Biehler-Gomez Lucie (Orcid ID: 0000-0001-6674-7850)
Mattia Mirko (Orcid ID: 0000-0002-5445-9453)

Mercury poisoning in two patients with tertiary syphilis from the Ca' Granda hospital (17th century Milan)

Authors: Lucie Biehler-Gomez, PhD[1], Mirko Mattia, MA[1], Carlotta Sala, MA[1], Gaia Giordano, MS[2], Domenico Di Candia, PhD[2], Carmelo Messina, MD, PhD[3 4], Luca Maria Sconfienza, MD, PhD[3 4], Antonia Francesca Franchini, MD, PhD[5], Alessandro Porro[5], MD, PhD, Paolo Maria Galimberti, MA[6], Fabrizio Slavazzi, PhD[7], Cristina Cattaneo, MD, PhD[1]

[1] LABANOF, Laboratorio Di Antropologia E Odontologia Forense, Sezione Di Medicina Legale, Dipartimento Di Scienze Biomediche per La Salute, Università Degli Studi Di Milano, Milan, Italy

[2] Sezione Di Medicina Legale, Dipartimento Di Scienze Biomediche per La Salute, Università Degli Studi Di Milano, Milan, Italy

[3] Unità Operativa di Radiologia Diagnostica ed Interventistica, IRCCS Istituto Ortopedico Galeazzi, Milan, Italy;

[4] Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, Milan, Italy

[5] Dipartimento di Scienze Cliniche e di Comunità, Università Degli Studi Di Milano, Milan, Italy

[6] Servizio Beni Culturali, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[7] Dipartimento di Beni Culturali e Ambientali, Università Degli Studi Di Milano, Milan, Italy

Running title: Mercury poisoning with tertiary syphilis

Statements[1]

[1] **Statements**

Conflicts of interest: *none*

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/arcm.12721

Abstract

Syphilis was a widespread infectious disease in the 17th century Italy, commonly treated with mercury-based ointments and fumigations. Few reports exist on the analysis of abnormally high mercury levels in bone as a result of exposure to mercury-containing anti-syphilitic medicine. In this research, two crania recovered among the 2.9 million commingled bones resting under the crypt of the former hospital of the poor of Milan were submitted to pathological, radiological and toxicological analysis. The crania showed gummatous lesions characteristic of tertiary syphilis and ICP-MS analysis revealed over the double values of mercury in bone relative to that of the control sample. Archival documentation confirms the presence and use of mercury-based treatments in the pharmacy of the hospitals of Milan. Consequently, the individuals probably came into contact with mercury as a treatment for syphilis, confirming its medical use in the 17th century Milan and strengthening our knowledge of the history of medicine.

Introduction

Syphilis (from the Latin syphilis, idis) is a term coined in 1521 by the medical poet Girolamo Fracastoro (1476 or 1478-1533), that became known after the publication of his didactic poem *Syphilis sive de Morbo Gallico libri tres* in 1530. The protagonist of the poem, the shepherd Siphilus, grew unfaithful to the Sun god and as punishment, unclean ulcers appeared on his body. With this work, Fracastoro provided the first complete description of syphilis (Marcovecchio 1992). The term syphilis also refers to the Greek σιφλός (or shameful) (Blancardus 1683), as syphilis was in fact called the "disease of shame".

Venereal syphilis is one of the four treponemal diseases, a group of bacterial infections caused by the spirochetes *Treponema pallidum*, along with bejel, pinta and yaws. Syphilis, also referred to as "the great mimicker" because of its large array of clinical manifestations, progresses in three main clinical stages: primary syphilis subsists a few weeks and is classically marked by the formation of a painless chancre at the site of inoculation that heals swiftly,

Funding: *L'Oréal-UNESCO grant "For Women in Science" Italian edition awarded to Lucie Biehler-Gomez. The Ca' Granda project has been funded by the Lombardy Region for three years (Bando anno 2018 per la promozione di interventi di valorizzazione di aree archeologiche, siti iscritti o candidati alla lista UNESCO e itinerari culturali in Lombardia – artt. 17, 18 e 20 l.r. 25/2016*).

Correspondence to: Mirko Mattia, MA - LABANOF, Laboratorio di Antropologia e Odontologia Forense, Sezione di Medicina Legale, Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, Via Mangiagalli 37, 20133 Milan, Italy. E-mail: mirko.mattia@unimi.it

clearing locally the presence of the spirochetes. In secondary syphilis, the systemic dissemination of spirochetes induces after a few months an extensive skin rash as well as other possible symptoms, including malaise, weight loss, muscle aches, lymphadenopathy, meningitis, hepatitis and ocular inflammation (among others), which resolve spontaneously. The bacteria then enter an asymptomatic latent stage of variable duration and, if left untreated, their reactivation causes tertiary syphilis with multiple organ involvement, years to decades after the onset of infection (LaFond and Lukehart 2006; Peeling and Hook 2006; Ho and Lukehart 2011). At this point, the damage is primarily neurologic (with symptoms including vertigo, insomnia, emotional instability, memory impairment, hallucinations, personality changes, paresis and tabes dorsalis, and may progress to meningovascular syphilis), cardiovascular, or gummatous (i.e., benign necrotic nodular lesions) (LaFond and Lukehart 2006). Osteitis and periostitis may be seen in secondary syphilis (Ortner 2003) but characteristic bone changes are found in tertiary syphilis and consist in gummatous bone lesions in the cranium and long bones as well as extensive periosteal reactions on long bones (Hackett 1975).

