2004). Instead, this study is the first to investigate differences in mercury concentrations in relation to gender and socioeconomic status. This study joins an extremely small body of literature on patient illness-experiences of syphilis in England, but uses these and a larger body of literature on mercury, syphilis, class, and gender to interpret differing levels of mercury (Hg), established using X-Ray Florescence Spectrometry (XRF), in a pathological sample of skeletons showing evidence of infection with syphilis and a larger, non-pathological control sample.

Background

Mercury and Treatment of Syphilis

Mercury treatments, in the form of unctions and fumigations, had been used in Europe for rashes, ulcers, and genital sores for centuries before the emergence of syphilis in 1495 (Swiderski 2008). This precedent paved the way for the very early use of mercury as a treatment for the pox, with chroniclers documenting its use by the early 16th century (von Hutten [1519] 1945). Mercury was not the only anti-syphilitic in use; nearly a dozen other metals, including bismuth and arsenic, and nearly two dozen plant based materials, including china root, sarsaparilla, and mercury's greatest rival, guaiac, were used as alternative treatments in an effort to find a less toxic chemotherapeutic agent (Proksch 1895). Rationales for mercury treatments followed the principles of humoral

medicine and later, theories of contagion. Following these ideologies, poisons—and specific to theories of contagion—infectious particles, could be flushed through excretion. As mercury is a potent diuretic and in toxic doses, induces copious salivation, it produced a dramatic and thus curative flushing effect (Debus 1977; O'Shea 1990; Rawcliffe 1995).

Mercury was administered in three main ways. Fumigation, wherein sufferers were placed in tent or overheated room for weeks to months at a time and forced to inhale vapors from heated cinnabar (mercury oxide), inunctions of mercurial compounds, and, in much lower doses, ingestion of the metal in pill or liquid form. The latter became increasingly popular in the 18th and 19th centuries. Mercuric chloride ($HgCl_2$), is corrosive, easily sublimating, and highly poisonous. When combined with sodium chloride and copper sulfates it was used in fumigations as early as the 16th century. It was also incorporated into unctions, which caused localized ulceration; inhaled, ingested, and injected (Goldwater 1972; Proksch 1895). Mercury chloride (Hg_2Cl_2), a mercury salt also known as 'sweet mercury', or calomel, is less toxic and was much more commonly used. Like mercuric chloride, it was administered orally as well as by injection, ointments, and in unctions (Habershow 1860; Mracek 1899; Proksch 1895). Related compounds, such as mercury bromides (Hg_2Br_2) are less toxic (Goldwater 1972; Proksch 1895) but were administered less frequently (O'Shea 1990). Both salts and fumigations were capable of causing acute and chronic mercury toxicity.

Prescribed dosage and duration of treatment varied over the period. English physicians prescribed lower doses than their continental peers (O'Shea 1990), but salivation treatments tended to last at least four to six weeks, with an average of six

(Astruc 1754). Some prescribed daily oral doses of calomel for over two years (O'Shea 1990), which in the 16th century may have been, on average, 5 grains (≈325 mg). However, there was no standard regimen. Instead, physicians titrated doses to fit the individual physiological requirements of their patients (Habershow 1860; Hamilton 1819; Keogh 1913; Proksch 1895). Some 19th century medical textbooks did, however, stress that doses should be sufficiently low as to not cause stomatitis and proteinuria, which were recognized as early signs of toxicity (Keogh 1913; Lees 1931; Osler and Macrae 1920). The level of adherence to these recommendations by both practitioners and patients is unknown. Patient accounts and secondary descriptions of mercury treatments are replete with instances of patients who abandoned therapy prematurely, too terrified or incapacitated by the symptoms of mercury toxicity to withstand the treatments, or disenchanted with its effectiveness (Quétel 1990; Siena 2004).

The effectiveness of the remedy continues as a subject of debate. While many early modern physicians were fully confident in its effectiveness against the pox, a growing number over the period criticized its use, particularly in relation to the treatment's serious side-effects (Goldwater 1972). Mercury has spirilocidal effects and can clear cutanoeus lesions of spirochetes (Holmes 1984; Keogh 1913; Lees 1931; Osler and Macrae 1920); its anti-mitotic and anti-inflammatory effects may also have ameliorated these lesions, as many early writers proclaimed (Fabricius 1994; Goldwater 1972). Mercury has also been documented as inducing a Jarisch-Herxheimer reaction, or the systemic release of large quantities of endotoxins as bacteria die during (antibiotic) treatment (Holmes 1984). However, there are no in vitro studies of the effects of mercury on syphilis to evaluate the validity of these assumptions. The natural, spontaneous

resolution of primary and secondary lesions may have also confused physicians. This phenomena had been noted by 19th century practitioners (Ferguson 1812) but was only confirmed in the mid 20th century by Gjestland's (1955) finding of a high incidence of early[8] spontaneous cures in the Oslo Study of Untreated Syphilis, one of two studies of the natural (largely untreated) history of the disease. This reaffirmed the view that many of the 'cures' attributed to mercury were more likely due to the fluctuating nature of untreated syphilis.

That the 'cure' was often worse than the disease was less ambiguous. Even acute exposure with small amounts of mercury can produce substantial signs of toxicity. Larger doses can produce severe, chronic, and even occasionally fatal effects (Swiderski 2008). Acute exposure[9] can cause pulmonary impairment and profound central nervous system defects, including psychosis (Liang et al. 1993; McFarland and Reigel 1978; Ngim et al. 1992). Chronic exposure results in a broad range of symptoms, including spasms, personality changes, erethrism, oral inflammation and ulceration, weight loss, and gastroenteritis (Bidstrup 1964; WHO 1976). These symptoms were recognized—and dreaded—by contemporaries; von Hutten ([1519] 1945) who was treated in the early 16th century, described experiencing stomatitis, tooth loss, gastroenteritis, salivation, 'Hatters Shakes', oliguria, and pneumonitis.

Treating the pox in early modern England: the medical marketplace and institutional care

[8] Ranging from one month to a year after initial infection (average 3-6 months).
[9] For example, 4 to 8 hours of exposure to Hg levels of 1.1 to 4.4 mg/ m^3

Scholarly debate exists over the existence and degree of differences in access to mercury treatments in relation to the convergent effects of gender and socioeconomic status. Up until recently, many historians presumed that mercury was only accessible to high to middling status sufferers in the pre-Enlightenment era, with limited availability and high cost keeping it out of the reaches of lower status groups (Allen 2000; Bynum 1987; Petrie 1999; Williams 1996). Instead, Siena and others have demonstrated that free or inexpensive mercury treatments were available to lower status sufferers via institutional care as early as the early 16th century in London. Indeed, the converse may have been true; those with resources employed them to avoid the unpleasant side effects, conspicuousness, and methods of mercury treatment, leaving high dose therapy to the lower classes.

Overall, high to middling status sufferers may have had significantly reduced exposure to mercury treatments than those of lower status, particularly after the mid 18th century. In the early modern era, patient demand had a powerful effect on medical care and provision (Fissell 1991; Jewson 1974; Porter 1989). The most common demand of pox sufferers, according to medical treatises and medical advertisements, was privacy (Siena 2001). Even suspected infection could cost men and women of all social strata their social and sexual reputation and in turn, their employment, though this effect may have been intensified for women (Gowing 1998a; Klein 1995; Trumbauch 1998). In addition to being excruciating, one of the main complaints about salivation was that it was highly conspicuous (Porter 1989). Confinement was required for several weeks (Astruc 1754), as sufferers salivated profusely, had foul breath, and occasionally even acquired a metallic sheen or tint to the skin (Quétel 1990). Several medical treatises

describe the complaints of high status patients over these shameful and suspicious absences (de Sigogne 1724). Extended absences could have equally severe consequences for the working classes, but the majority were incapable of affording the high price alternatives; treatments for the pox were among the most expensive on the market (Porter 1989). In response to these concerns, by 1740 low mercury treatments and non-mercury vegetable cures proliferated on the market (McAllister 1996) and salivation plummeted in popularity (Wilson 1999). Because of their expense, these resources—low mercury and no-mercury treatments—were in general only accessible to the middling and higher status individuals. Entering a hospital was a last resort for the critically ill or disfigured but given the price of treatments, the poor were likely very infrequent and short-term customers (Siena 2004).

Intriguingly however, the impoverishing effect of the pox may mean that some sufferers crossed this divide, initiating low dose or mercury-free care in the private fee-based medical marketplace but ending with salivations in publicly funded institutional care. The recurrent nature of secondary and tertiary infection means that expensive private treatment required significant resources over a sustained period, even a lifetime. Infection and treatment could thus have devastating economic effects (Siena 2004). As such, some (formerly) middling to high status individuals may show higher concentrations of mercury.

Those unable to afford private care or who exhausted their funds relied upon institutional care, provided by royal hospitals, uni-sex hospitals, such as the Lock for men and Kingsland for women, and as a last resort, workhouses. Hospital care was free and thus accessible to all impoverished and working class sufferers in the 16th and much of

the 17th centuries. However, in the late 17th, fiscal constraints (and likely prejudice) led hospitals to charge fees for care of all but a small number of the most destitute of patients. This effectively precluded treatment for most of the very poor. As a last recourse, these sufferers could to apply for a governor's nomination or parish relief to cover their fees or seek treatment through a parish workhouse. These required either political and community connections or parish membership; impoverished individuals and recent immigrants to London would have lacked these. From the early 18th century on, workhouse hospitals provided care to many of the most poor, but primarily for women. Workhouses carried a significant social stigma and were harshly disciplinary by nature (Andrew 1998); those who could afford other treatment options avoided entrance. However, many women could not and sought lodging and treatment in workhouses as the last alternative to absolute destitution and homelessness (Hitchcock 1985). In consequence, many of the destitute as well as the thousands of youthful rural migrants who characterized early modern England's urban populace (Beir and Finlay 1986; Porter 1995) may have had no access to treatment at all until the opening of the London Lock Hospital in the mid 18th century. Even there, patients were mostly men (Siena 2004).

Of the poor, lower, and lower middling status individuals who did succeed in gaining access to treatment, options were also much more limited. Guaiac and other mild non-mercury vegetable cures were prescribed for some public hospital patients, but this luxury was largely eliminated in the late 16th century with declines in hospital finances. After about 1670, salivation was nearly ubiquitous for hospital patients (Parsons 1932; Siena 2004a; Wilson 1999). Temkin (1977) has suggested that this served as social discipline: rough therapy doubling as a moral punishment. Discipline did become policy

at one hospital, St. Thomas's, where pox patients returning for repeat treatment after recurrent infection were publicly whipped, which is in keeping with the contemporary prevalence of 'rough music', charivari, and other forms of ritual shaming and modes of cultural policing (Amussen 1995; Dabhoiwala 2001). It also follows what Quétel (1990) sees as an increasing moral contempt of pox sufferers in the 17th century. Instead, Siena (2004) attributes salivation more to fiscal constraint. Nonetheless, the product is a mixed bag; some of the poor may have experienced high dose mercury, whereas some could, if only briefly, afford no or low dose care. Others could have received none at all.

Gender also likely played a significant role in treatment for the pox over the period. It has been widely argued that venereal disease in men and women was conceptualized and treated in essentially the same way in the early modern period, based on Galenic, one-sex models (ie. Laqueur 1990; Maclean 1980; McLaren 1984; 1985). However, recent scholarship has questioned this (Adelman 1999; Crawford 1981; Maclean 1983). Churchill (2005) has demonstrated that for physicians, women's unique physiology influenced the quantity and timing of treatments prescribed, including those for the pox and other sexually transmitted diseases. However, this line of inquiry has not expanded to discern whether this ideology translated into quantitative gender-based differences in the temporal duration or dosage of treatment nor whether this applied to the treatment of the pox with mercury specifically (Churchill utilized the generic term, 'treatment'). Physicians also primarily treated the middling and higher classes. As such, differing dosages of mercury may only be evident among these sufferers, though these ideologies may also have trickled down to affect care of the lower classes (Lindemann 1999).

When combined with socioeconomic status, gender had profound effects on access to treatment. If medical advertisements are any indication, treatment options may have been unlimited for higher to middling status male sufferers. While this was less true for their female peers, advertisements indicate that an entire industry of female healers existed in London to provide care for women. These practitioners advertised specialized knowledge of the female body and physiology, and most importantly, discreet care and inconspicuous low-dose or vegetable-based private therapy (Siena 2001). However, concerns over sexual honor may have prevented some from partaking of these options. For other women, particularly those from higher status households, the principles of feminine sexual honor and of male privilege, may have meant that many women were ignorant—or were intentionally kept ignorant by physicians and husbands—of the nature of their infection and thus did not seek treatment specifically for the pox (Rizzo 1996; Stewart 1996). In contrast, lower status and poor men and women did not have the luxury of discreet, private care—they had to confess their infection to male public hospital administrators, often in public circumstances, which may have been especially discouraging for women.

Overall, many poorer women seem to have simply had less access to treatment than women of higher status and than their lower status and poor male peers. Hospitals, for example, reserved progressively less ward space for women than men in the 17th and 18th centuries (Siena 2004). This may have been a punitive product of gendered prejudice, as many popular and medical treatises still attributed the origin of infection to women (Spongberg 1997). It may also be due to gendered economic realities: many women were simply unable to afford the fees. Those that could not—as with the proportionately

smaller amount of men that were unable to muster enough for the fees—had to apply, in person, for outside assistance for their fees, either to administrators and clergymen within their parish, or to the city governor. Perhaps unsurprisingly, many more women received parish than gubernatorial support. Presumably this process also had a similarly discouraging effect on those seeking care (Siena 2004). Of those that persevered however, many women were instead sent to parish workhouses rather than supported for a stay at a hospital. Both McGough (2005) and Siena attribute this to greater stigma associated with infected women than men and thus less sympathy as to their 'moral worth' from administrators. Workhouses provided medical care to many poor urban women in the 18th and 19th century, but at great personal cost and as a last resort for both genders (Boulton 2000; Siena 2004). By the end of the 17th century, shifting gender ideologies and an increased emphasis on policing working class women's sexuality fostered the opening of the Lock Asylum, catering especially to poor urban young women. But, faced with its harsh, moralistic regime, a great many still avoided entry or left early in the course of treatment (Merians 1996b; Spongberg 1997; Williams 1996). Thus, while upper status women and men may have experienced low dose therapy, or given the impoverishing effects of the disease, high doses later in life, poorer men and women could have received high doses or low dose therapy for a short term. A significant segment of the population, particularly women, may have had no access at all (Siena 2004).

Mercury and Human Tissue

Mercury (Hg) can be accumulated in human bone, though the mechanism remains unclear. The Hg^{2+} ion may substitute for Ca^{2+} in the bone carbonate or hydroxyapatite (Geneser 2004). Alternatively, it is possible that other species of mercury, e.g. $Hg(CH_3)_2$, might be embedded in the organic component in the bone. Unlike other heavy metals like lead, wherein 90 to 95% of lead stored in the body is contained in the skeleton (Smith and Hursh 1977), concentrations of mercury are lower in bone than in soft tissues. Garcia et al. (2001), for example, reported autopsy findings of levels lower than 0.05 ppm in bone but 0.25 and 0.14 ppm in the kidney and liver, respectively. These levels are far too low, according to Rasmussen et al. (2008), for any feasible mapping technique to reveal even the location of Hg in bone. Therefore, it is very difficult to assess whether bone diagenesis of Hg has occurred.

Diagenetic Exposure

Diagenesis is a critical consideration in trace element analyses of excavated skeletal material (Hedges 2002). Trace element concentrations can be affected by chemical changes occurring after death due to leaching from soil, groundwater, and/ or exposure to biotic activity; elements may be mobilized from the bone and soft tissue and diffuse into the soil or invade bone from the soil. Trace elements become associated with bones by forming complexes with the organic components, by being absorbed onto the surface of the hydroxyapatite, or by being incorporated into the hydroxyapatite matrix (Elliott and Grime 1993). As such, several methods have been used to estimate degrees of diagenesis in excavated bone (see Lee-Thorp and Sealy 2008). For example, Hedges and

Millard (1995) used the porosity of bones as a measure of the dissolution of hydroxyapatite crystals. Nelson and Sauer (1984) analyzed soil samples in close association to skeletal material to eliminate the possibility of the migration of elements from bone to soil. Yamada et al. (1995) and Rasmussen et al. (2008) both estimated mobilization of elements to bone through analysis of *in situ* soil samples, the latter employing those from several layers of adjacent strata near several individuals in their study. However, the degree of diagenesis for mercury remains unknown and potentially very slight in various contexts. Yamada et al. found that Hg levels graves associated with Hg bearing skeletons were largely below detection limits; when detectable, there was no correlation between soil and bone concentrations. Likewise, Rasmussen et al. found variability in the relationships between Hg levels in soil and associated bone but no evidence of systematic transport of Hg from the soil into the bone and vice versa. Soil samples were not uniformly collected for all nor skeletal individuals during excavation but when available for both pathological and control skeletons, were evaluated to assess evidence of systematic diagenesis (see Methods in Chapter Two).

