

Original Study

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More Harm than Healing? Investigating the Iatrogenic Effects of Mercury Treatment on Acquired Syphilis in Post-medieval London.

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Abstract: Mercury was commonly used to treat syphilis in post-medieval Europe, but debate persists about whether it ameliorated infection or exacerbated it. As there are no *in vitro* studies on mercury's effectiveness, Hg levels were characterized using an established technique, portable X-Ray Florescence Spectrometry (pXRF) in syphilitic skeletons (N=22) from six post-medieval London cemeteries. Levels were assessed against proxies for syphilitic infection severity (lesion type, episodic involvement, extent of involvement), oral health indicators, and age at death. The findings are equivocal, likely obfuscated by background poor oral health and high mortality, and cannot elucidate whether mercury 'killed or cured'.

Keywords: syphilis, mercury, pXRF, post-medieval, London, trace element analysis, paleopathology.

1 Introduction

Syphilis was a significant, though still underestimated, public health problem in post-medieval England (Siena 2004). Various lines of evidence, including chronicler's reports, physicians', hospital, and military records, suggest that rates of infection were extremely high in post-medieval London and, presumably, other urban centers in Europe (Trumbauch 1998). These records also suggest that a large number of sufferers actively pursued medical treatment for their infection. More than half of the 17th to 18th century medical advertisements (c. 1660-1715) held by the British Library, for example, advertised treatments for the disease (Siena 2001). Records of London's Royal Hospitals, St. Bartholomew's and St. Thomas', the city's two public hospitals, also reveal that it was the single most common disease treated there. 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 and post-medieval disease concepts grouped multiple conditions, including chancre, syphilis and gonorrhea, under the umbrella of 'lues venerea,' 'venereal disease' or most commonly, 'the pox,' it is incorrect to assume that all of these patients were syphilitics (Siena 2005). However, the records do nonetheless suggest widespread infection or at least diagnosis and treatment of high rates of the disease, and a correspondingly large medical marketplace.

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A variety of treatments for the pox¹ were employed in post-medieval Europe, ranging from vegetable-based cures, such as guaiacum, to arsenic and bismuth, but mercury was by far the most commonly used in England and the rest of Europe (Goldwater 1972, Quétel 1990). Mercury had been in use since the early medieval period to treat skin conditions (Swiderski 2008), and was used first against the pox nearly simultaneously with the disease's emergence in the late 15th century (Goldwater 1972). It was used well into the 19th century, commonly mixed with other compounds, such as arsenic, despite well-documented and serious complications of treatment, which resulted from mercury toxicity, and long-running debates about its effectiveness (Quétel 1990).

Late medieval physicians all the way up to modern medical historians have argued that when it came to syphilis and mercury, the cure may have been worse than the disease. Goldwater (1972) for instance, has proposed 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.” Many physicians questioned the efficacy of mercury treatments, particularly as they had profound side effects, including oral ulcers, excessive salivation, and tooth loss, as well as neuropathies and even kidney failure, with some patients even dying of mercury toxicity during or shortly after treatment (Siena 2004). Debates have centered on whether mercury treatments ameliorated infection with syphilis or instead exacerbated it, deteriorating health and causing early death. Ortner (2003) argued that many 19th century European skeletons exhibit manifestations of syphilis far more severe than any archaeological case he had observed and proposed that mercury treatments may have been harm-causing or iatrogenic to patients with syphilis. Extrapolating from this, Ortner cautioned that pre-antibiotic era cases of any condition should not be assumed to be typical of natural, untreated disease as many other treatments in the past could have been iatrogenic as well. Because large doses of mercury can cause acute and potentially fatal poisoning and small doses, endured for a long duration, can cause chronic poisoning (Goldwater 1972), it is possible that a negative synergy may have existed between infection with syphilis and toxicity from mercury, degrading patient health and reducing immunological competence. As one of the primary intellectual contributions of paleopathology is an understanding of the expression and natural history of untreated disease, an examination of whether mercury was indeed iatrogenic is critical to understanding the extent of what paleopathologists can learn about the evolution and ecology of syphilis from the skeletal record.

As no *in vitro* studies of the effects of mercury on syphilis exist in the published literature, here several archaeological skeletal samples from 17th to 19th century London underwent an osteological and trace element analysis to assess the effects of mercury treatment on the severity of syphilitic skeletal manifestations, mortality, and oral health, using portable X-Ray Florescence Spectrometry (pXRF). Use of this analytical method is based on previous work (Zuckerman 2016) which established that pXRF can be used to detect evidence of mercury treatments for syphilis in human skeletal material. Mercury (Hg) levels were characterized in a pathological sample (N=22) of skeletons displaying lesions *suggestive* of or *specific* to syphilis, following Harper et al. (2011) and Hackett (1976). Mercury levels were assessed against skeletal age to examine relationships between mercury exposure and mortality; against oral pathologies to examine relationships between mercury levels and oral health; and against evidence for repeat episodes of skeletal involvement the presence of gummatous syphilitic lesions, and the extent of skeletal involvement to examine relationships between mercury levels and the severity of infection.