The first recorded outbreak of syphilis occurred among the French troops of king Charles VIII in 1495 when entering Naples, leading the French to commonly refer to the disease as “le mal de Naples” and the Italians as “il mal franzese” or “morbo gallico” (or Gallic disease). By the 17th century, syphilis was a widespread and common condition in Italy, treated with various chemical and natural methods: ointments, potions and fumigation (Tognotti 2006). Ointments were composed of mercury, pork fat, sulfur, frankincense and myrrh (among other substances), and smeared on the joints several times a day (Micozzi and Santini 1993). There is mention from 1552 of the use of resin, bark and wood from a tall plant called *Guaiacum sanctum*, commonly known *lignum vitae* or *lignum sanctum*. Guaiacum treatments were administered externally in ointments by friction, and internally in potions. The plant was imported from the Dominican Republic and as the disease was thought to originate from that region, following the principle *ubi morbus, ibi remedius,* the cure must be sought in the place where the disease emerged. However, given its high costs, regulations from 1578 aimed to limit its usage (Cosmacini 1999; Eppenberger et al. 2017). Another tropical plant exported from the New World and adopted as an anti-syphilitic treatment is Sarsaparilla: roots of the plant of the genus *Smilax L.* were crushed to make a decoction (Branda Castiglioni 1668). Lastly, fumigation was a painful treatment used to stimulate the release of "corrupt moods" through salivation, sweat and diarrhea: the patient was enclosed in a wooden barrel suffused with smoke of cinnabar (i.e., red mercury sulphide), from which only the head came out (Micozzi and Santini, 1993).

The present case report will discuss the finding of two crania in the sepulchral chamber O of the Ca' Granda crypt with pathological bone signs of tertiary syphilis and the results of Inductively Coupled Plasma Mass Spectrometry (ICP-MS) to measure the levels of mercury remaining in the bones.

Materials and Methods

The Ca' Granda crypt

The *Ospedale Maggiore*, called "Ca' Granda" by the Milanese, was founded in 1456 by Francesco Sforza in the heart of the city. It became one of the main institutions in Milan in the 16th century and a model during the Renaissance for similar healthcare institutions across Italy and Europe because of its innovative and avant-garde free medical assistance to the poor, care of the ill and scientific activity. From 1637 to 1697, the crypt located below the church of the *Beata Vergine Annunciata* within the hospital grounds became the place of burial of the deceased patients of the hospital (Cosmacini 1999; Cosmacini 2001; Vaglienti and Cattaneo 2013; Agosti and Stoppa 2017, pp.67–71). As part of the Ca' Granda Project undertaken by the University of Milan and the Hospital Foundation for Cultural Heritage of the *Ospedale Maggiore*, campaigns of archaeological excavations of the sepulchral chambers of the crypt have revealed the presence of an estimated 2.9 million commingled bones. Their archaeological excavation and anthropological study of the remains are currently underway and organized by the University of Milan and LABANOF (*Laboratorio di Antropologia e Odontologia Forense* – Laboratory of Forensic Anthropology and Odontology).

Crania CG19O-706 and CG19O-1808

Both crania were found among the commingled remains of the sepulchral chamber O, dated through detailed historical records and archives of the hospital specifying its use from 1637 (date of creation of the sepulchral chambers) to 1697 (date of creation of a cemetery dedicated to the deceased patients of the hospital outside of the city walls).

Anthropological analysis

The crania were assessed for age-at-death, sex and population affinity using standard methods (Ubelaker 1978; Mann et al. 1991; Walker 2008; Hefner 2009; Hefner and Ousley 2014). Pathological analysis was performed following standard methods and references (Aufderheide and Rodríguez-Martín 1998; Ortner 2003; Waldron 2008; Buikstra 2019) and paleopathological diagnosis of tertiary syphilis following Hackett (1975; 1976).

Radiological imaging

The two crania were imaged using computed tomography (CT). Both crania were placed on the CT table by lying on the skull base, to ensure greater stability during scanning. As a consequence, the resulting scans were directly obtained on a coronal plane. CT scans were performed using a 64-slice CT system (Somatom Definition As, Siemens Medical Imaging, Erlangen, Germany). We used a standard protocol for brain CT acquisition, with the following parameters: field of view (FOV) = 200 mm, section thickness = 1 mm with a reconstruction interval of 0.625 mm, 120 kVp, 138 mA. CT images were post-processd with multiplanar reconstructions by applying different types of filters using the Siemens Syngo-via console.