Mercury is available both atmospherically and geologically on a global level. It is an extremely rare element in the earth's crust, having an average crystal abundance by mass of only 0.08 ppm (Ehrlich and Newman 2008), generally <10 ng/g in non-mercuriferous crustal minerals, such as granites, feldspars, and clays, and 50 to 200 ng/g in non-mercuriferous crustal soils and sediments in background areas not directly impacted by anthropogenic discharges or volcanic emissions. Concentrations in both increase with proximity to modern urban areas. These levels may be due to global transport and deposition of anthropogenic mercury over the past three hundred years.

They are estimated to represent a three to five fold increase over the presumed preindustrial background levels (Davis et al. 1997). Significant anthropogenic mercury concentrations can also predate industrialization; for example, contamination of groundwater from heavy metals has been documented in several regions in England dating to the 13th century. Geochemical analysis of alluvial deposits associated with rivers in Yorkshire demonstrate contamination from the early medieval period onwards and that industrial run off upstream of the city caused contamination for a considerable distance (Hudson-Edwards and Macklin 1999).

Atmospheric rates, which would be associated with both diagenetic and endogenous exposure, have varied significantly over time from both anthropogenic and volcanic causes (Ehrlich and Newman 2008; Krabbenhoft and Schuster 2002). Pre-industrial ice cores unaffected by volcanic activity from North America, Greenland, and Antarctica have Hg concentrations ranging from 1 to 4 ng/L. Atmospheric deposition increased significantly with industrialization. Based on modern industrial sources of atmospheric mercury (Pacyna et al. 2006), in early industrial England in the 18th and 19th centuries, it would also have been generated by coal burning and non-ferrous metal production, such as smelting, mercury production, and pig iron production.

While atmospheric deposition is presumably uniform across the cemetery sites under consideration here, geological concentrations and anthropogenic activity are not and could, through diagenetic transfer into skeletal materials, be responsible for variation in Hg levels found in the analyzed bone. To assess whether diagenetic transfer might generate error within the results, soil samples recovered in direct proximity to several of the skeletons were analyzed with XRF to assess evidence of any systematic diagenetic

transfer.

Mercury in Post-Medieval and Early Modern England

Endogenous exposure to mercury is also an important consideration in this study. In addition to treatments for venereal disease, and in the medieval period, leprosy, mercury was used in a variety of contexts and likely found its way into the body of most contemporary humans. Mercury was most infamously used in felt hat making, but was incorporated into a variety of other industries, such as developing daguerreotypes, silvering mirrors, and gilding (Homer 1991). Calomel was added to sugar confectionaries and chocolate as an adulterant, which became more widely available in the 19th century (Wohl 1983). It was also administered as a diuretic and topical disinfectant as well as in pill or syrup form (Blue Mass) in the mid to late 19th century to treat conditions ranging from depression to childbirth and toothaches (Goldwater 1972). Production of mercury for all of these applications would also have involved crushing and washing ore, smelting, tempering, soldering, cleaning flues and other processes (Campbell 1991). As such, numerous individuals—those receiving treatments, preparing and administering treatments, consuming mercury, and those involved in craft and industry—could have been exposed to unusually high levels of mercury. However, diseases such as syphilis and leprosy are the only ones of these conditions that we have osteological evidence for; very few diseases leave lesions upon the skeleton (Ortner 2003). Consequently, individuals in the sample group were excluded if they displayed evidence of co-infection with another infectious diseases (except for tuberculosis, which is not known to have

been treated with mercury). Those in the control were excluded if they displayed signs of any infectious condition but all other sources of dietary, occupational, and therapeutic exposure cannot be excluded (see Discussion).

X-Ray Florescence

This study is one of only a few analyses to measure mercury levels in archaeologically derived human bone and the first do so using XRF. While XRF is fast becoming an established technique for non-destructive trace element analysis of inorganic an organic artifacts, its use is still novel for use on human skeletal remains. Other analyses of Hg content have employed atomic absorption spectrophotometry (AAS) and inductively coupled plasma mass spectrometry (ICP-MS). These analytical techniques have lower detection limits for trace elements (<0.5–600 ng/g) than does XRF, which has a detection limit in the range of ≥1 ppm. This potentially makes them more suitable for trace element analyses in some contexts (Wobrauschek et al. 2002).

However, XRF is uniquely well suited to investigations of mercury treatment for syphilis. Concentrations below the detection limit have been found in studies of modern dry bone, ranging from .02 to .5 ppm (Emsley 2001; Garcia et al. 2001; Lindh et al. 1980). However, all published analyses of Hg in archaeologically derived bone have reported significantly higher levels, from 1.5 and 2 ppm to 8.2 ± 3.3 ppm, even in populations with no known occupational exposure (Tucker 2007; Yamada et al. 1995). The two other published studies of mercury treatments for syphilis in archaeological dry bone in the early modern era, Tucker's (2007) analysis of mercury levels in ten syphilitic

skeletons from London, all of which are included here, and Rasmussen et al.'s (2008) of eleven from Denmark, also found levels within the detection limits of XRF. Using ICP-MS, Tucker found concentrations ranging between 1.38 and 17.24 ppm. Using AAS, Rasmussen et al. (2008) found levels between .017 and 3.12 ppm, with an average of .506 to .793 ppm, perhaps indicating systematic lower dosages in Denmark than contemporary England.

The low sensitivity and specificity of skeletal involvement from syphilis also necessitates a large sample size, which is best accommodated by XRF. While syphilis is one of only a few infectious diseases to leave distinctive lesions on the skeleton (Roberts and Manchester 1999), it does so infrequently, in as few as 1.5% to 20% of cases, with a commonly cited average of 10% (Resnick and Niwayama 1995: 2496). Additionally, generally low life expectancies in post-medieval urban England (Wrigley and Schofield 1981) may have prevented many infected individuals from expressing these lesions, as they can take several years to decades to manifest on the skeleton (see Fournier 1899; Singh and Romanowski 1999). Given a very high prevalence of syphilis in urban England in the 17th to 19th centuries (Anselment 1989; Siena 2004), many individuals may have been infected and manifested soft tissue symptoms that required treatment, but have no skeletal evidence of the disease. In combination with variable levels of background endogenous exposure to mercury from a variety of sources, the result is that any given individual in a skeletal sample could exhibit high concentration of mercury without bearing skeletal pathologies. Analyses that employ a small sample size run the risk of inadvertently incorporating individuals with anomalously levels of mercury and thus generating a skewed background level of mercury exposure. For example, perhaps due to

issues of cost or conservative policies for destructive sampling, Tucker (2007) used only two skeletons taken from a Roman era site in Cambridge as a control for ten skeletons derived from sites in London. Rasmussen et al. (2008) employed seventeen control skeletons as a control for fifteen pathological skeletons from the same site, with one syphilitic skeleton from another site lacking any control data. XRF can be used to circumvent this issue, because unlike AAS and ICP-MS, it is non-destructive, time efficient, and inexpensive, allowing an exponentially larger control sample to be analyzed. In this study, to accommodate concerns over accurate assessments of endogenous background exposure to mercury, a control sample approximately three times the size of the pathological sample was employed. This estimate can also act as basic information pertinent to discussion of present day mercury pollution (Rasmussen et al. 2008).

Methods and Materials

Reconstructing social identity: Gender and socioeconomic status

Socioeconomic status for the skeletons analyzed in this study was not assigned by the author. Instead, designations of socioeconomic status for cemetery sites, individuals, and their original communities, were derived from the designations adopted made by the historians, excavators and archaeologists, and osteologists who initially examined the samples. These designations were found in published and unpublished write-ups and assessments of the skeletal material (Brickley et al. 1999; Cowie et al. 2008; Miles et al. 2008; Miles and White 2008). These researchers used the clearest indicators of status for

early modern English burials evident from the archaeological record: coffin hardware and burial location (Litten 1998). This was supplemented by information on the status of the overall living community, derived from various historical materials (e.g., tax records, parish records).

Status estimations from coffin hardware have a variable degree of accuracy due to variation in preservation conditions. At many sites poor preservation eliminated some to nearly all evidence of the original coffin hardware, such as the Redcross Way/ Cross Bones site (e.g., Brickley et al. 1999). Estimates of status are also complicated by an increasing degree of social mobility during the early modern period, meaning that the status indicated archaeologically may be unrelated to that held in life (Miles 1992). This is a critical issue given the impoverishing effect of the pox and a particularly gendered one, as women were uniformly more economically unstable than men and events like widowhood and abandonment were often intractably economically disastrous (Mendelson and Crawford 1998).

The categories used are those standard in early modern English social history and bioarchaeology. Importantly, they do not represent the full spectrum of social strata present in contemporary society, only the social strata recovered from cemeteries that have yielded cases of syphilis, and only those that can be estimated using archaeological evidence—in other words, very broad categories. These were translated into a scoring system devised by the author to allow statistical analysis (see Table 6).

In an attempt to control for any status-based differences in endogenous exposure to mercury, control individuals were also selected whose funerary artifacts (e.g., coffin presence, shape, type, hardware, and decoration) most closely matched those of the

associated pathological (syphilitic) skeleton. This information was derived from unpublished archaeological site maps, site reports, skeletal reports, and osteological recording forms (context sheets).

Gender is notoriously more difficult to assign to skeletal material than socioeconomic status (Gilchrist 1999; Sørenson 2000). It has yet to be, along with other aspects of feminist theorizing, incorporated into bioarchaeological analyses in any substantial—or theoretically correct—manner (Geller 2008; Lamphere 2006; Stockett and Geller 2006). Much of this is due to the fact that gender is premised on performance, perception, and behavior, which is largely inscrutable in skeletal material. Archaeological theorists differ on the relationship between sex and gender (Gilchrist 1999; Sørenson 2000), with some viewing them as discrete and others as inseparable (Sofaer 2006). This study adopts the latter position, wherein both are viewed as dynamic, contingent, and culturally constructed (Gilchrist 1999; Gosden 1999; Joyce 2000; Meskell 1998; 2001; Voss 2000), though sex is, by necessity also understood to be archaeologically determinable via skeletal morphology (Sørenson 2000; Walker 1995; Walrath et al. 2004). Complexly, gender incorporates multivalent, intersecting aspects of social identity in living individuals, but very few indicators of these are detectable in archaeological and skeletal evidence. Gender is most commonly estimated through evidence of material culture accompanying burials (Gowland 2006). However, these are rare in early modern English burials and were not recovered with any of the skeletons included in this study; associated coffins seem to be gender neutral. Sex based differences in metabolic diseases and activity markers have also been used to tease out evidence of gendered behavior,

dietary adequacy, and disease exposure in English skeletal samples (Mays 1999; Sullivan 2004), but these are unrelated to the research question at hand.

Instead, here, a combination of historical context and skeletal evidence is used to assess evidence of gender (see Grauer 2003). As literature on the treatment of syphilis in early modern London suggests that gendered ideologies of sexual honor and gendered economic realities may have had systematic effects on access to treatment, skeletal evidence here is assessed for physical, embodied evidence of these schemas. With caution, interpretation of evidence consistent with or diverging from these may be viewed as evidence of the performance of gender (see Perry and Joyce 2001; Sofaer Derevenski 2000) or here, gendered differences in access to treatments for syphilis. To allow this approach, biological sex (i.e., male, female, indeterminate) is viewed as related to but not reductively based on gender (i.e., man, woman). 'Mollies' and other third gender individuals in England (Kaplan 2005; Trumbauch 1998) are understood to be potentially present in the samples but, given the absence of supporting archaeological or textual evidence, skeletally unidentifiable.

Sample Treatment and Selection

See Chapter Two for discussion of the criteria employed for selection of the pathological and control samples.

Skeletal Data Collection

See Chapter Two for pathological sample data collection and control sample data collection.

XRF

XRF sampling of skeletal material was conducted to detect concentrations of mercury in the pathological and control samples as well as in the soil samples using a Bruker Tracer III-V/III-SD handheld XRF® analyzer. Teeth are arguably better indicators of individual exposure to heavy metals (Martin et al. 2007), but due to their formation during the sub-adult period, they would not preserve biochemical evidence of treatment for a disease that manifests during adulthood. Because some debate exists over potential heterogeneity in the distribution of heavy metals in the skeleton and within skeletal elements, several elements and locations upon each were systematically analyzed. Published research has only addressed the distribution of lead (Gross et al. 1975; Schroder and Tipton 1968); a survey of the published literature suggests that the distribution of mercury throughout the skeleton and within individual skeletal elements has not been examined. Rasmussen et al. (2008) suggest that this is due to the extremely low concentration of mercury within the skeleton, precluding such studies. Studies of lead have shown age-dependent differences in the uptake of Pb between trabecular and cortical bone, with it being preferentially deposited in trabecular bone until the end of growth in the second decade, after which it is primarily stored in cortical bone (Wittmers et al. 1988). This difference is also reflected in slight differences in concentrations found

in metaphyseal *vs*. diaphyseal bone (Brotter et al. 1985; Drasch 1982; Gross et al. 1975; Strehlow and Kneip 1969). Significant differences in distribution, however, have not been found along long bone diaphyses, nor for lateral or vertical asymmetry. In this study, only cortical bone was sampled. Given bone remodeling rates, this represents averaged mercury concentrations for the last decade or so leading up to death (Manolagas 2000). Following Rasmussen et al. (2008), femorae were systematically sampled (left, preferentially) as well as ribs (1st left, preferentially) when available, following Tucker (2007). Five standardized flat locations were sampled on the femur and, as the density of cortical bone is much more evenly distributed on the rib, one on each (see Table 29).

Prior to sampling, the surface of the bone was gently abraded and cleaned with distilled water to limit surface contamination. When available, soil samples were also analyzed. These were collected during excavation from close proximity to their associated elements but their metric proximity was not recorded at this time (see Table 29). Readings were taken for 300 seconds for each soil sample and at each location on each element to maximize sensitivity. Emission values presented below in Table 29 and Figures 7 & 8 do not represent absolute ppm concentrations of Hg. Instead they represent quantified, comparative proportions of Hg at each given location. Future XRF analysis of controlled portions of Hg within samples of demineralized, powdered, modern human bone will be used to generate quantitative emissions values for comparative purposes and enable translation of the current results into ppm concentrations.

Analysis

Emissions for each soil sample and location on each element were calculated using Bruker ARTAX 7® software. Means and standard deviations were calculated for femur Hg emissions using Microsoft Excel® 2007. Statistical analyses were run using SPSS 17.0®. Parametric Pearson's chi-square (χ^2) test and non-parametric Spearman's rho was run to assess variation between mean femoral emissions and rib emissions at NLB to test $\mathbf{H_4b}$. A one-sample t-test was also run to assess variation between mean femoral emissions and mean rib emissions to test $\mathbf{H_4b}$. Kruskal-Wallis tests were also run to test $\mathbf{H_4c}$ and $\mathbf{H_4d}$, assessing any significant variation in both mean and non-mean aggregate femoral Hg emissions and aggregate rib emissions according to status or sex for both the aggregate pathological and control samples. Likewise, following an assessment of normality, a one-way ANOVA was run to assess $\mathbf{H_4d}$ and variation by sex in the two sites, NLB and FAO, with more than five pathological individuals. An artificial bivariate threshold intended to distinguish evidence of therapeutic treatment from background Hg values was not employed because of the possibility of great variation in endogenous mercury exposure in the control sample from a variety of sources.

Results

Variation in aggregate (non-mean) femoral Hg emissions (Hg L1) between the aggregate pathological and control samples for all sites was highly significant (p=.009;

p<.01). Likewise, mean femoral Hg emissions (mean L1) varied significantly between the pathological and control samples at all sites (p=.026; p<.05). In contrast, rib Hg values did not demonstrate a similar relationship. Mean femoral values (376.155, standard deviation of 303.35) were statistically different than mean rib values (254. 75, standard deviation of 101.79) (p=.026). Assessments of the relationship between mean femoral emissions and sex and status between the aggregate pathological and control samples for all sites found no significance. In the aggregate pathological sample for all sites (control excluded) there was also an insignificant relationship between mean emissions and status and sex. Analyses of diagenesis found no significant relationship between mean femoral Hg values and soil and sediment recovered directly adjacent to the element nor between rib Hg values and soil recovered directly adjacent. For the sites with more than five pathological individuals, NLB and FAO, no significance was found between mean values and status at FAO or mean values and sex at NLB, but significant variation exists between sex and mean Hg values at FAO.

Discussion

The significant differences for both aggregate and mean Hg values between the non-pathological control samples and the pathological samples of syphilitic skeletons presents strong evidence for systematic treatment of syphilis with mercury in early modern London, corroborating and greatly expanding upon Tucker's (2007) findings. This also establishes the ability of XRF to detect trace concentrations of mercury within human bone, even with its higher sensitivity than the established techniques of AAS and ICP-MS. The absence of significant relationships between sex and socioeconomic status

and Hg values for the aggregate control and pathological samples further substantiates this conclusion. This greatly reduces the possibility that these differences are attributable to gendered differences in chronic occupational exposure to mercury or to occupational exposure within certain social strata, such as lower and working class participants in industry or craft.