2 Background

2.1 Syphilis

Acquired syphilis is caused by a spirochaete bacterium, “*Treponema pallidum* subspecies *pallidum*”. When not treated with antibiotics, syphilis expresses as a multi-stage chronic disease with diverse and

¹ Here, the term “syphilis” is used to refer to the infectious condition caused by *Treponema pallidum* subspecies *pallidum* and manifestations of the disease in skeletal material, while “the pox” refers to the condition documented by historical records.

numerous manifestations (Singh, Romanowski 1999), several of which result in identifiable skeletal lesions (Ortner 2003). Importantly, it is the consensus in paleopathology that lesions attributed to syphilis cannot be distinguished from those caused by other treponemal variants, namely yaws and bejel (Harper et al. 2011, Ortner 2003). However, there is no historical evidence to suggest that any treponemal variants other than syphilis were endemic in post-medieval London, meaning that the treponemal lesions explored in the pathological sample can be attributed to syphilis with a high degree of certainty (Zuckerman 2010). The primary stage, which lasts for weeks to a few months, involves a chancre at the site of infection, and systemic inflammation, but few, impermanent, and non-diagnostic skeletal lesions. Secondary stage infection, which initiates two weeks to six months after infection, can cause a slew of symptoms ranging from rashes to fever, malaise, lesions on mucous membranes, baldness (alopecia), meningitis, and transient, non-diagnostic skeletal lesions. After approximately one year, sufferers enter latent (asymptomatic) stage infection, which can last for years to decades; during this stage, a small proportion of cases (c. 25%) experience recrudescence secondary stage infection. Infection resolves in most cases after this stage, but in a small portion, approximately 15 to 30%, tertiary stage arises one to as many as two decades after initial infection. Tertiary infection encompasses cardiovascular involvement, such as aortic aneurysm, neurosyphilis, including general paresis and tabes dorsalis (Singh, Romanowski 1999), and in a small number of cases (c. 10-20%) skeletal involvement, producing periosteal reactions, osteitis, gummata, or granulomatous gummy tumors in any organ, and *caries sicca* on the cranium, among other lesions (Ortner 2003).

2.2 Mercury and Treatments of Syphilis

Mercury was administered against the pox in several forms. Calomel or sweet mercury (Hg_2Cl_2) was taken orally or by injection. It and mercuric chloride (HgCl_2), which had a corrosive effect, were also applied as salves. Fumigation became popular in the early 16th century and was in use against the disease until the 1920s (O'Shea 1990). In this method, patients were placed in a tent, barrel or overheated room for weeks to months at a time and forced to inhale vapors from mercuric chloride, heated cinnabar (HgS), and metallic mercury. As Beck (1997) describes it, a typical treatment with mercury involved seclusion in a heated, congested room and vigorous rubdowns with mercury ointments several times a day near a hot fire, which patients were then left near to encourage sweating, as is shown in Figure 1. Treatments would last for weeks to months and repeated if the disease persisted, often over the course of years. This gave rise to the saying, "A night with Venus, and a lifetime with mercury" (Dobson 2007:140).



Figure 1. The Martyrdom of Mercury. The scourge of Venus and Mercury, represented in a treatise of the venereal disease. John Sintelaer. 1709. London: G. Harris.

All of these methods of administration could result in mercury toxicity, which has debilitating to fatal effects. Mercury toxicity has diverse symptoms, including personality changes, oral inflammation, tooth loss, stomatitis, proteinuria, weight loss, and gastroenteritis (Swiderski 2008). Acute exposure (e.g., 4–8 hours at 1.1–4.4 mg/m³) to low levels can also cause pulmonary impairment (Bidstrup 1964, WHO 1976); acute exposure to higher levels can produce profound central nervous system defects, including psychosis. Chronic exposure to low levels (e.g., 0.7–42 µg/m³) can cause *erethism mercurialis*, featuring shyness, social phobia, depression, fatigue (McFarland, Reigel 1978), and tremors, and with further exposure, violent muscular spasms (Liang et al. 1993, Ngim et al. 1992). Most of these symptoms were recognized — and feared — by early modern physicians, the lay public, and patients alike. For instance, von Hutten ([1519] 1945), a 16th century German scholar who was treated with mercury, described experiencing tooth loss, excessive salivation, and ‘hatters shakes’.

The dosages prescribed and duration of treatment for the pox varied over time. Overall, doses were high in the 16th century and treatments long lasting, often four to six weeks, with mercury commonly administered through salivation following the principles of humoral medicine (O’Shea 1990). By the 17th century, dosages were lower and calomel, which is less toxic than other forms, was commonly used. From the 17th to 19th centuries, a typical dosage in England was 5 grains (≈325 mg) daily for up to two years, though there was not a standardized regimen; physicians and other practitioners titrated doses to fit the individual physiological needs of their patients. Some medical texts emphasized that doses should be low enough to not induce toxicity (Fagala, Wigg 1992, Foá 1985), but whether this was practiced is largely unknown. Numerous patient accounts from throughout the period describe deaths from overly high doses and early abandonment of treatment by those incapacitated by toxicity or disenchanted with its ineffectiveness (O’Shea 1990).

