

REVIEW ARTICLE

Rheumatoid Arthritis: An Examination of Arthropathy in Antiquity

Taylor Eagle

Department of Archaeology and Anthropology, College of Arts and Science, University of Saskatchewan

ABSTRACT

Arthropathy – or joint disease – is the most common post-cranial pathological change found in skeletal remains, both today and in the past. Responsible for a great amount of pain and discomfort in modern populations, arthropathy continues to be highly researched in current clinical and paleopathological studies. Despite its frequency in an archaeological context, differentiation between various types of arthropathy can prove challenging. Rheumatoid arthritis (RA), for example, is historically underrepresented in the archaeological record. This may be due to a combination of the poor preservation of hand and foot bones (the locale where the bony alterations of RA begin), the non-specific appearance of RA lesions on bones, as well as other biases inherent in the bioarchaeological record. This article analyzes the origins and antiquity of RA, as well as some of the issues with differential diagnosis using clinical and paleopathological literature, including probable and potential cases.

Keywords: rheumatoid arthritis, arthropathy, paleopathology, bioarchaeology, spondyloarthropathy

INTRODUCTION

Joint disease, also known as arthropathy, is the most common post-cranial pathological skeletal change found in past and current populations (Aufderheide and Rodriguez-Martin 1998; Black et al. 2012; Bašić et al. 2017). Regardless of the prevalence of joint disease in skeletal remains however, rheumatoid arthritis (RA) is historically underrepresented in the archaeological record. Today, the worldwide prevalence has been estimated at 0.24 percent (Cross et al. 2014), with estimates of RA prevalence in the United States and Europe being typically higher at 0.5 to one percent (Myasoedova et al. 2010; Hunter et al. 2017). RA visibility in skeletal remains is hampered by the poor preservation of small hand and foot bones, where the bony alterations of the

disease begin. Additionally, the non-specific appearance of the lesions RA leaves, which are commonly confused for other arthropathies, has led to a lack of differential diagnoses indicating RA in the archaeological record (Black et al., 2012; Roberts and Manchester, 2005). Lastly, RA is three times more common in females than in males (Cross et al., 2014; Waldron, 2008; Roberts and Manchester, 2005). Due to differential preservation, female remains preserve less readily than those of their male counterparts due to gracility and sexually dimorphic bone density (Roberts and Manchester, 2005; Aufderheide and Rodriguez-Martin, 1998). This differential preservation means that if the disease was present in ancient populations, it is less likely to be found due to lack of preservation (Roberts and

Manchester, 2005; Waldron 2008). As a result, this paper examines the origins and antiquity of RA, as well as some of the issues with differential diagnosis using clinical and paleopathological literature, including probable and potential cases.

MEDICAL HISTORY OF OSTEOARTHRITIS (OA)

Joint disease is responsible for a great amount of pain and disability in modern populations (Waldron, 2008). Clinical studies reveal that degenerative joint disease or osteoarthritis (OA) was one of the earliest disorders to be identified and characterized clinically (Lieverse et al. 2007; Lieverse et al. 2016; Scott, 2019; Gay et al. 2019; Horak et al. 2011). Numerous Neanderthal remains dating from around 250,000 to 35,000 years ago show signs of osteoarthritis, suggesting that joint disease was present in prehistoric populations (Boule and Vallois, 1957). Some of the earliest written records of arthritic diseases lie in the Ebers and Edwin Smith papyri (Nuki and Simkin, 2006; Schwartz, 2006). Both of these examples date from around 1550 BC and reference writings of Imhotep from 1000 years earlier wherein the symptoms of osteoarthritis are described. This finding suggests that the concept of arthritis existed even in the early centuries of Egyptian civilization more than 4,500 years ago (Nuki and Simkin, 2006).

Today, in modern clinical samples, OA is most commonly seen in the knee, hip, and hands (Waldron, 2008). OA affects as much as forty percent of people aged seventy years or older, making it more prevalent than any other form of arthritis in modern populations (Valdes and Spector, 2011). This prevalence in modern samples helps to explain why OA is also found so frequently in ancient skeletal materials (Rogers et al. 1987).to be found due to lack of preservation (Roberts and Manchester, 2005; Waldron 2008). As a result, this paper examines the origins and antiquity of RA, as well as some of the issues with differential

diagnosis using clinical and paleopathological literature, including probable and potential cases.