Differential bone growth and remodeling rates between femorae and ribs may explain the absence of a significant relationship between syphilis and rib Hg emissions. They may also greatly complicate assessments of mercury treatment for syphilis using only ribs, as performed by Tucker (2007). In ribs, bone growth formation is accelerated during growth but slows during adulthood, with osteon creation probably increasing only with metabolic or mechanical necessity. In contrast, bone growth in the femur extends into adulthood and is prolonged by lifelong biomechanical stress (Martin and Burr 1989). Especially if mercury, like lead (Wittmers et al. 1988), is preferentially distributed in cortical rather than trabecular bone following the cessation of development, femoral values may present a more accurate portrayal of adult exposure than ribs. Because syphilis is sexually transmitted it is most commonly acquired and symptomatic during adulthood. Thus rib Hg values may primarily represent mercury exposure prior to the onset of treatments for syphilis or for recurrent infection whereas femoral values represent element exposure after the second decade of life. Given the duplicate sampling of individuals from Tucker's data set in thus study, future quantification of the results will be used to test this assertion. The finding of a great degree of intra-element heterogeneity in mercury distribution, as indicated by the large standard deviations for mean femoral values (see Figure 7), may also complicate assessments of mercury

treatments which sample from only one location on the femur, (i.e., Rasmussen et al. 2008). This may be attributable to localized variation in remodeling rates due to localized biomechanical stress (Martin and Burr 1989). These results also contradict Rasmussen et al.'s assertion that Hg levels within bone are too small for any feasible mapping technique to reveal even the location of the element in bone. Results from this study suggest that these previous assessments, by testing only one skeletal element or location on an element, may have systematically under- or over-estimated Hg levels attributable to mercury treatments. Future analyses would be encouraged to adopt a multiple element and location sampling strategy.

In contrast, the absence of significant variation between mean femoral Hg values and rib values and associated adjacent soil samples suggests that there is no evidence for systematic diagenesis between human bone and mercury in soil, groundwater, or biotic activity (see Figure 8). These negative results are congruent with those found by Yamada et al. (1995) and Rasmussen et al. (2008). Further analysis will address any non-significant but related variation between these substrates to assess whether soil values may represent Hg concentrations in soft tissue from the associated corpse, as was speculated by Rasmussen et al.

As mentioned in the introduction, integration of historical, skeletal, and in this case, biochemical evidence enables the historical material to be interrogated for biases, non-conformities, and incompleteness against more direct lines of evidence. Working from this premise, the absence of sex and socioeconomic status-based differences in Hg values in both elements for the majority of sites is surprising given clear indications in the historical literature of differential preferences for mercury treatments as well as

differential access and opportunities for treatment between social strata and genders. There is little related work in bioarchaeology to compare this to; this is the first study to assess status and sex related differences in mercury concentrations from pre-modern treatment of syphilis. Rasmussen et al. (2008) did not consider the sex or status of syphilitic individuals in a late medieval Danish sample. Tucker's (2007) study only examined poor and lower status individuals. Siena and others' findings strongly suggest that higher and upper middling status individuals were able to avoid high level treatments while lower status individuals may have had no other options. Given this divergence, it is very possible that this result may be an analytical artifact generated by the methods employed in this study. As indicated above, the designations of socioeconomic status employed here are extremely rough. They are potentially problematic both in their scope—too many categories may have been employed here, effectively swamping any potential status-based variation—or they may be insufficiently representative of actual lived status. The categories were generated using archeological evidence, derived from artifacts associated with individual burials and the site as whole—and evidence, largely documentary, on the communities that the cemeteries served (see Brickley et al. 1999). However, due to poor preservation conditions at many of these sites, artifacts, such as coffins, grave goods, or clothing, were not found in association with the skeletons—both control and syphilitic—included in this study. Likewise, many of the communities—and as such, their cemeteries—which contributed skeletons to this sample were very heterogeneous in terms of socioeconomic status. This means that the status category imposed upon a skeletal sample here—such as 'poor' for the New London Bridge sample—does not necessarily accurately reflect the status of its individual constituents. In

addition, due to high degrees of both social and geographical mobility during the period, which in regards to the latter was more often downwards than upwards—especially for women—the status inferred after death is no guarantee of the status of status enjoyed by the living. This may have had a particularly direct effect on the results found here, due to the documented impoverishing effect of syphilis. The expense of low mercury or alternative treatments often meant that low status individuals could not afford them for a lengthy period of time, presumably resorting to high dose public treatments if their infection worsened or persisted. Though the period in which they could afford to avoid high dose treatments may have been longer for higher status and middling individuals, the cost of treating a chronic condition—or, for all social strata, the economic cost of having a stigmatized one—may also mean that they eventually resorted to high dose treatments. Consequently, it is very possible that syphilitic individual's socioeconomic status, and thus access to mercury, may have varied greatly during the course of their adulthood or even just a few years. As such, this phenomenon could result in the overall similarities in mercury values for all social strata detected here. It could also result in femoral than rib Hg emissions, as higher dose therapy was more likely received during adulthood than the developmental or young adulthood period. Unfortunately, direct evidence for this dynamic cannot be captured by analysis of bone, which reveals trace element profiles that represent an average of exposure over approximately the past ten years (Manolagas 2000).

Historical evidence also strongly suggests that a significant proportion of women, particularly impoverished individuals, may have had no access to mercury treatments at all. The results here instead demonstrate significant exposure to mercury among a

majority of female skeletons with evidence of syphilis. This in turn indicates that many women may have had access to treatment with mercury. Tucker (2007) also noted a similar though more circumscribed finding, that two female skeletons from NLB demonstrated very high concentrations of Hg. She argued that this contradicted Siena's assertion that poor women may have had a harder time accessing mercury treatments due to the low number of hospital beds provided for female patients. However, as these two were derived from a hospital cemetery, this finding does not bear much weight. Nonetheless, the disparity of the results found here from the expected schema suggested by the historical literature could also be interpreted as skeletal evidence of agential behavior on the part of women in the past. While not necessarily evidence of transgression against gender roles (Perry and Joyce 2001), as there is no evidence of gender-based prohibitions on treatment in the past, it does suggest that women may, on average, have had more access to treatment than the literature suggests. Women may have achieved this through the private marketplace, from which treatment records are patchily available or through venues such as workhouse hospitals, which also lack complete documentation.

Intriguingly, only syphilitic skeletons from FAO demonstrated clear sex-based differences in mean levels of Hg (female: 207.6/ male: 324.89). The significant difference in Hg emission values found at FAO, which archaeological and historical evidence suggests was a burial ground for generally low status individuals does not have clear interpretive significance. It may confirm the expectations generated by the historical literature that lower status males had more access to lower status females, through avenues such as private care for those with extra income, or hospitals and parish relief,

both of which were primarily accessed by men during the period (Siena 2004). If so, it may also represent the embodiment of gendered ideologies on syphilis and its treatment. Popular discourse, medical texts, and religious tracts from the 18th and 19th centuries clearly indicate an atmosphere of intensifying moralizing on the sexuality of lower class women (Walkowitz 1980). The 19th century witnessed the birth of various ideological, medical, and legal attempts at policing the behavior and sexuality of lower class and poor women. These women were accused of endangering the moral and physical health of the state through sexual promiscuity, infection with venereal diseases, and participation in prostitution (Acton [1870] 1972; Siena 1998; Spongberg 1997), or the 'social disease', which existed at extremely high levels throughout Victorian England. These sentiments culminated in the Contagious Disease Acts of 1864. This law, which was expanded upon throughout the 1860s, allowed police officers in many regions to arrest prostitutes and women suspected of prostitution, subject them to compulsory medical examination, and, if they were found to be infected, to incarceration and compulsory treatment in Lock hospitals (Walkowitz 1980). However, Siena's findings suggest that they may have been just as commonly denied treatment, especially in the earlier decades. Such practices would have been based on lay and medical beliefs that lower class women would have acquired the disease through promiscuity and lascivious behavior and that they were the primary transmitters of the disease (Spongberg 1999; Siena 1998), thus deserving of approbation rather than sympathy and treatment. As mentioned above, scholars have suspected evidence of gender-based biases and treatment (Quétel 1990; Spongberg 1997), but direct evidence for the phenomenon has yet to be found.

That levels of mercury were systematically present throughout the control sample suggests widespread endogenous exposure to mercury among early modern Londoners. This may be attributable to occupational exposure, or, particularly in the 19th century, consumption of adulterated foods and therapeutic treatment for a variety of conditions. Several control individuals, such as REW 89 sk 92 and those from the Saint Bride's Crypt (see Table 29 & Figure 7), have strikingly high values, which may indicate focused occupational exposure or, though it is not determinable, therapeutic treatment for condition not expressing on the skeleton. More likely is that it is primarily due to a more ubiquitous source of mercury, such as anthropogenic atmospheric and environmental deposition from industrialization, which would have steadily increased after 1800 in London and other urban centers. Assessment of whether this was a sufficient source for the background levels detected here awaits quantification of the Hg emissions. Further analysis will also address variation in these concentrations on an individual and site-specific level. Control sample concentrations will also be compared to those found by Rasmussen et al. (2008) in their non-syphilitic and non-leprous control samples from early and late medieval Denmark. They found average concentrations of 34 ± 15 ng/g in the early medieval sample and 53 ±30 ng/g in the late. While this increase is not significant, it does bear further investigation (Rasmussen et al. 2008). Consequently, further analysis will assess any temporal shifts in concentrations to detect any relationship between industrial contamination, anthropogenic mercury production, and concentrations in the control sample. As this would constitute the first large scale assessment of mercury exposure in a pre-modern, industrializing population, results would be pertinent to discussion of temporal trends in mercury pollution.

Significance

The results of these analyses suggest that syphilis was systematically treated with mercury in early modern London. This is at least true for individuals of a variety of social strata from multiple cemetery sites from throughout London who bear skeletal evidence of syphilis. Results also suggest a consistent level of background, endogenous exposure to mercury among early modern Londoners, at least as represented in the included samples. Future research may fruitfully explore the underlying source of this seemingly ubiquitous exposure as well as assess the extent and underlying cause of the significant heterogeneity revealed here in the distribution of mercury throughout the skeleton.

Chapter Seven: Conclusion

This study presents and ecological, evolutionary, and social history of acquired syphilis in early modern England. Analyses within this study have examined skeletal evidence for the evolutionary trajectory of the disease during the first decades after its emergence; for the effects of overall health on the pathophysiology of infection and its late stage manifestations; the mediating effects of biological sex on the stages and manifestations of the infection; and for direct evidence of differential access to mercury treatments.

Chapter Three evaluated whether skeletal evidence supported syphilis undergoing an evolution of virulence in the first few decades of its emergence in the Old World. In turn, it evaluated whether it might have done so in response to selection for milder symptoms or whether alterations in virulence reflect broad social changes in host nutrition and immunity. Preliminary results of the analysis of a smaller-than-desired skeletal sample show no alterations in the manifestations or duration of the disease consistent with the changes reported in the historical literature. Instead, the only significant relationships between skeletal lesions and time show increases in the frequency of facial destruction. This suggests that the most popular hypothesis for the underlying selective pressure for an evolution of virulence in syphilis, that *T. pallidum* was influenced by selective pressures to cause symptoms less evident to potential sexual partners, is false. Future work on this subject—pending access to additional individuals from the St. Mary Spital site—will reevaluate this research question in a larger skeletal

sample. Re-analysis of a larger skeletal sample is expected to produce more clear-cut results, regardless of whether they are negative or positive.

Chapter Four assessed direct evidence for the mediating effects of biological sex on expression of the stages and manifestations of syphilis. This was evaluated in an archaeologically derived skeletal sample and within a data set composed of data gleaned from three clinical studies and autopsy series of untreated syphilis dating to the 19th and 20th centuries. Prior to this, these data sets had not been analyzed comparatively nor to assess whether the different frequencies of various lesions and disease stages found among male and female cases were statistically significant. Results showed that skeletal evidence shows little evidence of sex based differences and that clinical and autopsy data demonstrates opposing sex-based differences, suggesting strong methodological and diagnostic differences between the studies. The effects of age and reproductive status could not be assessed in the clinical and autopsy data. However, skeletal evidence demonstrated a strong relationship between skeletal age, specifically late adulthood vs. early adulthood, and the presence and number of gummata. This suggests that the effects of senescence on the immune system may play an as yet unknown and undocumented role in the formation of gummata. Intriguingly, results of this analysis contradicted the consensus among 19th and 20th century physicians and syphilologists that the expression of syphilis was markedly different between the sexes. For example, neurological involvement, which was uniformly pronounced as being more severe in women than men by physicians, was found to be more frequent in men. These findings suggest that more investigation of the effects of sex on the pathophysiology of syphilis may be warranted.

Chapter Five examined associations between overall health, the pathogenesis of tertiary stage syphilis, and manifestations of tertiary disease, specifically the presence of gummata. This analysis was intended to investigate the implications of the osteological paradox, specifically differential susceptibility to disease or heterogeneity of frailty, in relation to syphilis, as this dynamic has yet to be assessed in the published literature. Results suggest that individuals with LEH and periodontitis are more likely to manifest tertiary syphilis, though the same association does not exist with dental caries, or between these indicators and evidence of gummata in the skeletal sample. These findings implicate inflammatory processes, potentially directly due to periostitis or to life long elevated exposure to infectious disease, but equally point to the destructive effects of life long stressors on immune responses. Either interpretation supports the conclusion that individuals with reduced overall health are also more susceptible to syphilis, or at least to the disease's progression to tertiary stage disease. This finding suggests that potential associations between these indicators and other systemic chronic diseases should be explored in the archaeological record.

Chapter Six investigated direct evidence for differences in access to mercury treatments related to gender and socioeconomic status suggested by historical literature via trace element analysis using XRF. Results clearly show systematically elevated levels of Hg in the pathological skeletal sample *vs*. a control sample of skeletons from the same sites. This reaffirms findings of other researchers that evidence of therapeutic treatment with syphilis can be detected in the archaeological record. It also demonstrates that XRF is a suitable technique for doing so. Results also suggest that XRF could be fruitfully employed to conduct other trace element analyses in human skeletal material. They also

suggest an unexpectedly high degree of heterogeneity in the distribution of mercury throughout the skeleton and suggest that sampling strategies employed by future researchers must take this into consideration. Results also revealed higher levels of mercury in skeletal material sexed as female than was expected based on historical literature suggesting that women may have had systematically less access to mercury treatments, at least those among the lower socioeconomic strata. Though this is tenuous, the latter findings could be read as evidence of undocumented, more equitable access to mercury by men and women. Alternatively, they could be interpreted as evidence of agential behavior on the part of women in seeking treatment for their infection. Immediately future work will quantify these results (ppm) in order to compare them to other published analyses (i.e., Rasmussen et al. 2008; Tucker 2007) of mercury treatments of syphilis in human skeletal remains.

In addition to these analyses, the data set accumulated for the purpose of this study will be utilized for future investigations of the manifestations of syphilis. As indicated in Chapter Two, more data was collected than was employed in the above analyses. Accordingly, several future studies are planned. For example, the distribution of skeletal lesions over the skeleton in syphilis has not been analyzed nor reported on since Fournier (1899). Assessment of the frequency and type of lesions manifesting within different regions and tissues within the body may illuminate some of still imperfectly understood processes underlying lesion formation. Results would build upon those of Buckley and Dias (2002) for yaws. As indicated in Chapters Five and Six, the efficacy of mercury treatments on the pathophysiology of syphilis persist as a source of speculation (Tucker 2007; Ortner 2003). The only assessment of this potential association, Tucker

(2007), found no evidence that high levels of mercury exacerbated the severity of the syphilitic manifestations nor heightened mortality. However, this study employed a very small sample size of impoverished individuals for whom infection severity may have been related to other ecological factors. Future work will assess covariance between mercury levels and indicators of morbidity and mortality associated with syphilis. Positive results would make mercury one of history's oldest known iatrogenic drugs and potentially confirm Goldwater's (1972) speculation that "the use of mercury in the treatment of syphilis may have been the most colossal hoax ever perpetrated in a profession which has never been free of hoaxes." Additionally, reanalysis of the material from Gjestland's (1955) study of untreated syphilis is planned. Norway has an unrivalled body of public health data stretching into the 19th century. As Gjestland included a vast body of information on the occupation, medical history, diet, and residence patterns of Boeck's original sample, none of which was included in this study, future analysis will examine any potential relationships between the life history trajectories of these individuals and their recorded mortality and morbidity in search of other, yet undetected variables affecting the pathophysiology of syphilis.