2.3 Effectiveness of Mercury Treatments Against Syphilis

Whether mercury constituted an effective treatment for syphilis remains unknown and still subject to debate. It is known that mercury has anti-inflammatory and spirilicidal effects (Holmes 1984, Keogh 1913, Lees 1937, Osler, Macrae 1920). Mercury has also been documented as inducing a Jarisch-Herxheimer reaction, the systemic release of large quantities of endotoxins as bacteria (i.e. spirochaetes) die during antibiotic treatment (Fabricius 1994, Goldwater 1972). O’Shea (1990) has speculated that mercury would have been ineffective during secondary infection, but that systemic and topical treatments may have occasionally aborted primary stage infection and helped to resolve tertiary, both stages when there are few spirochaetes in circulation; Holmes (1984) speculated that it may also have helped to resolve gummata. However, there are no published *in vitro* studies evaluating the validity of these assumptions. It is possible that the recrudescence nature of syphilitic infection, the spontaneous resolution of secondary stage infection, and potentially decades long latent stage may also have confused medical practitioners. These phenomena had been noted by 19th century practitioners (Holmes 1984, St John 1976) but were only empirically confirmed as characteristics of syphilitic infection in the mid-20th century (Gjestland 1955). This finding suggests that many of the ‘cures’ attributed to mercury treatment were more likely due to the fluctuating nature of untreated syphilis.

2.4 Mercury Treatments for the Pox in 17th to 19th century London

A vigorous scholarly debate has continued for several decades about use of and access to mercury treatments for the pox. Current scholarship demonstrates that socioeconomic status played a profoundly influential role in who was treated with mercury and what doses they received (Siena 2004). The poor and lower status relied primarily on institutional care, provided by the Royal hospitals throughout the period, and in the 18th and 19th centuries, gender-specific hospitals, like the Lock, and parish workhouses. Mercury, and even non-mercury treatments were provided for free in the 16th century, but by the late 17th century, fees were charged and mercury cures had become ubiquitous. Specifically, high dose mercury treatments had become nearly ubiquitous in institutional care by the late 17th century (Siena 2004). Some historians,

like Temkin (1977) have suggested that these treatments, because of their toxicity, functioned as a form of social discipline for infection with the pox, which had become highly stigmatized by this time. Others have suggested that they merely reflected fiscal constraint, as mercury was less expensive than non-mercury treatments, and higher doses might have been thought to preclude the need for future treatments (Siena 2004). In contrast, for as long as they could afford them, higher and middling status patients sought out non-mercury treatments, which were consistently more expensive than mercury treatments, and low-dose mercury treatments through the more discreet and private medical marketplace. These treatments were also less toxic and therefore less conspicuous, increasing their appeal (Siena 2001). This usage pattern was particularly true after the mid 18th century, as the pox's stigma deepened, even as low dose and non-mercury treatments became moderately less expensive (McAllister 1996). However, the notoriously impoverishing effect of the pox, due to the disease's stigma and the overall high cost of treatment, means that mercury was likely used across socioeconomic strata. Previous analysis of mercury levels via pXRF in the pathological sample has confirmed this, detecting consistently elevated mercury levels in all individuals, independent of socioeconomic status (Zuckerman 2016).

2.5 Mercury and Human Tissue

Mercury accumulates in bone, both in trabecular and compact bone, and is most likely incorporated into compact bone when Hg is present in excess in the body (Rasmussen et al. 2013). Importantly, unlike other heavy metals, such as lead, for which 90 to 95% of the element stored in the body is retained in bone (Smith, Hursh 1977), Hg levels in compact bone (Rasmussen et al. 2013) are lower than those in the soft tissue of a given individual. Garcia et al. (2001) for instance, has reported autopsy findings of less than 0.05 ppm of Hg in bone but 0.25 in the kidney and 0.14 ppm in the liver of a given individual. This means that Hg levels detected in human bone in this study are likely systematically lower than the soft tissue burden that these individuals would have experienced during life.

2.5.1 Diagenesis

Detection of diagenesis is fundamentally important to trace element analyses of archaeological skeletal material. Diagenetic alterations of trace element levels in buried bone can occur through leaching from the burial matrix or exposure to groundwater, as well as uptake from the surroundings (Hedges 2002). Particularly since the advent of industrialization, mercury has become a widely available element, both atmospherically and geologically (Ehrlich, Newman 2008, Krabbenhoft, Schuster 2002), with concentrations increasing in proximity to urban areas because of global transport or anthropogenic activity (Davis et al. 1997). Because of the long history of industrial activity in London, mercury is likely present in the sediments of many archaeological sites in the capital, and diagenesis was therefore a key consideration in this study. However, published analyses of mercury concentrations in archaeological bone using *in situ* soil samples have failed to detect any evidence of diagenetic transport of Hg between the surrounding soil and bone (Rasmussen et al. 2008, Rasmussen et al. 2013, Yamada et al. 1995). Further, pXRF analysis of eleven soil samples collected during excavation in direct proximity (<5 cm horizontally and vertically) to the pathological sample generated no evidence of diagenetic transfer of Hg, meaning that Hg levels detected in the sample reflect endogenous, antemortem exposure (Zuckerman 2016).