Toxicological analyses

Samples of about 0.5 g were cut with a handsaw from the occipital bone of both crania. In addition, a sample collected from the diaphysis of a radius with an incompletely fused proximal epiphysis (age-at-death <17 years) from the same sepulchral chamber and without signs of syphilis was chosen as control specimen. The bone of a juvenile individual was selected as a control sample based on the assumption that, given his age, the individual would be less likely to have been treated with or exposed to mercury in his short lifetime (external contamination), while representing the normal physiological concentration of mercury in Modern era Milan.

The samples were prepared and processed as conventional matrices following Di Candia et al. (2020a; 2020b). Validation data, metal dosage and instrumental conditions were performed as per previous studies (Di Candia et al. 2020a; Di Candia et al. 2020b).

Results

Cranium CG19O-706

The cranium was complete, only a portion of the right zygomatic process was damaged post-mortem and the mandible was absent. White staining of taphonomic origin remained on the anterior portion of the frontal bone, even after careful washing. Anthropological estimations of sex (Walker 2008) and age-at-death (Mann et al. 1991) revealed a male of 20-24 years.

The frontal, parietal and right zygomatic bones showed osseous lesions. In particular, confluent clustered pits converging in focal points can be seen on the zygomatic and parietal bones, whereas destructive changes on the frontal bone are more severe, showing clustered pits, marked cavitation and bone erosions and in some discrete areas, nodular formation (Figs 1 and 2). Cortical destruction of the outer table is more extensive than that of the diploe, suggesting an inward progression of the lesions. The observed cranial lesions correspond to stages 6-7 of caries sicca (Hackett 1975).

Cranium CG19O-1808

The cranium was complete, and the mandible was absent. Both zygomatic processes were damaged post-mortem, and the left maxilla showed a break of continuity of the bone tissue, corresponding to a post-mortem fracture. The left parietal and occipital bones evidenced taphonomic bone cracking and flaking, comparable to stage 2 of weathering (Behrensmeyer 1978), as well as a large region of loss of substance in the posterior area of the left parietal bone (about 43mm in diameter) of post-mortem origin. Anthropological estimations of sex (Walker 2008) and age-at-death (Moorrees et al. 1963; Ubelaker 1978; Mann et al. 1991; Mincer et al. 1993) showed a female between 16 and 20 years old.

Pathological lesions were present on the frontal and parietal bones and are comprised of fine clusters of pits encircling large and deep osteolytic lesions varying from 5 to 36mm in diameter, breaching both the external table and the diploe (Figs 3 and 4). The greater extension of the lesion on the outer table indicates an inward progression of the lesions. Two lesions in particular, located at the glabella and on the right parietal bone, also perforated the internal table. The cranial lesions correspond to a stage 6 of caries sicca (Hackett 1975).

ICP-MS results

ICP-MS analyses revealed the following mercury values: cranium CG19O-706 1.41mg/kg, cranium CG19O-1808 0.64mg/kg, control sample 0.38mg/kg.

Discussion

The anthropological and paleopathological analyses of the two crania revealed two young adults, a male and a female, with deformative osteolytic and osteoblastic lesions on the external table of the frontal and parietal bones including bone destruction and nodular formation, consistent with stages 6-7 caries sicca.

The major differential diagnosis for osteolytic cranial lesions includes taphonomic alterations, Langerhans cell histiocytosis, leukemia, multiple myeloma, metastatic carcinoma, and syphilitic caries sicca. Taphonomic degradation of bone, and in particular osteophageous insects and roots, do not show a preference for specific areas of the skeleton and would not show nodular cavitation (Ortner 2003). Langerhans cell histiocytosis encompasses three clinical syndromes predominantly affecting children (Dorfman and Czerniak 1998). Bone lesions in leukemia present as diffuse superficial solitary pits (Rothschild et al. 1997). Multiple myeloma and metastatic carcinoma predominantly affect individuals over 40, with bone lesions emerging within the diploe and progressing toward the external and internal tables (Strouhal 1991; Ortner 2003; Biehler-Gomez et al. 2019a; Biehler-Gomez et al. 2019b; Biehler-Gomez

and Cattaneo 2021). In the present case, destructive bone changes showed an inward progression. The abundant blood supply to the bone marrow and periosteum tends to make these structures a good reservoir of infection. The causative organism is borne through the blood stream to all parts of the body. The disease is thus propagated via the blood stream, and the invasion of the periosteum or bone is to be expected. The lesions observed in this study correspond to caries sicca, a pathognomonic marker of tertiary syphilis (Hackett 1975). On the one hand, cranium CG19O-706 showed destructive bone lesions as well as nodular bone lesions, observable both macroscopically and on CT-scans, suggesting a more advanced stage of progression of the gummatous lesion. On the other hand, cranium CG19O-1808 exhibited more extensive and severe osteolytic destruction, with a higher number of cortically erosive lesions and a more widespread distribution, but no nodular formation was noted through gross macroscopic observation or radiological examination.