MEDICAL HISTORY OF RHEUMATOID ARTHRITIS (RA)

Rheumatoid Arthritis (RA) was first recognized in French clinical literature in 1800, in Augustin Jacob Landré-Beauvais' (1772-1840) MD thesis. In this thesis, Landré-Beauvais described signs and symptoms of an unknown disease that he referred to as *goutte asthénique primitive* or primary asthenic gout (Landré-Beauvais, 1800; Landré-Beauvais, 2001; Tsoucalas and Sgantzios, 2017; Waldron, 2008). He described an affliction that was more common in women, involved many joints from the onset (notably in the hands and feet), and followed a chronic progression. Landré-Beauvais was confident that he had identified a new form of joint disease, and it is believed today that he was describing the signs and symptoms commonly associated with RA (Waldron, 2008).

The lack of RA recognition before the work by Landré-Beauvais signaled to some researchers and clinicians that RA was a relatively new disease, although, there have been suggestions that some historical figures such as Mary Queen of Scots (1542–1587), suffered from the disease (Wallace, 1964; Waldron, 2008). There is also paleopathological evidence for the antiquity of RA. Cases have been identified from the medieval and post-medieval periods of England, for instance, (Waldron, Rogers and Watt, 1994; Hacking, Allen and Rogers, 1994) and seventh to ninth-century France (Blondiaux et al. 1997). In addition to these numerous 'suspected' cases of RA in antiquity, see Table 1.

DIFFERENTIAL DIAGNOSIS OF ARTHROPATHIES

Joint diseases can be divided into those that proliferate – forming bone – and those that are erosive – taking bone away (Waldron,

2008). This section outlines the various joint diseases that can present similarly to RA in skeletal remains but reflect diverse underlying etiologies. The causal and diagnostic differences will be highlighted and discussed in the subsequent sections to better understand the difficulties in differentially diagnosing some of these diseases in antiquity, especially RA.

Degenerative Joint Disease: Osteoarthritis

Osteoarthritis (OA) is the most common joint disease found in modern and ancient populations. As a result of this disease prevalence, OA has been researched extensively, both in clinical and archaeological literature (Crubézy et al. 2002; Dürr et al. 2004; Gay et al. 2019; Horak et al. 2011; Lieveise et al. 2007; Lieveise et al. 2016). For the purposes of this article, I summarize the pathophysiology and etiology of this disease, while placing emphasis on skeletal diagnostic criteria and OA's classification as an erosive joint disease as these aspects pertain to OA's differentiation from RA and other arthropathies.

OA is a progressive joint disease that results from several complex co-occurring factors leading to subchondral bone changes and the loss of articular cartilage (for a thorough review of OA see Scott 2019). These factors include, but are not limited to, age, genetic predisposition, biological sex, obesity, trauma, and repetitive movement (Waldron, 2008). One or more of these factors will initiate a pattern of inflammatory events leading to the appearance of OA in the joint and ending in joint failure. The earliest visible manifestation of the disease is the loss of articular cartilage (Jurmain and Kilgore, 1995; Rogers and Waldron, 1995). As the disease progresses, bony changes develop as a result of this loss of protective articular cartilage including marginal osteophytes, the formation of new bone along the joint surface, pitting along the joint surface as a result of subchondral cysts,

changes in joint contour, and eburnation (Waldron, 2008).

Earlier research states that OA is a non-inflammatory joint disease of the elderly that overuse or mechanical stress places on particular synovial joints (Rogers and Waldron, 1995; Roberts and Manchester, 2005; Jurmain and Kilgore, 1995; Felson, 1988; Freedman et al. 2012). However, recent research recategorizes OA as an inflammatory joint disease that is known to affect individuals of varying age categories (Resch, 2003; Wood et al. 2013; Horak et al. 2011; Lieveise et al. 2016; Scott, 2019). Although OA is now categorized as an inflammatory joint disease, and inflammation does play a role in the early stages of the disease, OA does not cause inflammation to the same degree as other inflammatory arthropathies, such as RA, which will be discussed in the following sections (Resch, 2003; Wood et al. 2013). OA inflammation may be the result of trauma or other micro-injury (Black et al. 2012), with trauma severity being directly linked to OA risk factors (Wood et al. 2013; Resch, 2003; Jurmain and Kilgore, 1995).

It is also important to acknowledge that OA can be further differentiated into primary or secondary OA, depending on disease initiation. Primary OA affects joints with no known cause and is also referred to as idiopathic (Caroll, 2016). Secondary OA affects joints as a result of external trauma (injury) or disease (Capuano et al. 2015; Waldron, 2008). For example, secondary OA is often found in the joints of patients diagnosed with RA. Although OA is no longer considered a "wear and tear" degenerative disease of the elderly, due to the relatively low degree of inflammation in comparison to the other arthropathies, OA has been placed in its own distinct category.