2.5.2 Endogenous Exposure to Mercury

Endogenous exposure to mercury could also be an interpretive concern for this study. Mercury in various forms was in wide usage in early modern craft and industry in post-medieval England, such as mirror silvering and felt hat making (Homer 1991). It was also used as a food adulterant and for treating a range

of conditions, from disinfecting cuts and scrapes to depression and childbirth, throughout the 17th to 19th centuries (Goldwater 1972, Wohl 1983). Therefore, whether directly from therapeutic use, consumption, occupational exposure, or preparation of mercury for these applications, or indirectly, through environmental and atmospheric pollution, many Londoners were likely exposed to mercury (Campbell 1991).

To address this, Zuckerman (2016) compared Hg levels in the pathological sample to those in a non-pathological, control skeletal sample (n=51). The control sample consisted of approximately three skeletons 'matched' to each peer pathological skeleton and recovered from the same archaeological site. To accommodate chronological and socioeconomic status-related differences in endogenous exposure, each had funerary artifacts (e.g., shroud pins and coffin type, shape, hardware and decoration) highly similar to its peer skeleton, and was recovered in close spatial proximity (c. 5m horizontally and 1m vertically) to its peer. Control skeletons were also excluded if they displayed evidence of lesions attributed to syphilis, and if they displayed any of the pathological conditions excluded in the pathological sample (i.e. co-infection, periosteal reactions, non-infectious pathologies), following the same criteria. Exceptions were included when three control skeletons meeting these criteria were unavailable for each pathological skeleton, such as for St. Thomas' Hospital and Cross Bones, for which controls were included that manifested pathological conditions not known to have been treated with mercury, such as metabolic disease, osteoarthritis, and trauma. Hg levels in each pathological skeleton were assessed against those in the three peer control skeletons. Importantly, analysis revealed significant differences between Hg levels in both the pathological and peer control skeletons, and the pathological and control samples, in both mean and aggregate femoral Hg levels, with the pathological sample yielding much higher levels of Hg. Complemented by the absence of significant relationships between skeletal sex, translated into gender, and socioeconomic status, and Hg levels when analyzed in an aggregated sample, composed of the combined pathological and control sample, these findings indicate systematic treatment of syphilis with mercury and greatly reduce the possibility that Hg levels in the pathological sample can be attributed to occupational activities, rather than mercury treatments for syphilis (Zuckerman 2016).

2.6 Trace Element Analyses of Skeletal Evidence for Mercury Treatments for Syphilis

Only four published studies have presented trace element analyses of mercury treatments for syphilis in pre-modern Europe. Rasmussen et al. (2008) used atomic absorption spectrometry (AAS) to assess evidence of mercury treatments in twelve medieval skeletons from Denmark, finding elevated mercury levels consistent with mercury treatment in 40% of them. A work by Kepa et al. (2012) also detected evidence of elevated Hg in two medieval Polish skeletons that manifested lesions specific to syphilis. As discussed above, Zuckerman (2016) assessed Hg levels in relation to skeletal sex, translated into gender, and socioeconomic status on the same pathological sample employed here. Analysis yielded evidence of systematic mercury treatment for syphilis in the sample, but no relationship between Hg levels and skeletal sex, translated into gender, and socioeconomic status. Tucker (2007: 221), employing seven adult skeletons displaying syphilitic lesions from three of the archaeological sites sampled here, St. Thomas Hospital, St. Bride's Lower, and Redcross Way, assessed relationships between high Hg levels, age, "obvious" skeletal or dental changes, and an alteration of "typical" syphilitic skeletal lesions. Tucker notes that the small sample size hindered interpretation and the findings are ambiguous. Tucker did not find "striking" relationships between Hg levels and age-at-death or atypical syphilitic lesions, respectively, though the low age-at-death for the majority of the sample is notable. However, Tucker detected a strong relationship between levels of Hg and caries, and that "extreme new bone growth" was found in those with the lowest levels, suggesting that elevated exposure to mercury may have curbed bone involvement. According to Tucker, these findings support the idea that mercury treatments for syphilis were detrimental to health. Consideration of these findings in relation to that of the analysis presented here are included below.

3 Materials and Methods

3.1 Skeletal Samples

Skeletons in the pathological sample (n=22) were selected from six cemeteries excavated in and around London since 1990, which yielded skeletons exhibiting syphilitic lesions. Since their exhumation by the Museum of London Archaeological Service (MoLAS), the skeletons have been examined and stored (in acid free tissue and plastic bags within cardboard boxes) in a basement facility at the Centre for Human Bioarchaeology at the Museum of London.

Chelsea Old Church (OCU00). This cemetery served the Village of Chelsea, a relatively affluent community in suburban London. Following excavations, 198 skeletons were retained for analysis, all of which were buried between 1712 and 1842 AD. Various records and the mortuary context suggest that the majority of individuals were of high status, such as high end merchants (Cowie et al. 2008). One skeleton from this site was included in the pathological sample.

Redcross Way/ Cross Bones Burial Ground (REW92). The 148 skeletons exhumed from this site were buried between 1800 and 1853 AD, when the site served as a ‘pauper’s cemetery’ for the parish of St. Savior’s, Southwark. Various records and the mortuary context suggest that the individuals were low status, such as servants and laborers, to very poor, and the skeletons exhibit high frequencies—greater than 60% affected—of various pathologies, including syphilis (Brickley et al. 1999). Two skeletons from this site were included in the pathological sample.