Appendix: Tables and Figures

Figure 1 Map of all archaeological sites from which skeletons included in this study have been derived

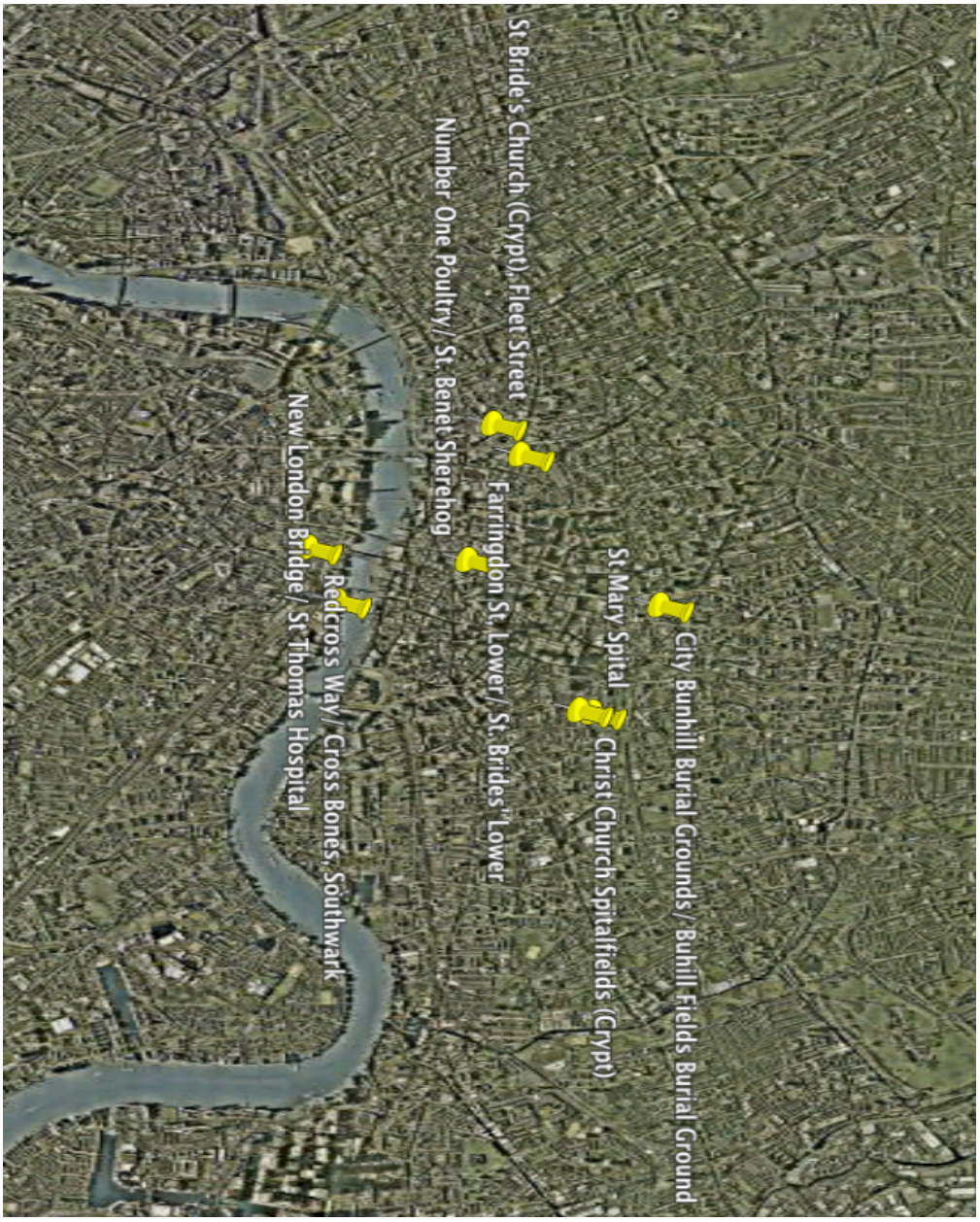

Figure 2 Map of the archaeological sites in London from which the sample has been derived

Archaeological Site	**Sample (N)** *recovered (analyzed)*	**Syphilitic sample (N)** **suggestive / specific*	**Site Date Range (AD)** *(dating method)*	**Individual****	**Individual Date Range (AD)**
Hull Magistrate's Court, Hull, Humberside	245(245)	4	1300-1450**	SK 1216	1425-1610 (*radiocarbon*)
				SK 932	1410-1475 (*radiocarbon*)
				SK 1121	1435-1625 (*radiocarbon*)
				SK 805	1300-1450 (*radiocarbon*)
Blackfriars Cemetery, Gloucester	140 (140)	1	1246-1538	SK 77	1442-1635 (*radiocarbon)*
Church of St. Margaret's incombusto, Norwich	436 (413)	4	11th c - 1468	SK 68	1453-1644 (*radiocarbon*)
				SK 129	1398-1519 (*radiocarbon*)
				SK 227	1399-1533 (*radiocarbon*)
				SK 305	1254-1468
St Helen-on-the-walls	1041 (1041)	1	1020-1549-50	SK 5556	1197-1419 (*radiocarbon*)
Ipswich Blackfriars Friary, Suffolk	250 (250)	1	1263-1538	SK 1965	1440-1620 (*radiocarbon*)
St. Mary and All Saints Church Rivenhall, Essex	229 (229)	1	9th -19th c.	SK 204	1295-1445 (*radiocarbon*)
Newcastle Infirmary, Newcastle upon Tyne	407 (407)	3	1753 - 1845	-	1753 -1845
St. Benet Sherehog, London	274 (231)	1	c. 1666-1853	-	c. 1666 -1853
Lower St. Bride's/ Farringdon Street, London	606 (544)	8	1770-1849	-	1770 -1849

St Bride's, Fleet Street	200 (200)	1	1770-1854	-	1770-1854
Chelsea Old Church, London	290 (198)	1	1712-1842	-	1712-1842
New London Bridge/ St. Thomas Hospital, London	227 (193)	26	c. 1600-1700	-	1600 -1700
Cross Bones Cemetery, London	148 (148)	2	1800-1853	-	1800 -1853
City Bunhill Burial Ground, London	239 (239)	1	1833-1853	-	1833 -1853
Spitalfields Market Site, London	~10,000(~10,000)	1***		SF 131	1197-1537
Christ Church Spitalfields Crypt, London	983(983)	2	1729 - 1857	-	1729 -1857
				CAS 84 2186	1678-1729
Kingston-on-Thames, London	360 (360)	1	1	-	1664 -1814
St Marylebone Church, London	372 (302)	2	1767-1859	-	-
St James and Mary Magdalene, Chichester	374 (374)	1	12th – 18th c.	-	-
Barbican Leisure Center site, York	550 (550) (medieval)	1	c. 1091-1539	-	-

Table 1 The skeletal sample (all chapters)

[1] Published date for the individual.

**This date, the primary one published for the site, is in reference to burials other than those included in the analysis.
*** The remainder of individuals from this site reported to display evidence of syphilis are not yet available for study.
****Individual skeletal accession numbers are provided when these individuals have been assigned different (narrower) date ranges than the overall site.

Specimen	Location	Lab ID (Year)	Uncalibrated Date (YBP)	Collagen d13C (‰)	Nitrogen d15N (‰)	delta R (local deviations from the global average	Estimated % marine carbon in diet**	Radiocarbon Date Uncorrected for Marine Signature	Radiocarbon Date Corrected for marine component	Radiocarbon Date Corrected for marine component assuming +/-20%	Reference
Gloucester 77	Blackfriars, Gloucester, UK	OxA-4875 (1994)	385 ± 45	-22.8		-20±36	0.0	1438-1635	--	--	Ortner (2003) & Roberts (1994)
Hull 1216	Hull Magistrate's Court, Hull, Humberside, UK	OxA-9478 (2000)	549 ± 33	-18.5	13.4	-33±90	27.8	1310-1435	1408-1611	1313-1645	von Hunnius et al. (2006)
		OxA-12037 (2003)	425 ± 25	-18.1	NA	-33±90	32.2	1428-1611	1492-1657	1436-1806	Roberts (2009)
Norwich 68	Church of St. Margaret Fyebriggate,	OxA-4872 (1994)	355 ± 50	-21.6	NA	-33±90	0.0	1451-1641	--	--	
Norwich 129	Magdalen St, Norwich, UK	OxA-4871 (1994)	465 ± 50	-20.1	NA	-33±90	10.0	1321-1621	1411-1633	1315-1654	(Stirland 2009)
Norwich 227		OxA-4941 (1994)	435 ± 60	-19.9	NA	-33±90	12.2	1402-1635	1434-1640	1320-1795	
St. Helen-on-the-Walls 5556	Church of St. Helen-on-the-wall, York, UK	HAR-6887 (1986)	680 ± 80	-21.3	NA	NA	0.0	1197-1419	--	--	Mays (1998)
Whithorn cranium	Whithorn, Scotland, UK	OxA-4873 (1994)	350 ± 45	-22.5	NA	NA	0	1459-1644	--	--	Roberts (2009)
Hull 932	Hull Magistrate's Court site,	OxA-12073 (2003)	461 ± 23	-17.8	NA	-33±90	35.6	1410-1475	1478-1647	1421-1801	Roberts (2009)
Hull 1121	Hull, Humberside, UK	OxA-12034 (2003)	398 ± 27	-18.1	NA	-33±90	32.2	1435-1625	1497-1671	1442-1952	
Ipswich 1965	Ipswich Blackfriars Dominican Friary, Ipswich, UK	UB-3202	380 ± 18	-19.3	16.1	-20±36	18.9	1440-1620	1518-1647	1436-1803	Mays, Crane-Kramer, and Bayliss (2003)
Norwich 412	Church of St. Margaret Fyebriggate,	OxA-5123 (1994)	955 ± 31	-18.1	NA	-33±90	32.2	1088-1328	1052-1270	1025-1290	Stirland (2009)

Rivenhall 204	Magdalen St, Norwich, UK St. Mary and All Saints Church, Rivenhall, UK	To-8315	550 ± 60	-19.5	12.9	-33±90	16.7	1295-1445	1303-1618	1294-1630	Mays, Crane-Kramer, and Bayliss (2003)

Table 2 Radiocarbon dates of the putatively Pre-Columbian specimens analyzed for evidence of an evolution of virulence: unadjusted and adjusted for marine signature (Chapter Three)

Derived from Harper et al. (Accepted)
*delta R was calculated by averaging marine sampling sites in geographic proximity to the archeological site using the CHRONO Marine Reservoir Database (accessed through Oxcal). In cases where no sites were nearby, the average value of -33 plus/minus 90 yrs for UK coastal waters was used (Barrett et al. 2000)
**Calculated using linear mixing model (Phillips and Gregg 2001) of d13 Ccollagen with terrestrial dietary endpoint of -21% and a marine dietary endpoint of -12%

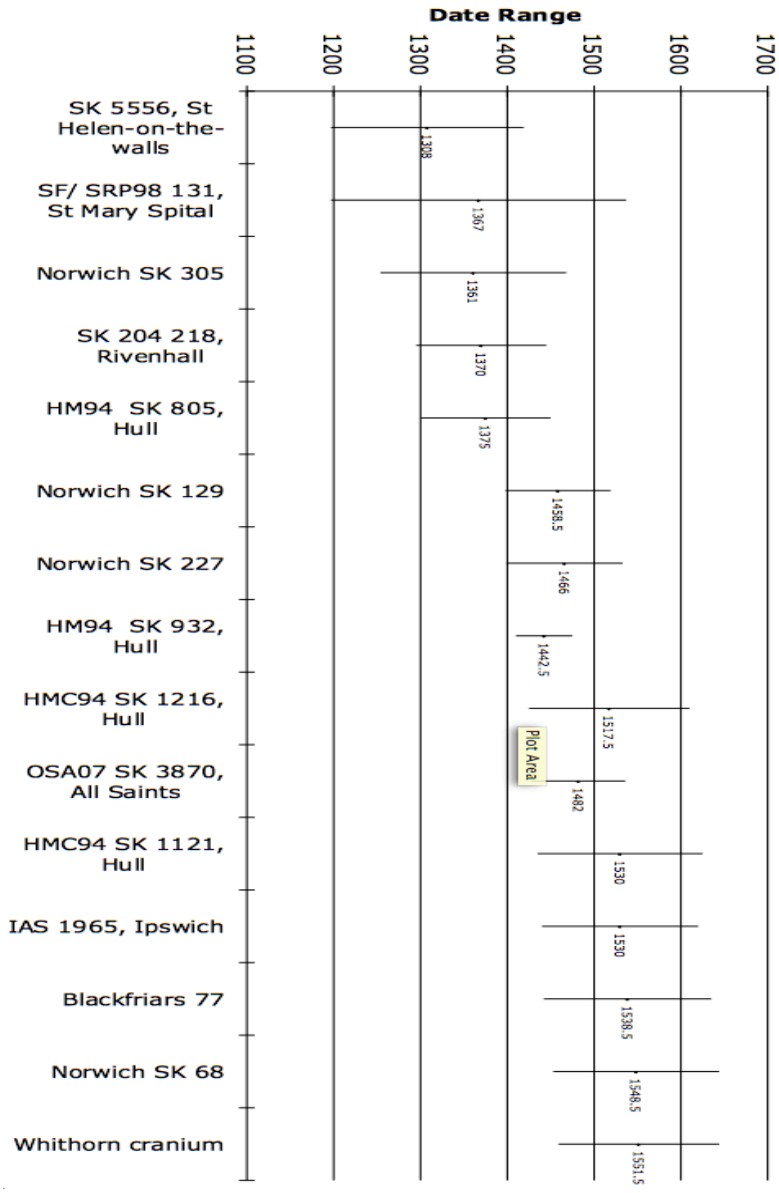

Figure 3 Published date ranges (and mean dates) for individuals in the skeletal sample used to assess evidence for an evolution of virulence (Chapter Three)

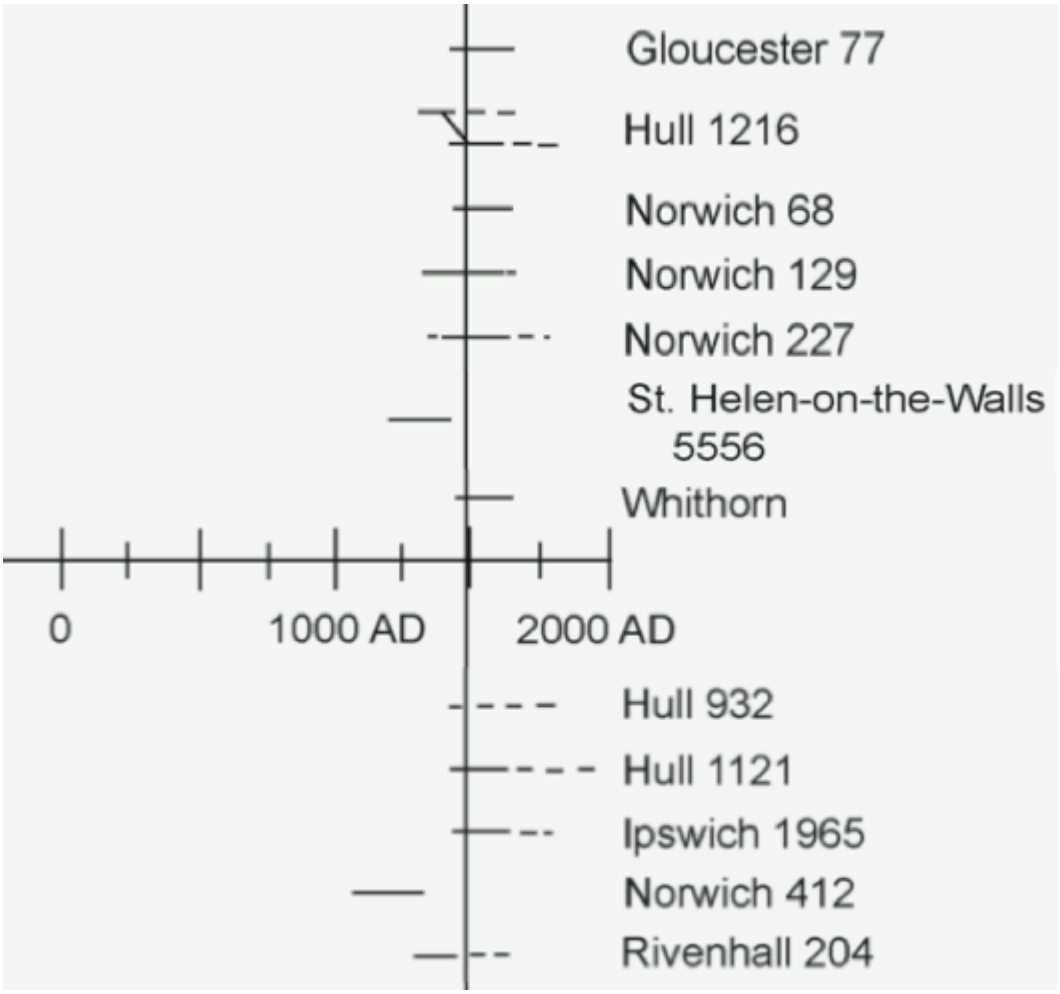

Figure 4 Date ranges for individuals in the skeletal sample assessed for evidence of an evolution of virulence (Chapter Three)

Study name	**Turner's Clinical Sample**	**Yale Autopsy Series**	**Oslo Study of Untreated Syphilis**
Study type	Retrospective and prospective	Autopsy	Oslo Study of Untreated Syphilis
Study Population	Patients at the Syphilis Division of the Medical Clinic of the Johns Hopkins Hospital	Cadavers dissected at the medical school	Patients admitted to the hospital with primary or secondary syphilis
Location	Johns Hopkins Hospital, Baltimore, MD, USA	Yale University School of Medicine, New Haven, CT, USA	University Hospital of Oslo, Norway
Study period	1916 - 1928	1917 -1941	1891-1910; Follow up on original cases: 1925- 1927
Total cases (N) of syphilis	10,000	380	1,978
Sex breakdown	Males: 5017/ Females: 4983	Males: 118/ Females: 38	Males: 446/ Females: 958
Method of diagnosis	Antemortem (clinical or serological (positive Wasserman))	Antemortem (clinical or serological)/ Additional postmortem diagnosis performed on a subset of these cases	Clinical
Treatment	Type not recorded but unknown proportion of patients in sample treated (presumably arsenical injections, heavy metal treatments, trypsaramide, and hyperpyrexia)	arsenical injections, heavy metal treatments, trypsaramide, and hyperpyrexia given to a small, unrecorded subset of the cases	Potassium iodide treatments given to 40% of patients; mercury to 3.6%
Data Recorded	Gross lesions	Gross lesions; histological changes	Cardiovascular, neurological, and cutaneous lesions; Wasserman reactions*
Source	Turner (1930)	Rosahn and Black-Schaffer (Black-Schaffer and Rosahn 1943; Rosahn 1946; 1943a; Rosahn and Black-Schaffer 1943b)	Gjestland (1955) and Clark and Danbolt (1964)

Table 3 The clinical and autopsy sample (Chapter Four)

*Performed twice: original sample and on a smaller subset of the 'still living sample'
**Performed once. Medical records examined for the deceased sample by Bruusgaard.