The *Ospedale Maggiore* was dedicated to the treatment of patients with curable or acute diseases and without financial means (Cosmacini 1992; Cosmacini 2001). By opposition, the *Ospedale del Brolo* was the Milanese hospital specialized in the care of syphilitic patients. However, as the Ca' Granda grew in notoriety, the Brolo lost in importance. The closure of the hospital was finally decided on December 12th, 1631, and all the patients hospitalized at the Brolo were progressively transferred to the Ca' Granda (Canetta 1887; Belloni 1958; Bevacqua 2004). Therefore, it is not surprising to find two cases with tertiary and long-standing syphilis in the crypt of the Ca' Granda as their presence could be the result of the closure of the *Ospedale del Brolo*. Another hypothesis could be that they presented to the hospital with acute symptoms (for instance, related to neurosyphilis or cardiovascular complications), which would explain the presence of two chronic long-standing cases of syphilis in the Ca' Granda. Moreover, these individuals may have been admitted to the hospital based on their social condition of poverty. Given the commingling situation in the sepulchral chambers, no other information could be extrapolated to clarify the reason for the presence of these two individuals in the Ca' Granda hospital.

The most common anti-syphilitic therapies in the modern era Italy were based on the use of mercury compounds (in the form of ointments by friction or fumigation) or phytopharmaceuticals derived from tropical plants imported from the New World, in particular Guaiacum and Sarsaparilla (in the form of decoction for ointments or potions) (Porro et al. 2009). In fact, discussions at the time divided physicians over the use of these two categories of medicine (Bellini 1934). The inventories of the hospital pharmacy of the main medical institutions of Milan (including the Ca' Granda and the *Ospedale del Brolo*), preserved today

in the archives of the former hospital of Milan, show that at the end of the years 1617 and 1623 were still present sarsaparilla, lignum sanctum, mercury ointment, ointment for the *morbo gallico*, "argento vivo" (or quicksilver, the common name for mercury) and "argento vivo ex(tint)o" (or extinct quicksilver, the name given to mercury that had been crushed until no metallic globule was visible) (Galimberti 2014). This finding shows that treatments based on mercury were indeed present in the pharmacy of the Brolo and Ca' Granda hospitals and used to treat syphilis in the 17th century Milan.

Background concentrations of mercury in trabecular and cortical tissues in long bones are set at 0.3 mg/kg and 0.08 mg/kg, respectively (Rasmussen et al. 2015). Generally, mercury levels are higher in trabecular bone tissues (Rasmussen et al. 2017). From the literature, it is not entirely clear what is the expected level of mercury in cranial bones, which is why the cranial samples were collected sampling both cortical and trabecular tissue. The mercury concentrations found in the syphilitic crania were over double the value found in the control sample (without bone signs of syphilis). The toxicological results obtained are in line with previous studies on dry bone mercury levels in syphilitic cases due to treatment (Tucker 2007; Rasmussen et al. 2008; Kepa et al. 2012). The bone tissue is composed of organic matrix, inorganic matrix, and water. The interaction between bone water and the blood stream is essential for metal ions incorporation. Thus, the ions are incorporated through the process of bone remodeling during primary or secondary mineralization. A fraction of mercury ions remains trapped inside the bone matrix and can be detected after death (Giordano et al. 2021). The high concentrations of the metal in the crania can be explained by its accumulation in the bone by contact absorption permeating from the mercury-containing ointment through the skin and diffusing to the tissues via the bloodstream (Kepa et al. 2012). The mercury levels detected in the control sample are consistent with normal mercury concentrations in humans and reflect the control values of previous research (Kepa et al. 2012). Cranium CG19O-706 showed over twice the concentration of mercury found in cranium CG19O-1808. Although a definitive explanation for this difference cannot be drawn, factors that may have had an influence on the bone concentrations of mercury include time, duration and quantity of metal exposure.

The treatment of mercury may not be associated to a specific hospital (i.e., the *Ospedale del Brolo* or the *Ospedale Maggiore*) as the pharmacy was shared within the district. Theoretically, and despite the knowledge that mercury-based remedies were present in the pharmacy of the hospitals at the time of hospitalization of both CG19O-706 and CG19O-1808, it is possible that these individuals may have been treated with mercury even before their admission to the hospital and then had required treatment at the Ca' Granda for other causes.

These findings suggest that a remedy with a mercury basis was applied in the two discussed cases and archival documents show that the pharmacy of the Ca' Granda and Brolo hospitals possessed large quantities of mercury-based treatments in the 17th century. Whether the institution administering the heavy metal as a medical treatment for syphilis was the *Ospedale del Brolo*, the Ca' Granda hospital or both, it cannot be confirmed, given that the patients of the Brolo hospital were transferred to the Ca' Granda after its closure. Even if the individuals had been patients at the Brolo hospital and were later admitted to the Ca' Granda, the finding of mercury ions can be associated to previous medical treatment for syphilis that remained entrapped in the bone matrix. Regardless of the impossibility to confirm where the mercury-based remedy occurred, these results attest of the use of mercury as a syphilitic treatment in the 17th century Milan, corroborating historical accounts (Micozzi and Santini 1993) and strengthening our knowledge of the history of medicine.