Immune and Inflammatory Joint Disease: Rheumatoid Arthritis (RA)

Compared to OA, RA is rarely seen in the archaeological record (Roberts and Manchester, 2005). RA is a chronic inflammatory autoimmune disease in which the body's immune system mistakenly attacks the synovial joints of the body (Caroll, 2016). RA affects synovial joints symmetrically, beginning in the smaller joints of the hands and feet, before progressing to the larger joints of the body, specifically the hip, knee, shoulder, and elbow joints (Waldron, 2008). The symmetrical appearance of the disease is used to distinguish RA from other forms of arthritis, such as OA (Capuano et al. 2015; Caroll, 2016).

Clinically, it is understood that an immune complex is formed when the Rheumatoid Factor (RF) in the blood binds with immunoglobulin G, triggering an inflammatory response (Capuano et al. 2015). In cases where this RF is present in the blood, this is known as seropositive rheumatoid arthritis (Capuano et al. 2015). Today, RF in the blood is used as a diagnostic hallmark of the disease; however, cases of RA have been diagnosed with no traces of RF in the blood, both through physical examinations, or anti-CCP counts in the individual's blood. These circumstances are known as seronegative RA (Rogers, 2000).

RA affects approximately 0.24 percent of the world's population, with approximately fifty percent of adults being unable to work within 10 years of disease onset, making it an incredibly debilitating disease (Meng et al. 2017; Cross et al. 2014). Today, the cause of the formation of the immune complex and development of RA is unclear, although a genetic component appears to be likely. Additional risk factors for the development of RA include sex, age, and environmental and behavioral factors. RA is found in every sex, age, and ethnic group; however, an estimated seventy percent of those diagnosed are women (Oelzner et al. 2008). This means that women are three times more likely to be afflicted with

the disease. Women diagnosed with the disease are typically diagnosed between the ages of thirty and sixty. This has been attributed to female hormonal levels, which may contribute to developing RA (Oelzner et al. 2008). Men with RA are commonly diagnosed later in life, typically between forty-five and seventy years of age, with their overall risk increasing with age (Zias and Mitchell, 1996).

The etiology and pathogenesis of RA are not completely understood, but RA is known to involve the synovial joints and leads to progressive joint destruction. As RA progresses, chronic inflammation leads to a loss of bone density around the joints and throughout the body, causing thin, brittle bones (Bromley and Woolley, 1984; Hochberg, 2009; Mcgonagle et al. 1999; Schett and Firestein, 2010; Vis et al. 2013). Visible macroscopic lesions that accompany RA can differ depending on the affected joint size. In smaller joints, such as those of the hands and feet, subluxation is often present in life. This is seen in skeletal remains by the extension of the articular surfaces of joints and marginal lipping (Roberts and Manchester, 2005). In larger joints, osteoporosis is commonly seen in the articular ends of bones with resorption of the subchondral bone. Lytic foci are also found, representing the remnants of subchondral cysts (Roberts and Manchester, 2005).

Immune & Inflammatory Joint Disease: Psoriatic Arthritis (PsA)

Psoriasis is a common skin condition in modern populations, affecting approximately one to three percent of the general population, and about five percent of sufferers develop joint changes (Waldron, 2008; Roberts and Manchester, 2005; Rogers, 2000). Clinically, males and females are affected equally, and the average age of onset is between twenty and forty years. Although its cause is unknown, genetic, nutritional and infectious factors likely play a role in disease development (Szentpetery et al. 2016; Gladman et al. 2005).

Few definitive examples of PsA have appeared in the archaeological literature (Rogers, 2000; Pasero and Marson, 2006; Zias and Mitchell, 1996). Given the prevalence of PsA in modern populations, it is safe to assume that its obscurity in antiquity likely reflects misdiagnosis of this disease for different erosive joint diseases. Such misdiagnosis may be the result of missing hand or foot bones (where the distinctive lesions of the disease present), or non-specific lesions on other bones that cannot be distinguished from those of other conditions. Another difficulty in the diagnosis of PsA in skeletal remains has to do with the highly variable nature of the disease (Rogers, 2000).

PsA can affect any synovial joint in the body, and a variety of clinical subsets of PsA have been identified and described, depending on the number of affected joints and the distribution of bony joint changes (Waldron, 2008; Szentpetery et al. 2016). In the majority of clinical cases, PsA presents as an asymmetrical erosive arthropathy, or a symmetrical polyarthritis, similar to RA (Waldron, 2008; Roberts and Manchester, 2005; Szentpetery et al. 2016). Tendon and ligament attachments to bone are also commonly involved, causing new bone formation or the development of enthesophytes (Pasero and Marson, 2006; Waldron, 2008; Gladman et al. 2005). The phalanges of the hands and feet become eroded at the joint surface and margins. PsA is often identified by distinctive ‘pencil and cup’ deformities in the distal interphalangeal joints and new bone formation on the phalanges, metacarpals, metatarsals, carpals and tarsals of the hands and feet and around the joints (Roberts and Manchester, 2005). Additionally, there can be involvement of spine and sacroiliac joints with ossification of vertebral ligaments (Roberts and Manchester, 2005).