St. Bride’s Lower Churchyard/ Farringdon Street (FAO90). This cemetery served the parish of St. Bride’s, London, and received burials between 1770 and 1849 AD. Various records and the mortuary context suggest that the 545 skeletons retained from excavations were poor to low status: servants, infants, vagrants, travelers from other parishes who died while visiting, and most likely, residents of the nearby Bridewell workhouse and inmates of Fleet prison. Paleopathological analysis revealed high frequencies—greater than 60% of skeletons affected—of various pathologies, including syphilis (Miles, Conheaney 2005). Eight skeletons from this site were included in the pathological sample.

St. Bride’s Fleet Street Crypt (SB). This crypt served the middling class and to a lesser extent, high status residents of St. Bride’s parish. This is a known-named sample (Schuer 1998); of the 200 plus individuals exhumed, two, both of middling status and with death dates of 1788 and 1828, respectively, were included in the pathological sample.

St Benet Sherehog (ONE94). This was the cemetery of St Benet Sherehog parish, London. Records suggest that the parish was affluent and that burials are primarily high status, through lower status parishioners were also buried there. The 231 retained burials primarily date to date to 1666 to 1849, and display moderate levels of various pathologies (c. 20% affected) (Miles, White 2008). Two skeletons from this site were included in the pathological sample.

New London Bridge/ St. Thomas’ Hospital (NLB91). Skeletons in this sample were excavated from mass graves, either for paupers or from a catastrophic event, associated with St. Thomas’ Hospital, Southwark. The hospital served poor, ill, and homeless individuals unable to afford private medical treatment. Paleopathological analysis of the 193 retained skeletons, which date to the 17th century, revealed high rates of various pathologies (greater than 60% affected), including syphilis (13% of skeletons affected), but very poor preservation (WORD database 2010). Seven skeletons from this site were included in the pathological sample.

3.2 Skeletal Sample Selection Criteria

Skeletons in the pathological sample (n=22) exhibit macroscopic lesions *suggestive* of or *specific* to syphilis (e.g., treponemal disease) following Harper et al. (2011) and Hackett (1976). As mentioned above, while skeletal manifestations of syphilis cannot be empirically distinguished from those of the other treponematoses, there is little historical evidence suggesting yaws or bejel were common in post-medieval England. Suggestive

lesions include finely striated nodes and expansions, coarsely striated and pitted expansions, and rugose nodes and expansions on long bones, and first three stages of lesions in the *caries sicca* lesion sequence (i.e., clustered pits, confluent pits, focal superficial cavitation). Specific lesions include the last three stages of the *caries sicca* sequence (i.e., serpiginous cavitation, nodular cavitation, *caries sicca*), and, on long bones, nodes or expansions with superficial cavitations (see Figure 2). To limit confounding factors, skeletons were also excluded if they displayed evidence of other pathological conditions, diagnosed following Ortner (2003), for which they might have been treated with mercury, including co-infection with another infectious disease (except tuberculosis, which was not treated with mercury), periosteal reactions, or a non-infectious pathology (excluding trauma) that historical evidence indicates may have been treated with mercury. These conservative criteria reduced the sample size, but were necessary to reduce the inclusion of false positive cases for syphilis infection and those treated with mercury for purposes other than syphilis infection.

There is no one objective, empirical measure of severity of infection with syphilis (or treponemal disease) in paleopathology, and so multiple measures were used here to capture this aspect of infection. Within this sample, evidence of single or repeat episodes of skeletal involvement, the presence of gummata, and the extent of involvement on the skeleton were recorded. A skeleton was recorded as exhibiting a single episode of skeletal involvement if all pathological lesions attributable to syphilis were macroscopically observed as being in approximately the same state of active destruction or healing. Repeat episodes were recorded when at least one lesion was observed as being in a very different state of active destruction or healing, such as a lytic lesion with no evidence of healing and a well remodeled lesion present within the same skeleton. Gummata were defined as focal, circumscribed lytic lesions with perifocal osteosclerotic reactions involving the cortex. They were recorded as present if found in any skeletal element. Lastly, it was recorded whether lesions *suggestive of* or *specific to* syphilis were found on less than or more than 50% of the elements of a given skeleton that were present for observation. Syphilis is a systemic condition (Singh, Romanowski 1999), and therefore the greater distribution of lesions across the skeleton can be employed as a proxy for gaging an aspect of the severity of infection as evident in skeletal material.