Conclusion

During archaeological excavations, two crania with extensive bone lesions were found in the sepulchral chambers of the crypt of the Ca' Granda hospital and submitted to anthropological, pathological, radiological and toxicological analyses. Results revealed two young individuals, a male and a female, with benign gummatous lesions typical of tertiary syphilis. Mercury levels showed very high concentrations of the metal in the crania with respect to the control sample. These results are consistent with a use of mercury as an anti-syphilitic remedy. Moreover, examination of the archives at the former hospital of the poor of Milan evidenced that mercury-based ointments and decoctions were present at the time of hospitalization of the two individuals of the present research, strengthening the possibility of mercury poisoning as part of an anti-syphilitic therapy. Very few studies investigating mercury levels in bones exist to test the possible use of the metal as a treatment against syphilis (or even leprosy). In this research, our results suggest that the individuals may have received mercury-based treatments for syphilis at the hospital, confirming that mercury was used as a treatment for syphilis in the 17th century Milan and strengthening our knowledge of the history of medicine.

Conflicts of interest: none

Funding: L'Oréal-UNESCO grant "For Women in Science" Italian edition awarded to LBG. The Ca' Granda project has been funded by the Lombardy Region for three years (*Bando anno 2018 per la promozione di interventi di valorizzazione di aree archeologiche, siti iscritti o candidati alla lista UNESCO e itinerari culturali in Lombardia – artt. 17, 18 e 20 l.r. 25/2016*).

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article.

References

Agosti, G., and Stoppa, J., 2017, *La Ca'Granda: da Ospedale a Università: atlante storico-artistico*, Vol. 6, Officina libraria.

Aufderheide, A. C., and Rodríguez-Martín, C., 1998, *The Cambridge Encyclopedia of Human Paleopathology*, Cambridge University Press, Cambridge, United Kingdom.

Behrensmeyer, A. K., 1978, Taphonomic and ecologic information from bone weathering, *Paleobiology*, **4**(2), 150–62.

Bellini, A., 1934, La venereologia e la sifilologia dal Rinascimento all'Epoca contemporanea, In *Storia della dermatologia e venereo-sifilologia in Italia*, 90–5, Cordani, Milan, Italy.

Belloni, L., 1958, La medicina a Milano fino al Seicento, In *Storia di Milano*, 624–6, Milan, Italy.

Bevacqua, Vi., 2004, L'Ospedale del Brolo, *La Ca' Granda*, **2**, 30–7.

Biehler-Gomez, L., Giordano, G., and Cattaneo, C., 2019a, Multiple myeloma bone lesions in skeletal remains: Report of two known cases from the 20th century CAL Milano Cemetery Skeletal Collection, *International Journal of Osteoarchaeology*(29), 101–7.

Biehler-Gomez, L., Giordano, G., and Cattaneo, C., 2019b, The overlooked primary: bladder cancer metastases on dry bone. A study of the 20th century CAL Milano Cemetery Skeletal Collection, *International Journal of Paleopathology*, **24**, 130–40.

Biehler-Gomez, L., and Cattaneo, C., 2021, *Interpreting Bone Lesions and Pathology for Forensic Practice*, Elsevier Academic Press.

Blancardus, S., 1683, *Lexicon Medicum graeco-latinum in quo termini totius artis Medicae, secundum Neotericorum placita, definiuntur vel circumscribuntur, Graeca item vocabula es ex originibus suis deducuntur*.

Branda Castiglioni, F., 1668, *De spiritibus, extractis, salibus, fucis […]*.

Buikstra, J. E., 2019, *Ortner's Identification of Pathological Conditions in Human Skeletal Remains*, Academic Press.

Di Candia, D., Biehler-Gomez, L., Giordano, G., and Cattaneo, C., 2020a, A case of thallium intoxication by walking in a field, *Forensic Science International: Reports*, **2**, 100102.

Di Candia, D., Muccino, E., Battistini, A., Boracchi, M., Gentile, G., and Zoja, R., 2020b, Thallium toxicity due to audultered infusion with thallium sulfate in eight members belonging to the same family nucleus: Autopsy findings and ICP-MS analysis (inductively

coupled plasma mass spectrometry) in a triple homicide, *Legal Medicine*, **42**, 101661.

Canetta, P., 1887, *Elenco dei benefattori dell'Ospedale Maggiore di Milano: 1456-1886*, L.F. Cogliati, Milan, Italy.

Cosmacini, G., 1992, La carità e la cura: l'Ospedale Maggiore di Milano nell'età moderna, *Ospedale Maggiore di Milano*.

Cosmacini, G., 1999, *La Ca'Granda dei milanesi: storia dell'Ospedale maggiore*, Laterza, Rome and Bari, Italy.

Cosmacini, G., 2001, *Biografia della Ca'Granda: uomini e idee dell'Ospedale maggiore di Milano*, Laterza, Rome and Bari, Italy.