Description	**Age Range**	**Code**	**Bivariate Code** (see Chapter Five)
Adolescent	12-17	6	-
Young adult	18-25 yrs	7	0
Early middle adult	26-35 yrs	8	
Later/ middle adult	36-45 yrs	9	
Mature adult	≥ 46 yrs	10	1
Adult	> 18 yrs	11	0

Table 4 Osteological data collection: Adult age groups

Description	**Code**	**Bivariate code**
Male	1	1
Male?	2	1
Intermediate	3	-
Female?	4	0
Female	5	0

Table 5 Osteological data collection: Sex groups

Socioeconomic status category		Description	Archaeological evidence	Code
Poor		'Paupers', street walking prostitutes, workhouse & prison populations	shroud burials, wooden coffins	1
Poor to lower status		Membership in either strata equally possible	Wooden coffins	2
Low status		Working class: servants, laborers	Wooden coffins	3
'Middling sort'	Lower	Lower 'middle-class'	Wooden coffins in vault burials	4
	Upper	Upper 'middle-class'	Wooden coffins in vault burials, decorated coffins in churchyard burials and churchyard overflow cemeteries	5
Higher status		'affluent' to elite	Decorated coffins within vault burials, lead coffins	6

Table 6 Socioeconomic status categories represented in the skeletal sample

Skeletal element group	Skeletal element	Recorded by side (R/L)		Skeletal element	Recorded by side (R/L)	Element division
Face	Zygomatics	X		Femorae	X	Proximal; Middle (shaft); Distal[10]
	Nasals	X		Tibiae	X	
	Maxilla	X		Fibulae	X	
Mandible		X		Innominates	X	Ilium; Ischium; Pubis
Skull	Frontal	X		Humerii	X	Proximal; Middle (shaft); Distal
	Parietal	X		Radii	X	
	Occipital	X		Ulnae	X	
Bones of hands and feet	Carpals/ tarsals	X		Scapulae	X	Glenoid fossa; Coracoid process; Acromion; Infraspinous portion of the blade
	Metacarpals/ metatarsals	X		Clavicles	X	Sternal third; Middle third; Acromial third
	Phalanges	X		Sternum	-	Body; Manubrium; Xiphoid process
Ribs		X	Not side-able	Vertebrae	X	Cervical; remainder (thoracic & lumbar)
Patellae		X				

Table 7 Osteological data collection: Divisions of the skeleton for data collection and coding

[10] Divisions of the actual element, not reflecting metaphyseal, dipahseal, or epiphyseal divisions, following a modification of Power (2008).

Code	Description
1	Tooth present
2	Post-mortem loss (sharp socket; no healing)
3	Ante-mortem loss (full or partial healing of empty socket)
4	Congenital absence
5	Tooth present (no socket observable)
6	Tooth erupting
7	Deciduous retention
999	Area absent

Table 8 Osteological data collection: Dental catalogue

Tooth	Metric	Description
Canine	mesiodistal	maximum diameter of the crown relative to the tooth long axis
	buccolingual	
Molar (1st)	mesiodistal	between interproximal contact points
	buccolingual	taken perpendicular to the mesiodistal plane
Periodontitis		
Stages	999	Alveolus damaged or absent
	0 (normal)	0-2 mm
	1	2-3 mm
	2	3-5 mm
	3	>5 mm

Table 9 Osteological data collection: Dental metrics and periodontitis

Code	Location of caries	Code	Severity of caries
1	Occlusal	1	Enamel destruction only
2	Lingual	2	Destruction of dentine without exposure of pulp chamber
3	Buccal	3	Destruction of dentine with pulp chamber exposed
4	Mesial	4	Gross destruction (crown largely destroyed)
5	Distal		
6	Gross (site of origin no longer identifiable)		
7	Root surface		

Table 10 Osteological data collection: Caries

Code	Description	Recorded by side (R/L)
999	Orbital roof absent	X
0	Normal bone surface	
1	Capillary like impressions on the bone	
2	Scattered fine foramina	
3	Large and small isolated foramina	
4	Foramina have linked into a trabecular structure	
5	Outgrowth in trabecular form from the outer table surface	

Table 11 Osteological data collection: Cribra orbitalia

	Code	Variable	Description	
Presence	999	Element presence	Area absent or cortex absent (taphonomic damage)	
	0	Lesion presence	Area unaffected	
Lesion type	1	Periosteal reactions/ proliferation	Sub-periosteal deposition and proliferation	
	2	Lytic pitting	(gummatous or non-gummatous)	
Lesion type	**Variable**	**Description**	**Code**	**Status**
	Gangosa	Palatal perforation and rhinomaxillary destruction	1	Present
	Gondou	Periosteal reactions on the maxilla	1	Present
	Caries sicca	Gummatous focal destruction, ulcers, necrosis, pitting, and excessive sclerosis on the cranial vault	1	Present
	Osteitis	Inflammation of the interior of bone	0	Absent (on any element)
			1	Present (on any element)
	Gumma	Focal necrotizing lesions	#	Absolute number recorded

Table 12 Osteological data collection: Syphilitic pathology (All Chapters)

Data set	Stage of infection	Manifestations of syphilis
Skeletal data	Tertiary	Gummatous involvement of the cranium; presence of gummata on the skeleton & presence of more than one gumma on the skeleton
Yale Autopsy Series	Tertiary	Gross anatomical and histological evidence of central nervous involvement
Oslo Study of Untreated Syphilis	Secondary	Cutaneous lesions
	recurrent secondary	-
	tertiary	Bone lesions (gummatous or not is unspecified); cardiovascular involvement (aortitis, aortic insufficiency, angina, aneurysm, myocarditis, gummata); central nervous system involvement (general paresis, tabes dorsalis (with optic atrophy, charcot's joints) tabo-paresis; paraplegia; optic atrophy; eighth nerve involvment; epilepsy; vascular involvment
Turner's Clinical Sample	Secondary	Cutaneous lesions
	recurrent secondary	-
	tertiary	Bone lesions (gummatous or not is unspecified); cardiovascular involvement (aortitis, aortic insufficiency, angina, aneurysm, myocarditis, gummata); central nervous system involvement (general paresis, tabes dorsalis (with optic atrophy, charcot's joints) tabo-paresis; paraplegia; optic atrophy; eighth nerve involvement; epilepsy; vascular involvement

Table 13 Information on the manifestations, timing, and duration of syphilis recorded in the skeletal data set, clinical study sample, and autopsy series sample (All Chapters)

Initial Epidemic: Summary					
Infection stage		**Reported symptoms**			**Source**
Early		Incubation period varying from 10 to 90 days, followed by a chancre. At 40 to 60 days later, secondary infection characterized by generalized symptoms, including fever, headache, sore throat, skin lesions, swollen lymph nodes, and bone, limb, and joint pain.			(Tognotti 2009)
Late		Early infection often followed by death. When present, tertiary infection followed within approximately 1 year, involving soft, ulcerative tumors (gumma)			
Initial Epidemic: Regional descriptions					
Region	**First reported appearance of the epidemic in the region**	**Date of observed symptoms**	**Infection stage**	**Reported symptoms**	**Source**
Italy	c. July 1495	5 July 1495 (Battle of Fornovo, (post-siege of Naples)	**Early (primary & secondary)**	Painful 'pustules,' resembling grains of millet covering the body and genitalia; mild pruritis; chancre which transformed into a 'gnawing ulcer' (gumma)	(Gruner 1789; Leoniceno 1497) cited in (Quétel 1990)
		December 1496		Joint pain, malaise lasting for several months, followed by a latent period (c. 1 yr) and recurrent symptoms	(di Silvestro 1496-1498) cited in (Tognotti 2009)
		1495	**Later (latent & tertiary)**	Within days: bone pain and large chronic (>1 yr duration) 'pustules'	(Gruner 1789) cited in (Tognotti 2009)
		April 1498		Scabs; joint and bone pain; pain in the genitals; boils; diarrhea, and mouth ulcers	(di Silvestro 1496-1498)
		c. 1495-1497		Destruction of face, appendages and genitalia common	(Benedetti 1497b; Benedicti 1497; Muralti ND) & (Fracastoro 1546) cited in (Tognotti 2009)
		1495-1497	**Overall**	Destruction of the nose, eyes, hands and feet; bony tumors (gumma)	(Benedicti 1497) cited in (Quétel 1990)

		15th – 16th c.		Severe bone pains	(Montesauri 1498) cited in (Quétel 1990)
				Destruction of the nose or penis	(Muralti ND) cited in (Tognotti 2009)
		Pre-1512		Debilitating boils and pains	(Dalle Tuade 1513) cited in (Tognotti 2009)
		1495		High mortality	(Guicciardini, [1532] 1836) cited in (Tognotti 2009)
Spain	June 1495	18 June 1495		Joint pain; itching; fever; scabs; swellings; tubercles; sponge-like excrescences which result in scars; disease does not endure for more than a year[1]	(Scillacio 1495) cited in (Tognotti 2009)
Germany	1495	Pre-1519		Painful, foul-smelling black and green, acorn-like ulcers and boils; fevers; 'burning' joint and bone pain	(von Hutten [1519] 1945)
China	c. 1504/ 1512	1504/12		Marked dermotropism	See (Quétel 1990)
Japan	c. 1504/ 1512	1504/12		Multiple ulcers and pustules present	(Briot, 1985) cited in (Quétel 1990)
All regions	1494	(synthesis of existing, first hand reports)		Mouth disorders and bone pains ubiquitous	(Astruc 1738)

Recorded changes in the manifestations of syphilis: Regional descriptions

Region	**Date of reported shift in manifestations**	**Infection stage**	**Reported symptoms**	**Source**
Italy	c. 1526 - 1540	**Early**	'pustulae' less numerous, harder, drier, and less 'filthy,' and found in small number of cases; alopecia present; joint and bone pain reduced	(Fracastoro 1546) (Fracastoro 1530) cited in (Quétel

	1516-1526[2] c. 1530		Alopecia now common	(Massa 1558) cited in (Quétel 1990) (Cirillo dell' Aquila 1530) [2] (Astruc 1738)
			Less violent fever; rashes just a 'reddening'	(see Gamberini 1872; Tognotti 2009)
	c. 1526 - 1540	**Late**	gummas (previously uncommon) now very common	(Fracastoro 1546) cited in (Quétel 1990)
			Gummy tumors only present in limited number of cases	(see Gamberini 1872; Tognotti 2009)
			Destruction of face and appendages and genitalia uncommon	(Benedetti 1497a; Muralti ND) & (Fracastoro 1546) cited in (Quétel 1990)
			Milder symptoms; reduction in bone and joint pain; decrease in number of gummata	(Cirillo dell' Aquila 1530), (Gamberini 1872; Paré 1568) cited in (Quétel 1990)
	1505-1510		Often does not occur: death often follows primarily and secondary infection	
	Post-1510		Mortality reduced	
	c. 1530-32	**Overall**	Mortality reduced	(Guicciardini [1532] 1836) cited in (Quétel 1990)
France	Pre-1568	**Overall**	Mortality reduced	(Paré 1568) cited in (Quétel 1990)
	Pre-1579	**Early**	Severity of joint and bone pains unchanged	(Fernel 1579) cited in (Quétel 1990)
	c. 1512-1520	**Early**	Multiple ulcers; severe cutaneous lesions; 'sharp' osteocopic pains	(Quétel 1990)

All regions	1516 & 1550-1562	**Overall**	Alopecia and tinnitus develop	(Astruc 1738)

Table 14 Reported manifestations of syphilis in the 15th and 16th centuries

[1] Date of reporting makes this an unlikely observation

Code	**Description**
999	Area absent
0	Joint present, no involvement
1	Joint present, involvement (syphilitic arthritis or gummatous arthritis)
Joint coded for involvement	**Each side recorded (R/L)**
Sternoclavicular	X
Acromioclavicular	
Glenohumeral	
Humeroulnar	
Humeroradial	
Radioulnar	
Radio-ulnar-carpal	
Carpo-metacarpal	
Metacarpophalangeal	
Femoro-patellar	
Tibio-patellar	
Tibio-fibular superior	
Tibio-fibular inferior	
Tibio-talar	
Fibulo-calcaneal	
Tarsal	
Tarso-metatarsal	

Table 15 Osteological data collection: Joint involvement

Element	Landmark
Femur (Left, preferentially)	Head (anterior aspect)
	Anterior mid-shaft
	Popliteal surface
	Area inferior to inter-trochanteric line
	Area superior to patellar groove (superior to subchondral surface)
Rib (Left 1st, preferentially)	Groove for the subclavian artery

Table 16 Locations analyzed on each skeletal element for trace element analysis (Chapter Six)

Presence of gummata (by element) in association with mean date

Skeletal element category	Average number of gummata	Minimum number of gummata	Maxiumum number of gummata	Preservation: percentage of skeletal element absent (%)	Poisson regression: mean date on number of gummata by skeletal element category (p-value)	Mean date parameter estimate	Mean date parameter estimate (95% CI)	
femur	0.5333	0	3	25	0.06 (0.7991)	0.0007	-0.0049	0.0064
tibia	1	0	6	25	0.00 (0.9488)	0.0001	0.0041	0.0044
fibula	0.0667	0	1	25	0.00 (0.9468)	0.0005	0.0156	0.0166
humerus	0.5	0	4	30	0.01 (0.9369)	-0.0003	0.0066	0.0061
ulna	0.3333	0	5	25	0.02 (0.8814)	0.0005	-0.0067	0.0077
radius	0.2667	0	3	25	0.05 (0.8242)	0.0009	0.007	0.0088
Innomin-ates	0.1538	0	2	35	0.08 (0.7728)	0.0016	0.009	0.0122
scapula	0.3846	0	3	30	0.52 (0.4689)	0.002	-0.0034	0.0073
clavicle	0.1538	0	1	35	0.02 (0.8839)	-0.0009	0.0129	0.0111
ribs	0.3846	0	4	35	0.06 (0.8081)	0.0008	0.0059	0.0075
vertebr-ae	0	0	0	35	0.00 (1.0000)	0.0000	4.57*10^-8	4.5696*10^-8
sternum	0.3333	0	1	70	0.02 (0.8779)	0.0008	0.0092	0.0108
cranium	5.8667	0	12	25	0.17 (0.6840)	0.0006	-0.0024	0.0036
Presence of specific lesion types in association with mean date								
gangosa	2.6667	0	12	11:20	8.24 (0.0041)****			
gondou	1.4444	0	12	11:20	4.96 (0.0259)***			
element destruction	0.2451	0	10	20	0.0001 (0.9934)			
joint involvement (any joint)	0.3411	0	3	20	0.02 (0.8711)			

Table 17 Results: Analysis of skeletal evidence for the evolution of virulence (Chapter Three)