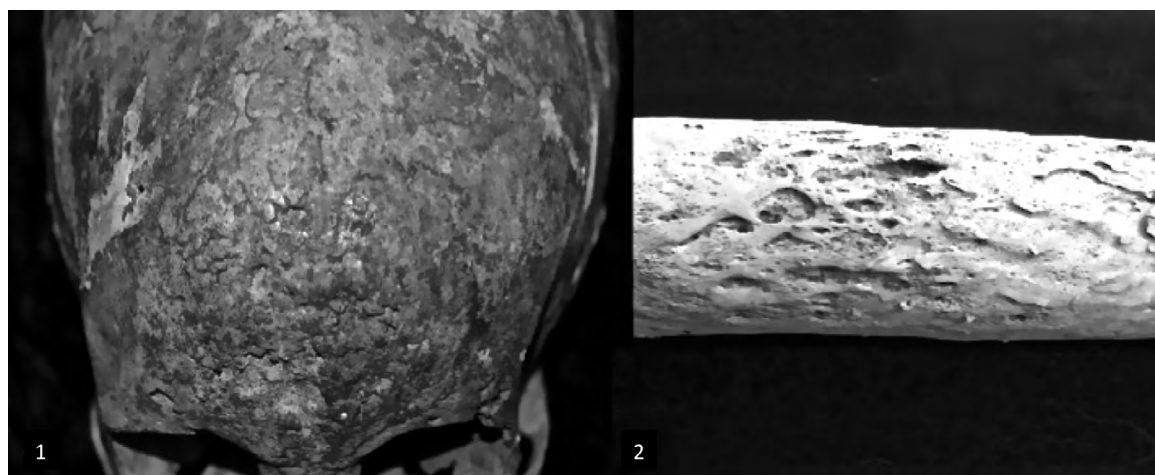


Figure 2. Macroscopic lesions suggestive of or specific to syphilis. 1. Cranium demonstrating stages three to six of the *caries sicca* sequence. 2. Femur demonstrating nodes and expansions with superficial cavitations.

3.3 Age Estimation

Adult ages (i.e., ages 18 years or older) were estimated based on age-related changes of the pubic symphysis (Brooks, Suchey 1990) and iliac auricular surface (Buckberry, Chamberlain 2002, Lovejoy et al. 1985). No sub-adults (<18 years) were included in this study, due to typically low frequencies of acquired syphilis infection in this demographic. Because of the small pathological sample size, age was collapsed into two analytical categories: early adult (18-35 years) and older adult (>35 years).

3.4 Oral Pathologies

The oral pathologies recorded included antemortem tooth loss, dental caries, and periodontal disease, following Buikstra and Ubelaker (1994). Skeletons were excluded from the pathological sample if they were not associated with dentition, which further reduced the sample size. Antemortem tooth loss was recorded for individual teeth, and was indicated by the absence of a tooth and full to partial healing of the socket; loss was not recorded when the socket was too damaged to detect healing. Dental caries are defined as the destruction of enamel, dentin, and cementum by acid produced by bacteria within dental plaque, evident as a cavity in the crown or root of a tooth (Hillson 1996). Caries were recorded by location for each individual tooth. Periodontitis, or periodontal disease, is caused by chronic oral bacterial infection, resulting in gingival inflammation and progressive destruction of periodontal tissues and alveolar bone (Irfan et al. 2001). In the skeleton, this is evidenced by lost alveolar bone and consequent porosity or reduction of the alveolar crest (AC) relative to the cemento-enamel junction (CEJ) (Larsen 1997). Periodontal disease was recorded as present if the alveolar bone displayed porosity or if the distance between the AC and CEJ was greater than 2 mm, with the alveolar bone surrounding each tooth score individually if present, and as ‘mild’ if 2 mm to 3 mm distance between the AC and CEJ existed, or severe if > 3mm of distance existed. To reduce interobserver error, these data were crosschecked against the osteological inventories of each individual in the sample in the Museum of London’s WORD Database (2010).

3.5 Trace Element Analysis via pXRF

pXRF analysis was conducted to detect Hg levels in the pathological (n=22) skeletal sample using a Bruker Tracer III-V/III-SD handheld XRF® analyzer. In its portable and stationary forms, XRF is a non-destructive technique for chemical compositional measurement in which X-rays of a known energy are directed towards a sample, causing atoms within the material to emit ‘fluorescent’ X-rays at energies characteristic of its elemental composition. While ICP-MS and AAS are more sensitive analytical techniques, pXRF is capable of detecting Hg levels in the 5 ppm range (B. Kaiser, personal communication) and Zuckerman (2016) demonstrated that pXRF was capable of detecting elevated Hg levels associated with mercury treatments for syphilis. Following Rasmussen et al. (2008), the cortex of the femur was analyzed. Left femora were preferentially sampled, though Hg concentrations do not seem to vary between the sides of the skeleton (Rasmussen et al. 2013). Because of the potential for bone remodeling turnover rates to potentially vary among bone positions, with the result that a sudden exposure to Hg in adulthood could result in systematic but large variation in Hg concentrations measured in different bone locations (Rasmussen et al. 2013), the cortex was analyzed in five standardized flat locations on the anterior and poster aspects of the femur (see Figure 3.A.). Given average bone remodeling rates, detected Hg levels represent mercury concentrations for approximately the last decade before death (Manolagas 2000).

Before analysis, the cortex of each femur was gently abraded and thoroughly cleaned with distilled water to limit surface contamination². To maximize detection, readings were taken at each location for 300 seconds at the recommended setting for a Bruker pXRF for detecting Hg in human cortical bone (0.001” Cu, .001” Ti, .012 Al Filter; 40 kV; 4 to 8 micro amps; no vacuum); at these settings and, given the average density of cortical bone, the resulting emissions should represent the Hg found in the 1st.5 cm of cortical bone (Kaiser 2011). Emission values presented in Figure 3.B. - 3.D. do not represent absolute ppm concentrations of Hg. Instead they represent quantified, comparative proportions of Hg at each given location generated from XRF emissions spectra. As of this time, a calibration standard for translating emissions spectra representing Hg in human cortical bone does not exist, thus ppm counts cannot be generated for this data.