Dorfman, H. D., and Czerniak, B., 1998, *Bone tumors*, Mosby.

Eppenberger, P., Galassi, F., and Rühli, F., 2017, A brief pictorial and historical introduction to guaiacum–from a putative cure for syphilis to an actual screening method for colorectal cancer, *British journal of clinical pharmacology*, **83**(9), 2118–9.

Galimberti, P. M., 2014, Monteggia e la salsapariglia: le cure per la sifilide nell'Ospedale Maggiore di Milano, In *Giovanni Battista Monteggia (Laveno 1762 – Milano 1815) e la chirurgia milanese del suo tempo. Atti del Convegno Internazionale, Laveno 1° dicembre 2012* (eds. G. Armocida, A. Frigo, and G. Mesumeci), 163–72, Merwan, Mesenzana, Italy.

Giordano, G., Biehler-Gomez, L., Seneci, P., Cattaneo, C., and Candia, D. Di, 2021, Detecting drugs in dry bone: a pilot study of skeletal remains with a post-mortem interval over 23 years, *International Journal of Legal Medicine*, 1–7.

Hackett, C. J., 1975, An introduction to diagnostic criteria of syphilis, treponarid and Yaws (treponematoses) in dry bones, and some implications, *Virchows Archiv A*, **368**(3), 229–41.

Hackett, C. J., 1976, *Diagnostic Criteria of Syphilis, Yaws and Treponarid (Treponematoses) and Some Other Diseases in Dry Bones*, Springer-Verlag, Berlin (Germany).

Hefner, J. T., 2009, Cranial Nonmetric Variation and Estimating Ancestry*, *Journal of Forensic Sciences*, **54**(5), 985–95.

Hefner, J. T., and Ousley, S. D., 2014, Statistical classification methods for estimating ancestry using morphoscopic traits, *Journal of Forensic Sciences*, **59**(4), 883–90.

Ho, E. L., and Lukehart, S. A., 2011, Syphilis: using modern approaches to understand an old disease, *The Journal of Clinical Investigation*, **121**(12), 4584–92.

Kepa, M., Kozłowski, T., Szostek, K., Drozd, A., Walas, S., Mrowiec, H., Stepańczak, B., Głab, H., and Grupa, M., 2012, Analysis of mercury levels in historical bone material from syphilitic subjects - Pilot studies (short report), *Anthropologischer Anzeiger*, **69**(3),

367–77.

LaFond, R. E., and Lukehart, S. A., 2006, Biological Basis for Syphilis, *Clinical Microbiology Reviews*, **19**(1), 29 LP – 49.

Mann, R. W., Jantz, R. L., Bass, W. M., and Willey, P. S., 1991, Maxillary suture obliteration: a visual method for estimating skeletal age, *Journal of Forensic Science*, **36**(3), 781–91.

Marcovecchio, E., 1992, *Dizionario etimologico storico dei termini medici*, Edizioni Festina Lente, Impruneta, Florence, Italy.

Micozzi, A., and Santini, G., 1993, L'omeopatia del mercurio, *Quaderni di ARIO*.

Mincer, H. H., Harris, E. F., and Berryman, H. E., 1993, The ABFO study of third molar development and its use as an estimator of chronological age, *Journal of Forensic Science*, **38**(2), 379–90.

Moorrees, C. F. A., Fanning, E. A., and Hunt Jr, E. E., 1963, Age variation of formation stages for ten permanent teeth, *Journal of dental research*, **42**(6), 1490–502.

Ortner, D. J., 2003, *Identification of Pathological Conditions in Human Skeletal Remains* 3rd ed., Smithsonian Institution Press, New York.

Peeling, R. W., and Hook, E. W., 2006, The pathogenesis of syphilis: the Great Mimicker, revisited, *The Journal of Pathology*, **208**(2), 224–32.

Porro, A., Franchini, A. F., Falconi, B., and Bock, G., 2009, Il viaggio delle malattie e dei loro rimedi, *Turismo e Psicologia. Rivista interdisciplinare di studi, ricerche e formazione*(2), 323–6.

Rasmussen, K. L., Boldsen, J. L., Kristensen, H. K., Skytte, L., Hansen, K. L., Mølholm, L., Grootes, P. M., Nadeau, M. J., and Flöche Eriksen, K. M., 2008, Mercury levels in Danish Medieval human bones, *Journal of Archaeological Science*, **35**(8), 2295–306.

Rasmussen, K. L., Skytte, L., Jensen, A. J., and Boldsen, J. L., 2015, Comparison of mercury and lead levels in the bones of rural and urban populations in Southern Denmark and Northern Germany during the Middle Ages, *Journal of Archaeological Science: Reports*, **3**, 358–70.

Rasmussen, K. L., Skytte, L., D'imporzano, P., Thomsen, P. O., Søvsø, M., and Boldsen, J. L., 2017, On the distribution of trace element concentrations in multiple bone elements in 10 Danish medieval and post-medieval individuals, *American journal of physical anthropology*, **162**(1), 90–102.