Immune & Inflammatory Joint Disease: Ankylosing Spondylitis (AS)

Ankylosing spondylitis (AS) is a progressive inflammatory disease affecting the axial

skeleton (Roberts and Manchester, 2005). It is the most common spondyloarthropathy recognized in skeletal remains (Waldron, 2008). Spondyloarthropathies are distinguished from other arthropathies as they involve inflammation of the joints of the spine. Although the prevalence estimates of AS vary from 0.25 percent to 4.5 percent in living populations, the frequency of the disease in the past has not yet been determined (Duyar, 2019). This disease of unknown etiology affects males two to three times more than females (Rogers, 2000), with an age of onset between fifteen and thirty five years (Roberts and Manchester, 2005). There are known genetic predispositions for the development of AS, including the HLA-B27 antigen (Wendling et al. 2018; Keat, 2012). Individuals with AS are at a fifty percent risk of passing the disease onto their children and are more commonly found among European and North American Indigenous populations (Vosse et al. 2013; Waldron, 2008).

AS is characterized by the involvement of the synovial and cartilaginous joints, entheses, and the erosion and fusion of multiple joints (Roberts and Manchester, 2005). Involvement and symmetrical fusion of both sacroiliac joints are considered to be the hallmark of the disease (Roberts and Manchester, 2005). The synovial joints of the spine begin to fuse, followed by the vertebral bodies, beginning in the lumbar spine and moving superiorly with no “skip lesions”, or normal vertebrae interspersed between those that are fused (Waldron, 2008). As the spine fuses, vertebral bodies remodel and lose their normal shape. In addition to the vertebral changes, there is marked ossification of the inter- and supraspinous ligaments, as well as the formation of vertebral syndesmophytes (Rogers and Waldron, 1995). As AS progresses, it causes the spine to fuse and is characterized by a ‘bamboo spine’ appearance, wherein the vertebral bodies become square and smooth, connected by the thin, vertically oriented syndesmophytes, giving the vertebral column a bamboo stalk

appearance (Rogers and Dieppe, 1990). Peripheral joints are additionally affected, with the hip, shoulder, knee, ankle, wrists, hands and feet being most common. The costovertebral joints may also be involved, where the ribs become fused to the vertebrae (Rogers and Waldron, 1995).

Immune Joint Disease: Diffuse Idiopathic Skeletal Hyperostosis (DISH)

Like AS, diffuse idiopathic skeletal hyperostosis (DISH) also affects the spine. However, it has specific bony changes elsewhere in the body that accompany the disease and distinguish it from AS (Rogers and Waldron, 1995). Statistically, men are affected slightly more than woman, and the average age of onset is typically fifty years or older. There is no known cause; however, clinically, DISH is often found in association with Type 2 diabetes and obesity (Roberts and Manchester, 2005; Waldron, 2008, Saffo et al. 2017; Khan et al. 2010; Cammisa and De Serio and Guglielmi, 1998). Physiologically, there is complete fusion of the spine, particularly in the thoracic region. The integrity of the vertebral body surfaces is maintained, as well as the joint spaces and apophyseal joints (Roberts and Manchester, 2005). Osteophytes are formed and produce a “dripping candlewax” appearance that is a hallmark of the disease (Resch, 2003). Cartilage also commonly ossifies, particularly around the cervical spine, and the ribs (Waldron, 2008). It is important to note that the fusion of four contiguous vertebrae is necessary for accurate diagnosis in an archaeological context (Roberts and Manchester, 2005).

Inflammatory Joint Disease: Septic Arthritis

Septic arthritis is often discussed in conjunction with tuberculosis, as it can be triggered by *Mycobacterium tuberculosis*; however, septic arthritis can be triggered by other pathogenic microorganisms such as *Streptococcus* or *Staphylococcus*, as well

(García-Arias, Balsa and Mola, 2011). The bacteria causing non-specific joint infections can spread one of two ways, through the blood to the joint cavity or from adjacent skin or bone to the joint (e.g., secondary to osteomyelitis) (Roberts and Manchester, 2005). Septic arthritis typically affects one joint – commonly the knee or hip – but other joints can be involved (Roberts and Manchester, 2005; Aceves-Avila et al. 1998). In a “healthy” joint, the synovial fluid nourishes the joint. In the case of septic arthritis, due to intra-articular pressure the cartilage is restricted of blood and nutrients, ultimately resulting in cartilage degeneration (García-Arias, Balsa and Mola, 2011).