² For conservation purposes, more intensive surface preparation was not permitted.

3.6 Analysis

Emissions for each femoral location were calculated using Bruker ARTAX 7® software. The five Hg emissions readings for each femur were aggregated, and means and standard deviations were calculated using Microsoft Excel 2011. Statistical analyses were run using R 3.2.2. A Welch's two sample T-test and a Spearman's rank correlation were conducted to assess whether age-at-death, categorized as young adults (18-35 years) or older adults (≥ 35 years), co-vary with mean mercury emissions. Linear regressions were conducted to assess whether correlations exist between mean mercury emissions and both frequencies of periodontal disease and severity of periodontal disease, frequencies of teeth with caries present, and frequencies of antemortem tooth loss, respectively. A Levene's test for homogeneity of variance and a Welch's two sample T-test were conducted to assess co-variance between mean mercury emissions and single or multiple episodes of skeletal involvement, the presence or absence of gummata, and the extent of skeletal involvement over less than or more than 50% of available skeletal elements.

4 Results

No significant results were generated. Young adults (18-35 years) were found to have higher mean Hg levels (Figure 3.B.) than older adults, but the medians and whiskers reveal a greater distribution of Hg levels in older adults. No linear relationship exists between age-at-death and mean Hg levels, but these two variables do negatively co-vary with each other: older age (≥ 35 years) was associated with lower levels, and younger with higher. There is a slight positive correlation between frequency of periodontal disease and mean Hg levels, but not in the severity of periodontal disease. No covariance was found between frequencies of caries, but a slight positive association exists between mean Hg levels and frequencies of antemortem tooth loss. No covariance was detected between mean Hg levels and single vs. multiple episodes of skeletal involvement. In contrast, positive relationships were detected between mean Hg levels and the presence of gummata (Figure 3.C.) and the extent of involvement across more than 50% of observable skeletal elements (Figure 3.D.).

5 Discussion

Overall, the findings are ambiguous, much like those of Tucker (2007). As with Tucker, much of this is likely attributable to the small sample size, which is further exacerbated by the high frequency of skeletons in the sample recovered without crania.

Several trends, however, are evident. First, younger age-at-death, eighteen to thirty-five years, is associated with higher mean Hg levels, and older age-at-death, above thirty-five years, with lower Hg. This suggests that greater exposure to mercury negatively impacted longevity, adding empirical support to historical patient, lay, and medical accounts of debility and occasional deaths associated with mercury treatments for the pox. This is especially true in light of demographic data for contemporary London, as the Bills of Mortality for 17th to 19th century London indicate that 20% to 30% of the population lived past the age of fifty (Roberts, Cox 2003). However, this conclusion is complicated by very high adult mortality evident in the two skeletal assemblages, St. Thomas Hospital and St. Bride's Lower, which the majority—82%—of the sample was drawn from. Only 9.3% of the skeletons recovered from St. Thomas Hospital were forty-six years of age or older, with most—40%—dying between eighteen and forty-five. At St. Bride's Lower, 26% of the individuals died between eighteen and forty-five years of age (Bekvalac et al. 2007, Kausmally 2008). These samples represent impoverished to very low socioeconomic status communities in post-medieval London—with St. Thomas Hospital yielding skeletons of the especially poor and sick—which were afflicted with especially low longevity in the early industrial period (Roberts, Cox 2003). This likely confounds the apparent association between mercury and longevity.