Rothschild, B. M., Hershkovitz, I., Dutour, O., Latimer, B. M., Rothschild, C., and Jellema, L. M., 1997, Recognition of leukemia in skeletal remains: Report and comparison of two cases, *American Journal of Physical Anthropology*, **102**(4), 481–96.

Strouhal, E., 1991, Myeloma multiplex versus osteolytic metastatic carcinoma: Differential diagnosis in dry bones, *International Journal of Osteoarchaeology*, **1**(3–4), 219–24.

Tognotti, E., 2006, *L'altra faccia di Venere. La sifilide in Italia dalla prima età moderna all'avvento dell'Aids*, Franco Angeli, Milan, Italy.

Tucker, F., 2007, Kill or cure ? The osteological evidence of the mercury treatment of syphilis in 17th - to 19th-century London, *London Archaeologist*, **11**(08), 220–4.

Ubelaker, D. H., 1978, *Human Skeletal Remain: Excavation, Analysis*, Aldire Publishering Company, Chicago.

Vaglienti, F., and Cattaneo, C., 2013, *La popolazione di Milano dal Rinascimento: fonti documentarie e fonti materiali per un nuovo umanesimo scientifico*, Edizioni Biblioteca Francescana, Milan, Italy.

Waldron, T., 2008, *Palaeopathology*, Cambridge University Press, Cambridge, United Kingdom.

Walker, P. L., 2008, Sexing skulls using discriminant function analysis of visually assessed traits, *American Journal of Physical Anthropology*, **136**(1), 39–50.

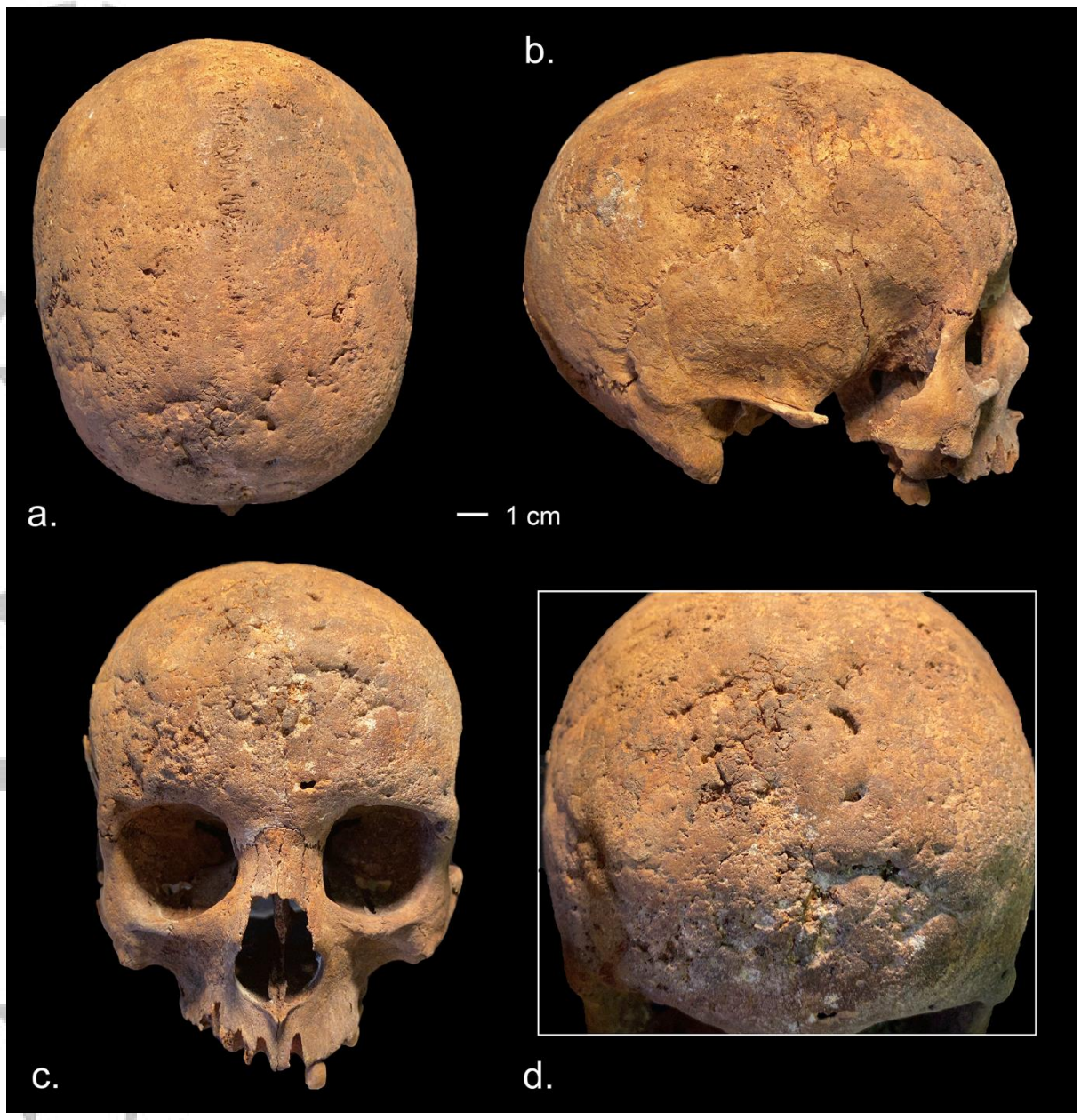

Figure 1: Cranium CG19O-706. a: norma verticalis; b: norma lateralis; c: norma frontalis; d: details of the osteolytic bone destruction and nodular formation on the frontal bone.