***Significant at the 0.05 significance level
****Significant at the 0.01 significance level

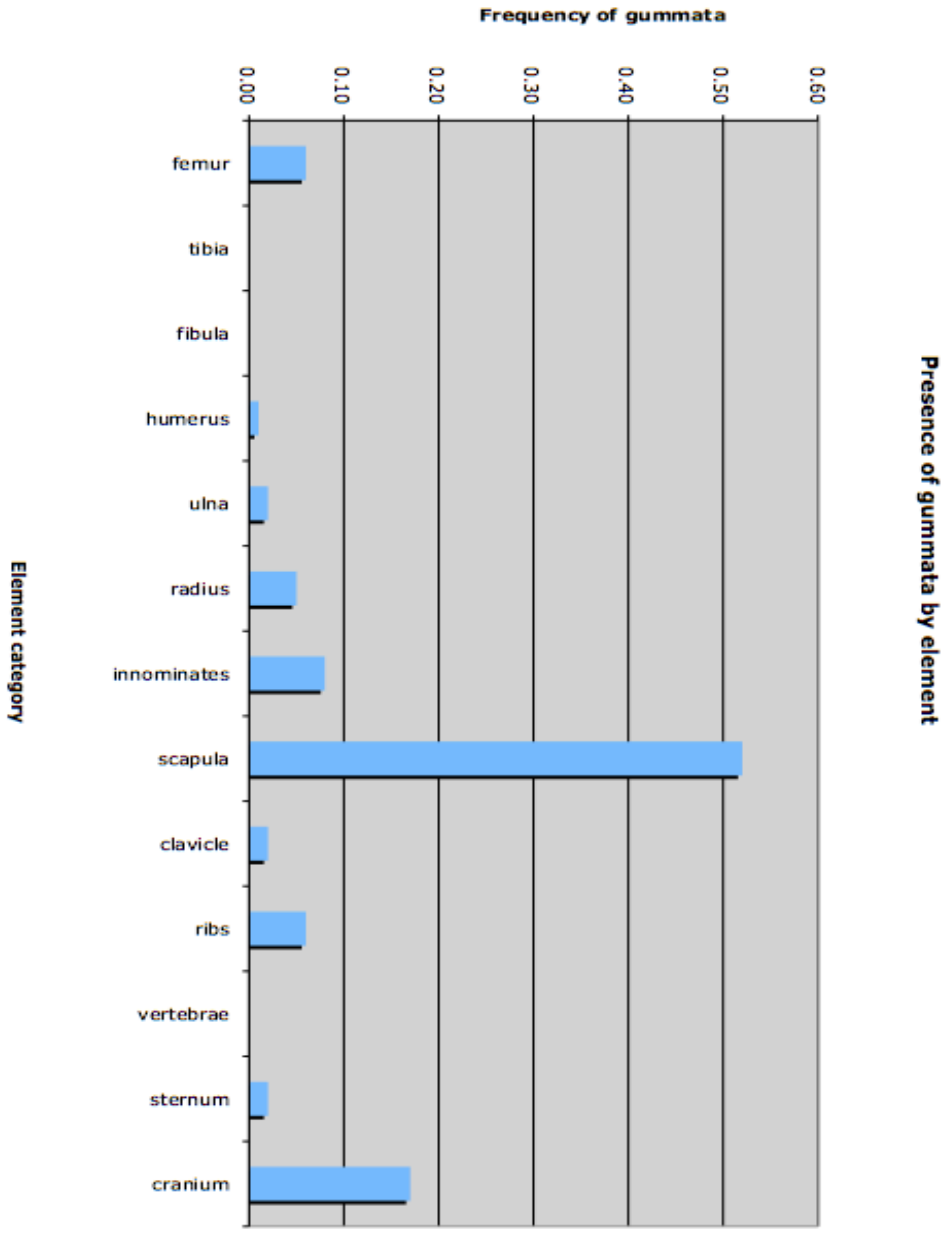

Figure 5 Results: Analysis of skeletal evidence for an evolution of virulence: frequency of gummata by skeletal element category over time (by mean date) (Chapter Three)

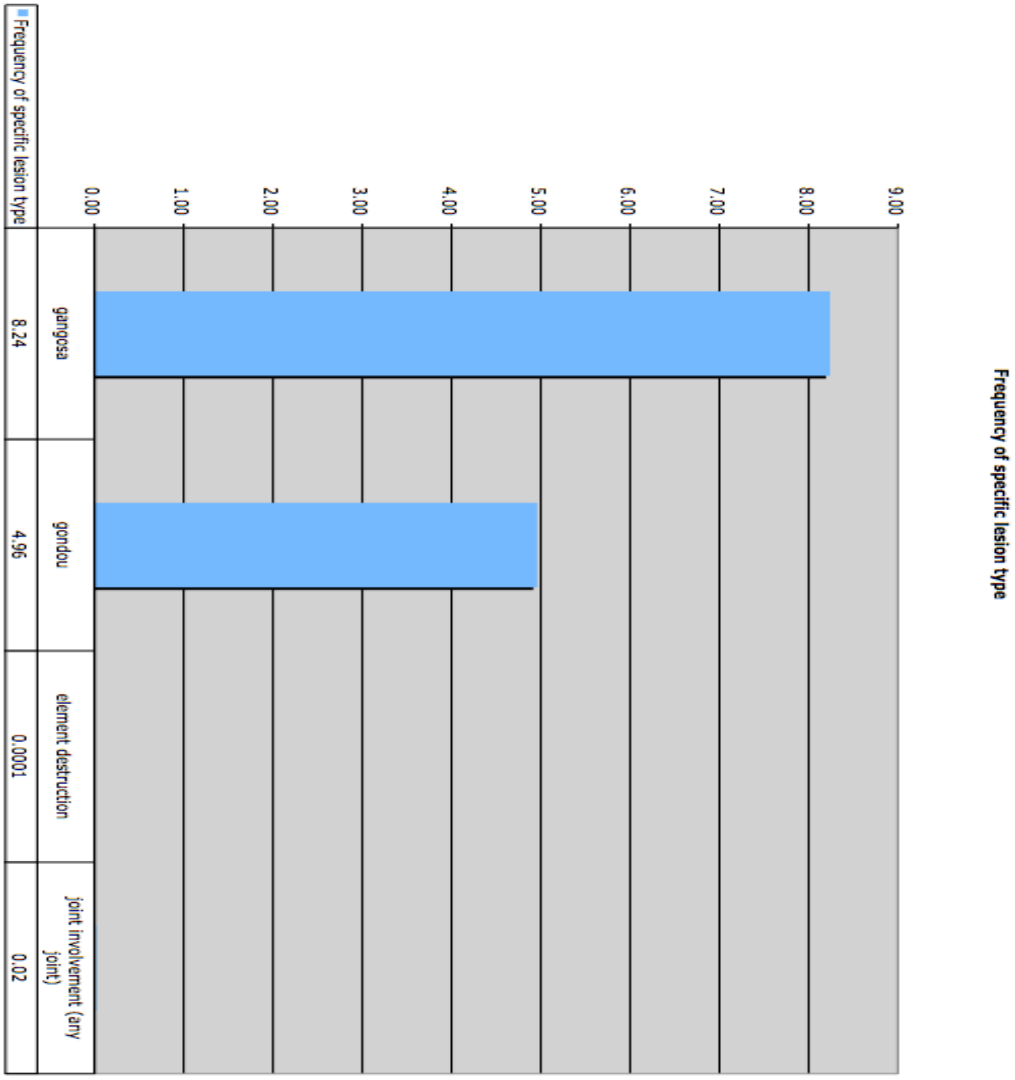

Figure 6: Results: Analysis of skeletal evidence for an evolution of virulence: frequency of specific lesion types over time (mean date) (Chapter Three)

Site	Context number	Skeletal element analyzed	Age	Sex	Status	Date (AD)	Pathology	Hg emissions	Average Hg (+/-)	Soil Hg
REW 92	118	L femur	36-45	F	poor	1800 - 1853	syphilis, multiple rib fractures and enthesopathies, lower thoracic trauma, septic arthropathy	539, 630, 374, 116, 248	381.4 +/- 209.1	
		L rib						111		
REW 92	120	L femur	>18	?	poor	1800 - 1853	NA	349, 1054, 485, 345	558.25 +/- 336.8	
		L rib						237		
REW 92	136	L femur	36-45	F	poor	1800 - 1853	NA	250, 932, 1431, 197, 162	594.4 +/- 565.1	
		L rib						276		
REW 92	101	L femur	>46	F	poor	1800 - 1853	NA	374, 271, 812, 294	437.75 +/- 253.4	
REW 92	99	L femur	18-25	F	poor	1800 - 1853	syphilis, residual rickets, CO	899, 932, 570, 231, 446	615.6 +/- 299.7	
		L rib						469		
REW 92	96	L femur	36-45	F?	poor	1800 - 1853	joint disease, enthesopath-ies	194, 233, 383, 264, 333	281.4 +/- 76.3	
REW 92	91	L femur	36-45	F?	poor	1800 - 1853	NA	1068, 722, 221, 165	544 +/- 429.8	
		L rib						94		
REW 92	89	L femur	>18	F	poor	1800 - 1853	NA	4249, 2981, 1459, 407, 200	1859.2+/- 1731.4	
FA0 90	1606	L femur	>46	M	low status	1770 - 1849	syphilis, congenital joint fusion (L foot)	386, 190, 269, 190, 132	233.4 +/- 98.2	
		L rib						133		
FA0 90	1635	L femur	>46	M	poor	1770 - 1849	OA on multiple joints	576, 243, 309, 326	363.5 +/- 156.1	
		L rib						561		
FA0 92	1637	L femur	>46	F	poor	1770 - 1849	erosive arthropathy with eburnation on multiple joints	389, 309, 275, 228, 265	293.2 +/- 60.8	
		L rib						193		

FA090	1687	L femur	>46	F	poor	1770 - 1849	erosive arthropathy, OA, CO	185, 381, 350, 278, 258	290.4 +/- 77.6
FA090	2274	L femur L rib	>46	M	low status	1770 - 1849	syphilis, rickets, CO, myostitis ossificans/ ossified haemotoma	341, 227, 467, 86, 92 170	242.6 +/- 163.9
FA090	2272	L femur	36-45	M	poor	1770 - 1849	CO	220. 363, 290, 331, 233	287.4 +/- 61.5
FA090	2300	L femur	36-45	F?	lower middling sort	1770 - 1849	NA	295, 169, 186, 333	245.75 +/- 80.6
FA090	2308	L femur	36-45	F	poor	1770 - 1849	healed R elbow fracture	171, 178, , 95, 112	145.2 +/- 38.7
FA090	2314	L femur L rib	36-45	M	poor	1770 - 1849	residual rickets	417, 295, 291, 157, 212 301	274.4 +/- 98.4
FA090	2332	L femur L rib	36-45	F	lower middling sort	1770 - 1849	CO, syphilis	152, 249, 231, 182, 224 180	207.6 +/- 39.6
FA090	1343	L femur					NA	312, 398, 633, 230, 307	376 +/- 155.5
FA090	1669	L femur	>46	M?	poor	1770 - 1849	OA with eburnation on multiple joints, erosive arthropathy	695, 434, 724, 338, 213	480.8 +/- 223.2
FA090	1932	L femur R rib	36-45	M	poor	1770 - 1849	syphilis possible yaws	417, 337, 241, 274, 134 387	280.6 +/- 105.9
FA090	1976	L femur	>46	M	poor	1770 - 1849	ankylosis and myostitis ossificans/ ossified haemotoma (L sacroiliac joint)	431, 684, 286, 285, 326	402.4 +/- 168.3
FA090	1727	L femur L rib	36-45	M	lower middling sort	1770 - 1849	syphilis, OA with eburnation on multiple joints	486, 344, 613, 324 320	441.75 +/- 135
FA090	1709	L femur	>46	F?	low status	1770 - 1849	Osteochondritis dissecans	391, 601, 323, 639, 306	452 +/- 157.2

		L rib				1770 - 1849		357	
FA090	1823	L femur	>18	?	lower middling sort	1770 - 1849	syphilis	298, 533, 378, 322, 407	387.6 +/- 92.1
FA090	1821	L femur	>46	M	poor	1770 - 1849	NA	421, 813, 191, 291, 141	371.4 +/1 269.1
		L rib				1770 - 1849		244	
FA090	1825	L femur	36-45	M	poor to lower status	1770 - 1849	OA with eburnation on multiple joints, fracture and atrophic non-union (L patella), gout, healed fracture (RMT 5 and LMT 2)	368, 333, 448, 333, 173	331 +/1 100
		L rib						143	
FA090	1055	L femur	26-35	M	low status	1770 - 1849	possible TB (ribs), syphilis, and CO	386, 337, 522, 361, 110	343.2 +/- 148.8
		L rib						495	
FA090	1061	L femur	36-45	M?	poor	1770 - 1849	NA	593, 476, 635, 636, 313	530.6 +/- 138.1
FA090	1563	L femur	36-45	M	poor to low status	1770 - 1849	possible TB (ribs), syphilis, myostitis ossificans/ ossified haemotoma, rib fracture, fracture (R 1st prox. Phalanx)	783, 519, 306, 253, 178	407.8 +/- 245.1
		L rib						279	
FA090	1617	L femur	18-25	M	poor	1770 - 1849	NA		
FA090	1693	L femur		M?	low status	1770 - 1849	CO	379, 897, 591, 415, 243	505 +/- 251.8
		L rib						262	
FA090	1649	L femur	36-45	F?	low status	1770 - 1849	NA	928, 850, 834, 418, 252	656.4 +/- 301.3

NLB 91	15	L femur	>46	M	poor	c. 1600 - 1700	syphilis, myostitis ossificans/ ossified haemotoma	181, 193, 201, 144, 159	175.6 +/- 23.7	
NLB 91	51	L femur	36-45	M	poor	c. 1600 - 1700	syphilis, localized trauma	393, 214, 240, 150	249.25 +/- 103	
NLB 91	66	L femur	26-35	F	poor	c. 1600 - 1700	syphilis, possible osteochond-ritis diseccans	262, 337, 284, 273, 370	305.2 +/- 46.3	
		L rib						165		
NLB 91	73	L rib	26-35	F	poor	c. 1600 - 1700	syphilis	149		151
NLB 91	79	L femur	26-35	M	poor	c. 1600 - 1700	syphilis, spondyloly-sis (C1), muscle microtrauma	500, 795, 171, 207, 315	397.6 +/- 256.4	1118
		L ribs						345		
NLB 91	83	L femur	36-45	M	poor	c. 1600 - 1700	syphilis, possible sinusitis, rheumatoid arthritis, gout, osteochond-ritis diseccans	215, 144, 214, 382, 123	215.6 +/- 101.7	124 (femur)
NLB 91	88	L femur	>18	?	poor	c. 1600 - 1700	syphilis	242, 175, 285	234 +/- 55.4	192 (femur)
NLB 91	166	L femur	>18	?	poor	c. 1600 - 1700	syphilis	330, 279, 116, 197	230.5 +/- 94	
NLB 91	181	L femur	26-35	?	poor	c. 1600 - 1700	syphilis	297, 460, 285, 193, 227	292.4 =/- 102.9	
NLB 91	192	L femur	36-45	?	poor	c. 1600 - 1700	syphilis	325, 279, 332, 290, 290	303.2 +/- 23.7	
NLB 91	194	L femur	26-35	M?	poor	c. 1600 - 1700	syphilis	392, 255	323.5+/- 96.9	
NLB 91	208	L femur	<18	?	poor	c. 1600 - 1700	syphilis	268, 351, 415, 227	315. 25 +/- 84.2	

NLB 91	218	L femur	18-25	M	poor	c. 1600 - 1700	syphilis, CO, cranial blunt force trauma	115, 115, 308, 239	194.25 +/- 95.7	
NLB 91	567	L femur	36-45	?	poor	c. 1600 - 1700	syphilis	382, 299, 413, 297	347.75 +/- 58.8	
		L rib						284		
NLB 91	108	L femur	>18	?	poor	c. 1600 - 1700	OA, myostitis ossificans/ ossified haemotoma	375, 299, 281, 442, 221	323.6 +/- 156	156
NLB 91	12	L femur	36-45	M?	poor	c. 1600 - 1700	NA	107		
NLB 91	19	L femur	>18	M	poor	c. 1600 - 1700	NA	327, 533, 284, 360	376 +/- 109.2	
NLB 91	145	L femur	>18	?	poor	c. 1600 - 1700	NA	300, 214, 350	288 +/- 68.8	
NLB 91	53	L femur	26-35	M	poor	c. 1600 - 1700	NA	260, 344, 270, 214	272 +/- 53.8	149
NLB 91	21	L femur	18-25	M	poor	c. 1600 - 1700	NA	476, 422, 309, 109, 247	312.6 +/- 145.3	
		L rib						354		
NLB 91	30	L femur	36-45	M?	poor	c. 1600 - 1700	NA	709, 285, 191, 360, 212	351.4 +/- 210.7	
NLB 91	41	L rib	>18	?	poor	c. 1600 - 1700	NA	140		
NLB 91	60	L femur	18-25	F	poor	c. 1600 - 1700	T12 malformation (non-metric variation)	439, 414, 485, 303, 362	400.6 +/- 70.3	
		L rib						282		
NLB 91	70	L rib	36-45	M	poor	c. 1600 - 1700	Hyoid L horn non-union	155		
NLB 91	82	L rib	18-25	?	poor	c. 1600 - 1700	NA	263	263	117

NLB 91	115	L femur	36-45	M	poor	c. 1600 - 1700	multiple osteophytes, small area of necrosis in L acetabulum	279, 361, 194, 234, 153	244.2 +/- 80.3	103
NLB 91	117	R femur	>18	?	poor	c. 1600 - 1700	healed trauma to R femoral head, congenital tarsal coalition	543, 479, 383, 307, 285	399.4 +/- 110.5	
NLB 91	178	L femur	>18	?	poor	c. 1600 - 1700	NA	575, 515, 324, 525	484.75 +/- 110.3	
NLB 91	186	R femur	>18	?	poor	c. 1600 - 1700	NA	372, 336, 213, 260	295.25 +/- 72	
NLB 91	254	L femur	>18	?	poor	c. 1600 - 1700	flattening of L tibia and femur (possible trauma or developmental deformity)	287, 363, 317, 297, 299	312.6 +/- 30.2	
NLB 91	67	L femur	36-45	F?	poor	c. 1600 - 1700	probable TB (spine; pott's fracture)	415, 271, 502, 270, 224	336.4 +/- 117.2	
NLB 91	74	L femur	>18	?	poor	c. 1600 - 1700	congenital deformity and osteophytes on R & L patellae, OA with eburnation on R elbow; compression fracture of T10	272, 281, 196, 210. 174	227 +/- 48	263
NLB 91	196	L femur	>18	?	poor	c. 1600 - 1700	healed possible fracture R femur	313, 499, 231, 273	329 +/- 118.2	
NLB 91	202	L femur	18-25	M	poor	c. 1600 - 1700	NA	391, 610, 329, 413, 193	387.2 +/- 151.2	
NLB 91	224	R femur	>18	F	poor	c. 1600 - 1700	Enthesophytes and subchondral cysts on multiple joints	214, 209, 209, 235, 188	211 +/- 16.7	