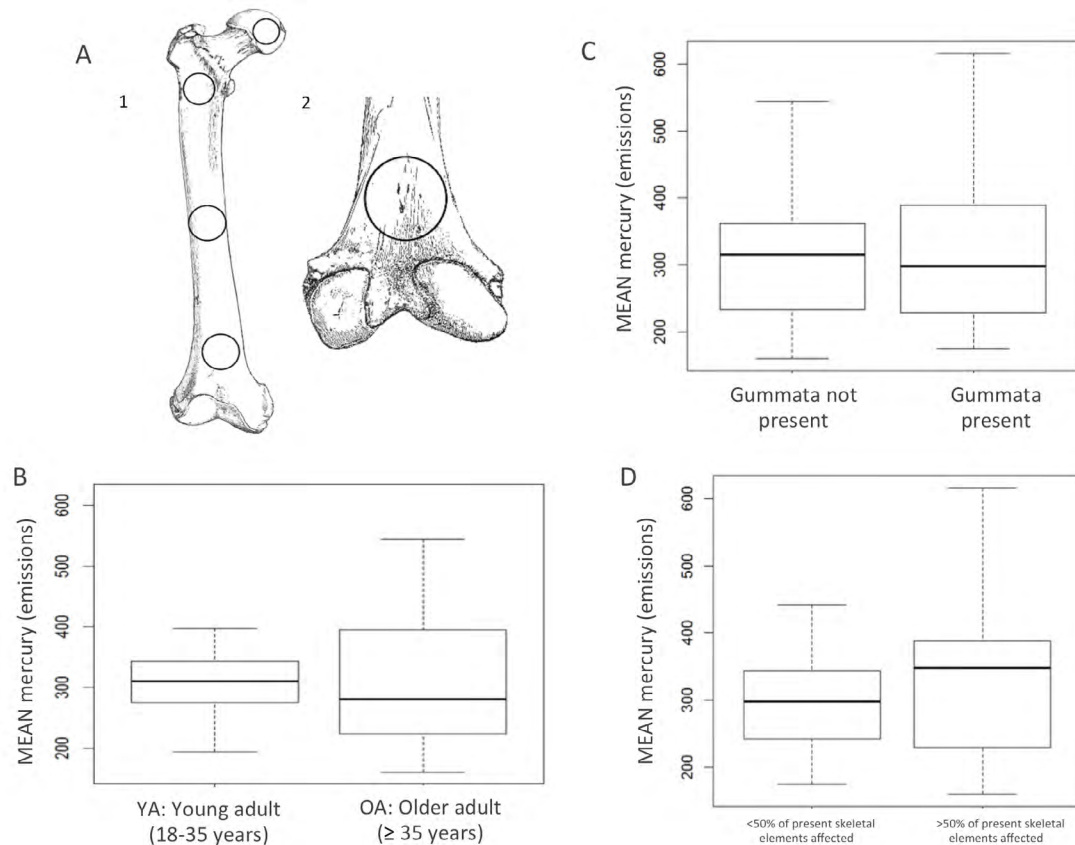


Figure 3. A. Sampling locations on the femur, 1. anterior, and 2. posterior. B. Mean mercury emissions in relation to age-at-death, categorized as young adult or older adults (“Welch’s” Two Sample t-test, p -value = 0.6768; p -value > 1.0). C. Mean mercury emissions relative to the present or absence of gummata anywhere on the skeleton (“Welch’s” Two Sample t-test, p -value = 0.8865; p -value > 1.0). D. Mean mercury emissions in relation the extent of lesions *suggestive of or specific to syphilis*, specifically in relation to whether lesions extend over more than 50% or less than 50% of observable skeletal elements (“Welch’s” Two Sample t-test data, p -value = 0.6892; p -value > 1.0).

Second, the findings on oral health relative to mean Hg levels are contradictory. Slightly positive correlations exist between mean Hg levels and the frequency of periodontal disease—but not severity of periodontal disease—and antemortem tooth loss, respectively, but not dental caries, one of the primary causes of antemortem tooth loss. These results generally contradict expectations generated from historical lay, patient, and medical reports, as well contemporary medical knowledge on mercury toxicity, that mercury exposure would be associated with oral inflammation and create an oral environment conducive to caries. They are in line, however, with historical reports of lost teeth during treatment. However, a more inclusive explanation for these trends is likely the high frequencies of oral pathologies found within the assemblages the sample was drawn from; 49.9% of skeletons from St. Brides exhibit dental caries, and 56% periodontal disease, while 74.6% of those from St. Thomas manifest dental caries and 77.8% periodontal disease (Bekvalac et al. 2007, Kausmally 2008). As with longevity, very high levels of oral pathology in these assemblages confound any association with mercury.

Lastly, findings on mean Hg levels relative to the extent and episodic nature of skeletal involvement and presence of gummata further demonstrate the absence of any clear effect of mercury exposure on health. No associations were detected between mean Hg levels and evidence of single or multiple episodes of skeletal involvement. This is unsurprising in light of physician and patient’s accounts that some patients returned for additional mercury treatments when their previously ‘cured’ infection recrudesced during secondary or tertiary stage infection, while others optimistically moved on to other, non-mercury treatments. The

positive associations between Hg levels and the presence of gummata and syphilitic skeletal involvement encompassing more than 50% of present skeletal elements, respectively, suggest that mercury may have been ineffective in ameliorating tertiary stage infection. These are unsurprising in light of current medical knowledge on the pathophysiology of syphilis; tertiary lesions, such as gummata, represent delayed-hypersensitivity immunological responses to the treponemal proteins that remain in bodily tissues following bacterial clearance during secondary stage (Salazar et al. 2002). Individuals progressing to tertiary stage immunologically fail to degrade and destroy treponemal bacteria, potentially due to reduced immunological competence (LaFond, Lukehart 2006). While the well-documented debilitating effects of high levels of exposure to mercury treatments may have played a role in this dynamic, degrading patient health and reducing immunological competence, the findings presented here cannot elucidate this issue.

6 Conclusion

Much like the origins and antiquity of syphilis, the question of whether mercury treatments 'killed or cured', exacerbating infection with syphilis or ameliorating it, have been intensively debated for centuries (Quétel 1990). Historical evidence on the question is ambiguous, no *in vitro* studies investigating the dynamic exist, and as demonstrated here, skeletal evidence cannot yet answer the question. While several intriguing trends were detected in this analysis, high background levels of oral pathology and high mortality in the sampled skeletal assemblages act as powerful confounders. Likewise, the evidence is inadequate to detect whether the debilitating effects of mercury treatment may have hindered immunological responses to syphilitic infection, empowering the effects of tertiary disease. Overall, this study cannot resolve whether mercury treatments represented a cruel hoax for the pocked or a salvation.

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