Figure 2: Coronal CT sections of cranium CG19O-706, note the osteolytic destruction of the external table (arrows) and the nodular formation around some osteolytic lesions (asterisks)

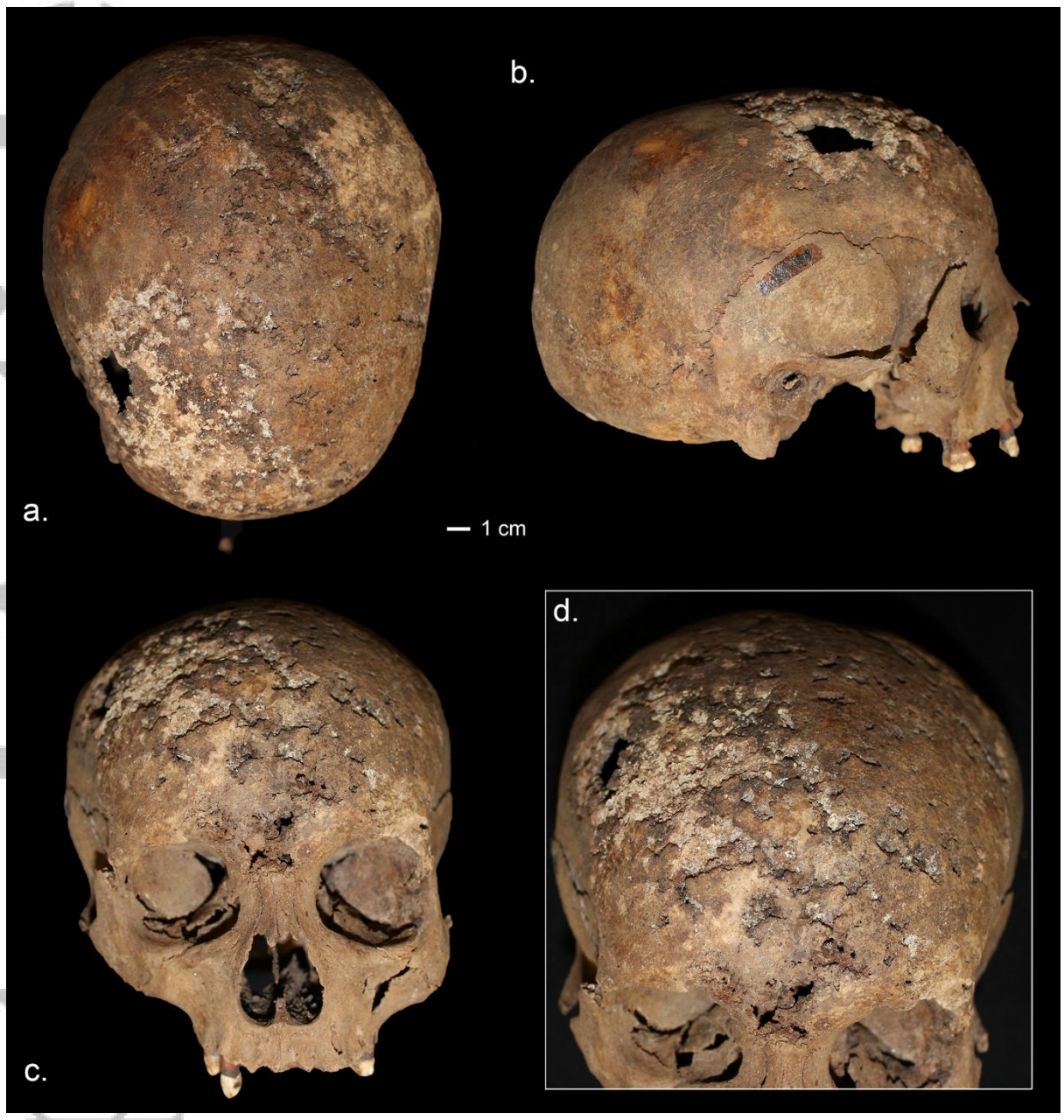

Figure 3: Cranium CG19O-1808. *a:* norma verticalis; *b:* norma lateralis; *c:* norma frontalis; *d:* details of the osteolytic bone destruction on the frontal bone.

Figure 4: Coronal CT sections of cranium CG19O-1808, note the extensive bone destruction of the external table and to a lesser extent, the diploë (arrows)