NLB 91	23	L femur	>46	F	poor	c. 1600 - 1700	NA	370, 262, 202, 199, 142	235 +/- 86.6	
NLB 91	30	L femur	36-45	M?	poor	c. 1600 - 1700	NA	709, 285, 191, 360, 212	351.4 +/- 210.7	
NLB 91	98	L rib	<12 -17	?	poor	c. 1600 - 1700	NA	100		133
NLB 91	99	L femur	>18	?	poor	c. 1600 - 1700	NA	434, 764, 432, 486	529 +/- 158.6	
NLB 91	109	L femur	26-35	M	poor	c. 1600 - 1700	NA	619, 348, 204, 143	328.5 +/-	211.9
		R rib						220		
NLB 91	112	L femur	18-25	F?	poor	c. 1600 - 1700	OA on multiple joints	350, 304, 297, 489, 408	369.1 +/- 80.1	
NLB 91	123	L femur	36-45	F	poor	c. 1600 - 1700	OA on multiple joints	251, 400, 145, 466, 178	288 +/- 139.8	
NLB 91	125	L femur	36-45	F	poor	c. 1600 - 1700	OA on multiple joints	405, 257, 249	303.6667 +/- 87.8	
NLB 91	126	L femur	>18	?	poor	c. 1600 - 1700	NA	441, 482, 363, 375	415.25 +/- 56.2	
NLB 91	128	L femur	26-35	M	poor	c. 1600 - 1700	OA on multiple joints	447, 489, 384, 279, 361	392 +/- 81	
NLB 91	129	L femur	>18	F?	poor	c. 1600 - 1700	OA on multiple joints	302, 523, 186, 253, 401	333 +/- 132	148
NLB 92	138	L femur	36-45	M	poor	c. 1600 - 1700	NA	118, 447, 372, 165, 308	282 +/- 138.4	
NLB 93	141	L femur	>46	M	poor	c. 1600 - 1700	OA on multiple joints	379, 428, 371, 316, 130	324.8 +/- 115.9	
		L rib						358		
NLB 94	142	L femur	18-25	M	poor	c. 1600 - 1700	OA on multiple joints	558, 360, 242, 332	373 +/- 133.2	

NLB 95	151	L femur	18-25	F	poor	c. 1600 - 1700	OA on multiple joints	421, 383, 414, 349, 138	341 +/- 117
NLB 96	160	L femur	18-25	?	poor	c. 1600 - 1700	NA	398, 305, 310, 394	351.75 +/- 51.2
		L rib						323	
NLB 97	165	L femur	>18	?	poor	c. 1600 - 1700	NA	658, 457, 349, 213	419.25 +/- 187.9
NLB 91	134	L femur	>18	?	poor	c. 1600 - 1700	OA on multiple joints	392, 346, 261	333 +/- 66.5
ONE 94	106	L femur	36-45	M	high	1666 - 1849	syphilis, arthropathy	399, 276, 555, 406, 248	376.8 +/- 122.3
		L rib						229	
ONE 94	459	L femur	>18	?	high	1666 - 1849	hallux valgus (L), OA	269, 336, 303, 317,	306.25 +/- 28.3
ONE 94	102	L femur	>18	?	high	1666 - 1849	enthesopathy	645, 207, 106, 227, 245	286 +/- 207.8
ONE 94	802	L femur	>46	F	high	1666 - 1849	pedal osteophyes and possible scoliosis	233, 184, 206, 181, 103	181.4 +/- 48.5
ONE 94	429	L femur	>18	M?	high	1666 - 1849	syphilis, os acromiale, possible TB	169, 152	160.5 +/- 12
		L rib						184	
ONE 94	523	L femur	>46	M	high	1666 - 1849	multiple enthesopath-ies, OA, spondylol-ysis (L5), sacroiliac ankylosis	476, 219, 189, 163, 261	261.6 +/- 125.3
ONE 94	433	L femur	>46	F	high	1666 - 1849	Enthesopathy OA, possible osteoporosis	327, 595, 369, 267, 166	344.8 +/- 159.3
ONE 94	875	R femur	>18	?	high	1666 - 1849	multiple enthesopath-ies, OA with eburnation	636, 533, 180, 197	386.5 +/- 232.6
OCU 00	392	L femur	18-25	F	high	1712 - 1842	syphilis, CO, possible PH	385, 285, 224, 265, 221	276 +/- 66.7
		L rib						253	
OCU 00	281	L femur	26-35	M	high	1712 - 1842	0	733, 782, 463, 394, 235	521.4 +/- 231.5

OCU 00	285	L femur	36-45	M	high	1712 - 1842	enthesopathy depressed cranial fracture (healed blunt force trauma)	600, 703, 808, 464, 215	558 +/- 230.1	
OCU 00	323	L femur	36-45	M	high	1712 - 1842	OA with eburnation on upper limbs, healed reduced fractures on R ulna and left foot	388, 388, 125, 123, 201	245 +/- 134.3	
SB crypt	56	L femur L rib	36-45	M	upper middling sort	1722 - 1755	syphilis	1231, 563, 175, 205 216	543.5 +/- 491.1	418
SB crypt	71	L femur	>46	M	upper middling sort	1755 - 1823	OA on L foot, DISH, isolated area of periosteal reaction	1116, 895, 180, 235	606.5 +/- 470	
SB crypt	89	L femur	>46	F	upper middling sort	1759 - 1826	DISH, healed L humerus fracture, minor lipping on R and L hands, enthesopathies and trauma and DISH-related long bone asymmetry	575, 1028, 417, 527	636.75 +/- 269.1	
SB crypt	120	L femur L rib	>46	F	upper middling sort	1800 - 1851	healed rib fracture, enthesopathies	733, 739, 255, 167, 191 134	417 +/- 293	
SB crypt	218	L femur	36-45	M	upper middling sort	1772 - 1828	syphilis	741, 365, 254, 447, 795	451.75 +/- 208.4	766
SB crypt	146	L femur	>46	F	upper middling sort	1781 - 1827	slight scoliosis, bilateral ankylosis of sacroiliac joint, enthesopathies	444, 472, 174		

SB crypt	150	L femur	>46	M	upper middling sort	1737 - 1793	bilateral lumbar spondylolysis, possible osteochondritis dissecans on L hand, enthesopathies	909, 574, 1425, 584, 592	816.8 +/- 368.1
		L rib						242	

Table 18 Site codes, individual numbers, sex, status, pathology, and mercury emissions (average emissions, emissions for each location analyzed on the femur, and for ribs) and soil sample mercury emissions (Chapter Six).

* Cells with gray as the background color indicate individuals diagnosed with syphilis.
* Cells without a gray background are control individuals.

Descriptive Statistics

	N	Range	Minimum	Maximum	Sum	Mean		Std. Deviation	Variance	Skewness		Kurtosis	
	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic	Statistic	Statistic	Std. Error	Statistic	Std. Error
Femur: Hg L1 (aggregate)	445	4163.0	86.0	4249.0	167389.0	376.155	14.3800	303.3474	92019.645	6.711	.116	71.842	.231
Femur: Mean L1	97	1714.0000	145.2000	1859.2000	36315.8000	374.389691	19.7360755	194.3778013	37782.730	4.897	.245	35.280	.485
Sex	103	4.0	1.0	5.0	288.0	2.796	.1557	1.5803	2.497	.177	.238	-1.449	.472
Status	103	5.0	1.0	6.0	215.0	2.087	.1778	1.8047	3.257	1.296	.238	-.005	.472
Rib Hg	36	467.0	94.0	561.0	9171.0	254.750	18.6316	111.7894	12496.879	.832	.393	.573	.768
Site	428	5.00	1.00	6.00	1243.00	2.9042	.04777	.98831	.977	.822	.118	1.309	.235
Valid N (listwise)	30												

Table 19 Descriptive statistics on the characteristics of the skeletal sample employed in Chapter Six: Hg emissions in relation to sex, status, and site

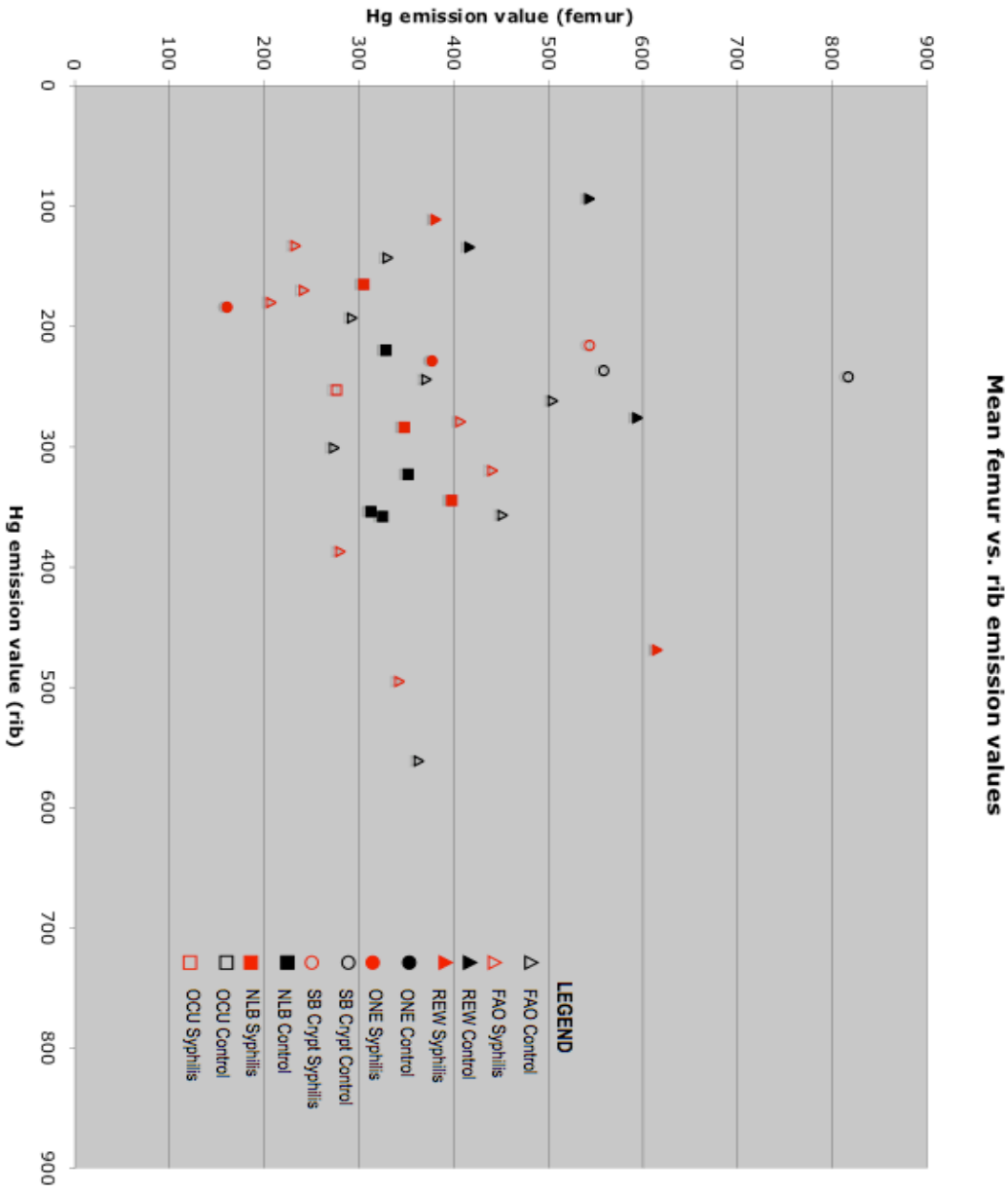

Figure 7 Results: Comparison of Hg emission values by element: femoral (mean) vs. rib for control and syphilitic individuals for each included skeletal sample/ archaeological site (Chapter Six)

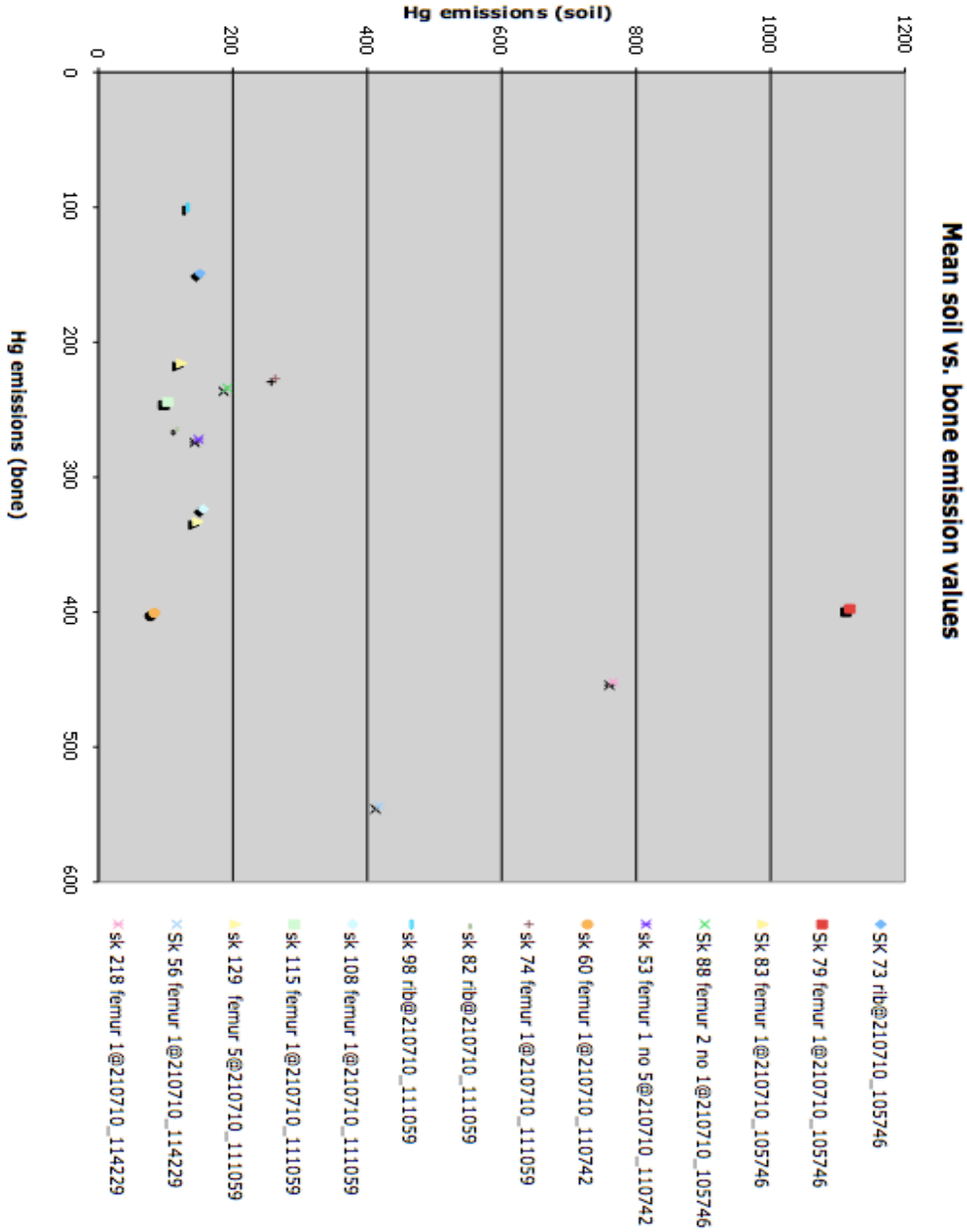

Figure 8 Results: Evaluation of evidence for diagenesis. Comparison of soil Hg emission values vs. femoral (mean) Hg emission values or rib Hg emission values

Results: "Raw Data"

Logistic regression				
Log likelihood:	-18.977288		*Number of observations*	28
			LR chi2(1)	0.86
			Prob > chi2	0.3533
			Pseudo R2	0.0222
gummaonskull	*Odds Ratio*	*Std. Err.*	*z*	*P>|z|*
agebiv	2.4	2.31862	0.91	0.365
			[95% Conf. Interval]	
			.3613037	15.94227

Table 20 Skeletal age (bivariate) in relation to the presence of gummata on the cranium, at all sites (Chapter Four)

Logistic regression				
Log likelihood:	-25.960721		*Number of observations*	42
			LR chi2(1)	5.92
			Prob > chi2	0.0150
			Pseudo R2	0.1024
anygumma	*Odds Ratio*	*Std. Err.*	*z*	*P>|z|*
agebiv	10.15385	11.52828	2.04	0.041
			[95% Conf. Interval]	
			1.097008	93.98347

Table 21 Skeletal age (bivariate) in relation to presence of any gummata on the skeleton, at all sites (Chapter Four)

Logistic regression				
Log likelihood:	-17.224885		*Number of observations*	42
			LR chi2(1)	13.85
			Prob > chi2	0.0002
			Pseudo R2	0.2868
Morethanonegumma	*Odds Ratio*	*Std. Err.*	*z*	*P>|z|*
agebiv	36	42.59286	3.03	0.002
			[95% Conf. Interval]	
			3.541735	365.9224

Table 22 Skeletal age (bivariate) in relation to the presence of more than one gummata on the entire skeleton, at all sites (Chapter Four)

Logistic regression				
Log likelihood:	-19.285698		*Number of observations*	28
			LR chi2(1)	0.24
			Prob > chi2	0.6207
			Pseudo R2	0.0063
gummaonskull	*Odds Ratio*	*Std. Err.*	*z*	*P>|z|*
sexbiv	.6111111	.6134214	-0.49	0.002
			[95% Conf. Interval]	
			.0854478	4.370586

Table 23 Skeletal sex (bivariate) in relation to the presence of gummata on the cranium, at all sites (Chapter Four)

Logistic regression				
Log likelihood:	-19.285698		*Number of observations*	39
			LR chi2(1)	0.42
			Prob > chi2	0.5193
			Pseudo R2	0.0077
anygumma	*Odds Ratio*	*Std. Err.*	*z*	*P>|z|*
sexbiv	.6117647	.4682085	-0.64	0.521
			[95% Conf. Interval]	
			.1364976	2.74185

Table 24 Skeletal sex (bivariate) in relation to presence of any gummata on the skeleton, at all sites (Chapter Four)

Logistic regression				
Log likelihood:	-23.126083		*Number of observations*	39
			LR chi2(1)	0.15
			Prob > chi2	0.7000
			Pseudo R2	0.0032
Morethanonegumma	*Odds Ratio*	*Std. Err.*	*z*	*P>|z|*
sexbiv	.7272727	.5954985	-0.39	0.697
			[95% Conf. Interval]	
			.146125	3.619678

Table 25 Skeletal sex (bivariate) in relation to the presence of more than one gummata on the entire skeleton, at all sites (Chapter Four)

Logistic regression						
Log likelihood:	-18.701548		*Number of observations*		28	
			LR chi2(1)		1.41	
			Prob > chi2		0.4933	
			Pseudo R2		0.0364	
gummaonskull	*Odds Ratio*	*Std. Err.*	*z*	*P>|z|*	*[95% Conf. Interval]*	
sexbiv	.4666667	.4841181	-0.73	0.463	.0610905	3.564839
agebiv	2.857143	2.84692	1.05	0.292	.4052993	20.14133

Table 26 Skeletal sex (bivariate) and skeletal age (bivariate) in relation to the presence of gummata on the cranium, at all sites, (Chapter Four)

Logistic regression						
Log likelihood:	-18.701548		*Number of observations*		39	
			LR chi2(1)		6.61	
			Prob > chi2		0.0367	
			Pseudo R2		0.1227	
anygumma	*Odds Ratio*	*Std. Err.*	*z*	*P>|z|*	*[95% Conf. Interval]*	
sexbiv	.4735253	.3842386	-0.92	0.357	.0965255	2.322974
agebiv	11.19547	12.92756	2.09	0.036	1.164523	107.6308

Table 27 Skeletal sex (bivariate) and skeletal age (bivariate) in relation to the presence of any gummata on the skeleton, at all sites (Chapter Four)

Logistic regression				
Log likelihood:	-19.285698		*Number of observations*	39
			LR chi2(1)	0.42
			Prob > chi2	0.5193
			Pseudo R2	0.0077
anygumma	*Odds Ratio*	*Std. Err.*	*z*	*P>|z|*
sexbiv	.6117647	.4682085	-0.64	0.521
			[95% Conf. Interval]	
			.1364976	2.74185

Table 28 Skeletal sex (bivariate) in relation to presence of any gummata on the skeleton, at all sites (Chapter Four)

For Results of 'sex assessed in relation to infection stage, lesion type, and organ system involvement in the clinical and autopsy samples (Chapter Four)', see 'Results" "Raw Data".

Logistic regression				
Log likelihood:	0.9834885		*Number of observations*	121
			LR chi2(1)	9.85
			Prob > chi2	0.0001
			Pseudo R2	0.2834
periodontitis	*Odds Ratio*	*Std. Err.*	*z*	*P>|z|*
pathbiv	32	42.59286	3.13	0.004
			[95% Conf. Interval]	
			2.534235	361.4561

Table 29 Presence of tertiary syphilis in relation to the presence of periodontitis, New London Bridge sample

Logistic regression				
Log likelihood:	0.9834885		*Number of observations*	106
			LR chi2(1)	3.51
			Prob > chi2	0.0011
			Pseudo R2	0.2994
LEH	*Odds Ratio*	*Std. Err.*	*z*	*P>|z|*
pathbiv	15	2.34286	2.29	0.03
			[95% Conf. Interval]	
			1.1456235	314.4143

Table 30 Presence of tertiary syphilis in relation to the presence of LEH, New London Bridge sample

Logistic regression						
Log likelihood:	-18.701548		*Number of observations*		119	
			LR chi2(1)		3.61	
			Prob > chi2		0.0317	
			Pseudo R2		0.0027	
Periodontitis	*Odds Ratio*	*Std. Err.*	*z*	*P>|z|*	*[95% Conf. Interval]*	
LEH	13	.2462386	1.20	0.021	.0976255	9.47574
Pathbiv	6	3.95756	1.36	0.011	1.179023	79.1408

Table 31 Presence of tertiary syphilis in relation to the presence of periodontitis and LEH, New London Bridge sample

Logistic regression				
Log likelihood:	19.1769083		*Number of observations*	98
			LR chi2(1)	3.22
			Prob > chi2	0.91860
			Pseudo R2	0.3002
dentalcaries	*Odds Ratio*	*Std. Err.*	*z*	*P>|z|*
pathbiv	.12222793	.5690985	-0.91	0.547
			[95% Conf. Interval]	
			.326125	5.119456

Table 32 Presence of tertiary syphilis in relation to dental caries, New London Bridge sample

Logistic regression				
Log likelihood:	-3.500083		*Number of observations*	25
			LR chi2(1)	0.58
			Prob > chi2	0.12349
			Pseudo R2	0.3002
LEH	*Odds Ratio*	*Std. Err.*	*z*	*P>|z|*
gummatabiv	.913578	.9564785	0.989	0.123
			[95% Conf. Interval]	
			0.987125	0.00008

Table 33 Presence of gummata in relation to LEH, among pathological (syphilitic) individuals, New London Bridge and Lower Farringdon St samples

Logistic regression				
Log likelihood:	-13.000018		*Number of observations*	20
			LR chi2(1)	0.45
			Prob > chi2	0.6791
			Pseudo R2	0.0174
caries	*Odds Ratio*	*Std. Err.*	*z*	*P>|z|*
gummatabiv	.2144649	.4410081	-0.84	0.119
			[95% Conf. Interval]	
			.1664566	3.119865

Table 34 Presence of gummata in relation to caries, among pathological (syphilitic) individuals, New London Bridge and Lower Farringdon St samples

Logistic regression						
Log likelihood:	-11.901638		*Number of observations*		22	
			LR chi2(1)		0.56	
			Prob > chi2		0.1135	
			Pseudo R2		0.0467	
periodontitis	*Odds Ratio*	*Std. Err.*	*z*	*P>|z|*	*[95% Conf. Interval]*	
gummatabiv	.4666367	.4231171	-0.99	0.652	.0712945	2.914838

Table 35 Presence of gummata in relation to periodontitis, among pathological (syphilitic) individuals, New London Bridge and Lower Farringdon St samples

Turner (1930): Proportion of individuals manifesting secondary stage infection				
OBSERVED				
	with	**without**		
males	0.50	0.16	0.66	
females	0.50	0.16	0.66	
	1.00	0.32	1.32	=CHI SQR
			1.00	= DEGREES OF FREEDOM
			0.250	= p (one-tailed)
Turner (1930): Proportion of individuals manifesting recurrent secondary stage infection				
OBSERVED				
	w	**wo**		
m	14.01	2.06	16.07	
f	13.54	1.99	15.53	
	27.55	4.05	31.59	=CHI SQR
			1.00	= DEGREES OF FREEDOM
			0.000	= p (one-tailed)
Turner (1930): Proportion of individuals manifesting cutaneous lesions, secondary stage				
OBSERVED				
	w	**wo**		
m	5.89	0.34	6.24	
f	5.70	0.33	6.03	
	11.59	0.68	12.27	=CHI SQR
			1.00	= DEGREES OF FREEDOM
			0.000	= p (one-tailed)
Turner (1930): Proportion of individuals manifesting tertiary stage infection				
OBSERVED				
	w	**wo**		
m	12.28	22.03	34.31	
f	12.37	22.18	34.55	
	24.65	44.21	68.86	=CHI SQR
			1.00	= DEGREES OF FREEDOM
			0.000	= p (one-tailed)
Turner (1930): Proportion of individuals manifesting tertiary stage infection				
OBSERVED				
	w	**wo**		
m	3.04	0.27	3.31	
f	2.70	0.24	2.94	
	5.74	0.52	6.25	=CHI SQR
			1.00	= DEGREES OF FREEDOM
			0.012	= p (one-tailed)
Turner (1930): Proportion of individuals manifesting bone lesions, tertiary stage				

infection				
OBSERVED				
	w	**wo**		
m	27.95	1.94	29.89	
f	28.14	1.95	30.09	
	56.09	3.89	59.98	=CHI SQR
			1.00	= DEGREES OF FREEDOM
			0.000	= p (one-tailed)
Turner (1930): Proportion of individuals manifesting cardiovascular involvement, tertiary stage infection				
OBSERVED				
	w	**wo**		
m	80.29	10.41	90.71	
f	80.84	10.48	91.33	
	161.14	20.90	182.03	=CHI SQR
			1.00	= DEGREES OF FREEDOM
			0.000	= p (one-tailed)
Turner (1930): Proportion of individuals manifesting neurological involvement, tertiary stage infection				
OBSERVED				
	w	**wo**		
m	0.38	0.29	0.68	
f	1.19	0.91	2.10	
	1.58	1.20	2.78	=CHI SQR
			1.00	= DEGREES OF FREEDOM
			0.096	= p (one-tailed)
Rosahn and Black-Schaffer (1943; 1943; 1946): proportion of individuals manifesting secondary stage infection				
OBSERVED				
	w	**wo**		
m	188.93	124.45	313.38	
f	276.88	182.38	459.27	
	465.81	306.83	772.64	=CHI SQR
			1.00	= DEGREES OF FREEDOM
			0.000	= p (one-tailed)
Gjestland (1955): proportion of individuals manifesting secondary stage infection				
OBSERVED				
	w	**wo**		
m	0.04	0.00	0.04	
f	0.01	0.00	0.01	
	0.06	0.00	0.06	=CHI SQR
			1.00	= DEGREES OF

				FREEDOM
			0.807	= p (one-tailed)
Gjestland (1955): proportion of individuals manifesting recurrent secondary stage infection				
OBSERVED				
	w	**wo**		
m	0.07	0.01	0.08	
f	0.02	0.00	0.02	
	0.09	0.01	0.10	=CHI SQR
			1.00	= DEGREES OF FREEDOM
			0.752	= p (one-tailed)
Gjestland (1955): proportion of individuals manifesting tertiary stage infection				
OBSERVED				
	w	**wo**		
m	0.26	1.14	1.39	
f	0.12	0.53	0.65	
	0.37	1.67	2.04	=CHI SQR
			1.00	= DEGREES OF FREEDOM
			0.153	= p (one-tailed)
Gjestland (1955): proportion of individuals manifesting bone lesions, tertiary stage infection				
OBSERVED				
	w	**wo**		
m	3.63	0.39	4.02	
f	1.76	0.19	1.94	
	5.39	0.58	5.97	=CHI SQR
			1.00	= DEGREES OF FREEDOM
			0.015	= p (one-tailed)
Gjestland (1955): proportion of individuals manifesting cardiovascular involvement, tertiary stage infection				
OBSERVED				
	w	**wo**		
m	13.59	1.21	14.80	
f	5.31	0.47	5.78	
	18.90	1.68	20.58	=CHI SQR
			1.00	= DEGREES OF FREEDOM
			0.000	= p (one-tailed)
Gjestland (1955): proportion of individuals manifesting neurological involvement, tertiary stage infection				
OBSERVED				
	w	**wo**		
m	10.61	0.52	11.13	
f	4.14	0.20	4.34	

	14.75	0.72	15.47	=CHI SQR
			1.00	= DEGREES OF FREEDOM
			0.000	= p (one-tailed)

Table 36 Results: Sex assessed in relation to infection stage, lesion type, and organ system involvement in the clinical and autopsy samples (Chapter Four)

One Way ANOVA

Femoral Hg emission values (Mean L1)

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	21824.889	3	7274.963	.585	.631
Within Groups	298595.073	24	12441.461		
Total	320419.962	27			

Table 37 Femoral Hg emission values (mean) between control and syphilitic individuals, assessed by sex, for all sites

One Way ANOVA

Femoral Hg emission values (Mean L1)

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	434206.326	1	434206.326	4.759	.030
Within Groups	4.042E7	443	91247.214		
Total	4.086E7	444			

Table 38 Femoral Hg emission values (mean) between control and syphilitic individuals, at all sites

One Way ANOVA

Femoral Hg emission values (Mean L1) & Soil Hg emission values

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	45749.618	5	9149.924	.733	.607
Within Groups	274670.344	22	12485.016		
Total	320419.962	27			

Table 39 Femoral Hg emissions (mean) in relation to status, between control and syphilitic individuals, at all sites

One Way ANOVA

Rib Hg emission values

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	21331.167	3	7110.389	.491	.694
Within Groups	188210.833	13	14477.756		
Total	209542.000	16			

Table 40 Rib Hg emission values between control and syphilitic individuals, assessed in relation to sex, for all sites

One Way ANOVA

Rib Hg emission values

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	16581.643	5	3316.329	.189	.961
Within Groups	192960.357	11	17541.851		
Total	209542.000	16			

Table 41 Rib Hg emission values, assessed in relation to status, for control and syphilitic individuals, at all sites

ANOVA

Mean L1

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	146173.931	4	36543.483	4.133	.014
Within Groups	168013.464	19	8842.814		
Total	314187.395	23			

Table 42 Femoral (mean) Hg emissions in relation to sex, at the Lower Farringdon St site/ sample (FAO90), among syphilitic individuals

ANOVA

Hg L1

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	100772.376	1	100772.376	3.067	.083
Within Groups	3778383.744	115	32855.511		
Total	3879156.120	116			

Table 43 Femoral (mean) Hg emission values, at the Lower Farringdon St site/ sample (FAO90), between control and syphilitic individuals

ANOVA

Mean L1

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	43214.741	3	14404.914	1.063	.387
Within Groups	270972.654	20	13548.633		
Total	314187.395	23			

Table 44 Femoral Hg emissions (mean) in relation to status, among syphilitic and control individuals at the Lower Farringdon st site/ sample (FAO90)

ANOVA

Hg L1

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	25920.613	1	25920.613	1.354	.246
Within Groups	4095862.720	214	19139.545		
Total	4121783.333	215			

Table 45 Femoral Hg emissions (mean) between syphilitic and control individuals at the New London Bridge site/ sample (NLB91)

One Way ANOVA

Hg L1

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	412432.692	4	103108.173	3.273	.014
Within Groups	3780775.436	120	31506.462		
Total	4193208.128	124			

Table 46 Femoral Hg emissions (aggregate) by site, among syphilitic individuals (variation in Hg by site)

ANOVA

Mean L1

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	15554.304	4	3888.576	.535	.711
Within Groups	312645.763	43	7270.832		
Total	328200.067	47			

Table 47 Femoral Hg emissions (mean) in relation to sex, for syphilitic and control individuals at the New London Bridge site/ sample (NLB91)

ANOVA

Mean L1

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	73511.472	4	18377.868	1.712	.182
Within Groups	246908.490	23	10735.152		
Total	320419.962	27			

Table 48 Femoral Hg emissions (mean) among syphilitic individuals, assessed in relation to site (variation in mean Hg by site)

ANOVA

RibHg

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	10746.952	4	2686.738	.162	.954
Within Groups	198795.048	12	16566.254		
Total	209542.000	16			

Table 49 Rib Hg emissions among syphilitic individuals, assessed in relation to site (variation in Hg by site)

Correlations

		Mean L1	SoilHg
Mean L1	Pearson Correlation	1	.464
	Sig. (2-tailed)		.208
	N	48	9
SoilHg	Pearson Correlation	.464	1
	Sig. (2-tailed)	.208	
	N	9	13

Table 50 Femoral Hg emissions (mean) in relation to soil Hg emissions (for soil recovered in direct proximity to each femora)

Non-Parametric Correlations

			Mean L1	SoilHg
Spearman's rho	Mean L1	Correlation Coefficient	1.000	-.117
		Sig. (2-tailed)	.	.765
		N	48	9
	SoilHg	Correlation Coefficient	-.117	1.000
		Sig. (2-tailed)	.765	.
		N	9	13

Table 51 Rib Hg emissions in relation to soil Hg emissions (for soil recovered in direct proximity to each rib)

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