Septic arthritis that is not identified in conjunction with tuberculosis (non-specific) is characterized by erosion of the bone marginal to the articular surface and often less destructive to the surfaces of affected joints (Rogers and Waldron, 1995; Roberts and Manchester, 2005). On the other hand, septic arthritis found in conjunction with tuberculosis commonly erodes the joint surfaces and primarily affects children more than adults (Rogers and Waldron, 1995). In general, septic arthritis is infrequently identified in the archaeological record, and differentiation between non-specific septic arthritis and septic arthritis found in conjunction with tuberculosis is incredibly difficult in skeletal remains (Waldron, 2008).

Metabolic Joint Disease: Gouty Arthritis

Gouty arthritis is considered much less common than some of the joint diseases that have been briefly summarized above. Archaeologically, there are no more than a few definitive cases of the disease in antiquity (Elliot-Smith and Dawson, 1924; Rogers, 2000; Rothschild and Heathcote, 1995). In modern clinical populations, gouty arthritis has a prevalence between one and three percent (Rogers, 2000; Roberts and Manchester, 2005; Yoo et al. 2011). Gouty arthritis is characterized by a

high level of blood uric acid, or “hyperuricemia”, which in turn is caused by reduced kidney function. This obstructed function results in an excess of uric acid production in the kidneys, which normally act to excrete uric acid (Heathcote, 1995; Waldron, 2008). Gouty arthritis appears to be a disease of lifestyle and is typically associated with excessive and chronic alcohol intake, a high protein and fatty diet, diabetes, and heart disease (Neogi, 2011). It is found twenty times more frequently in males than in females, and disease onset is typically initiated in individuals fifty years of age or older (Roberts and Manchester, 2005).

As the disease progresses, urate crystals form in the synovial fluid of joints, which ultimately leads to the inflammation and destruction of cartilage and subchondral bone (Messerli et al. 2011). The joints most commonly affected are those of the feet, hands, wrists, elbows, and knees with the first metatarsophalangeal joint being involved in ninety percent of all clinical cases (Neogi, 2011). Joints are affected asymmetrically, in contrast to RA, which is affected symmetrically. In addition to the morphological changes to the skeleton, urate crystals also form in tendons and ligaments (tissues associated with the joints) (Waldron, 2008). Accumulations of crystals, known as tophi, are also found in the fingertips and soles of the feet that appear as swollen, bulbous growths under the skin. (Roberts and Manchester, 2005; Messerli et al. 2011; Yoo et al. 2011).

DIAGNOSTIC CRITERIA FOR RA

The diagnostic criteria for RA in the paleopathological literature have evolved over time. Today the diagnosis of RA relies heavily on the presence of osteoporotic bone, subchondral bone thinning or porosity, resorptive (lytic) lesions caused by the presence of subchondral cysts, and the presence of osteophytes (Roberts and Manchester, 2005). RA is known to affect multiple joints simultaneously, beginning in the small joints of the hands and feet, before

moving into the larger joints of the body (e.g., shoulder, knee, elbow, and hip joints) (Roberts and Manchester, 2005; Waldron, 2008). RA is also known to present symmetrically in skeletal remains, meaning that the left and right sides of the body should be affected equally (Aufderheide and Rodriguez-Martin, 1998). This section presents all diagnostic criteria employed in the past and present day to diagnose RA in a paleopathological context.

Clinically, RA passes through a succession of three stages, the first being simple synovitis and proliferation of the synovial membrane, followed by inflammatory lesions which result in necrosis of the synovium and a more intense inflammatory response, lastly, tendon rupture, and joint deformity (Aufderheide and Rodriguez-Martin, 1998; Arnett et al. 1988; Bromley et al. 1984; Goldring et al. 2002). Despite its destructive potential, the progression of RA can be variable with some patients experiencing only mild oligoarticular illness of brief duration and minimal joint damage, and others having progressive polyarthritis with severe functional impairment and systemic manifestations (Caroll, 2016).

The diagnosis of RA in the clinical context of today relies heavily on patient history, physical examinations, and selected laboratory testing to identify characteristic features. An individual's medical history will focus heavily on joint pain, reported swelling, and the presence, location, and duration of morning stiffness (Schumacher, 1998). The longer symptoms persist, the more likely the diagnosis of RA becomes (Hochberg, 2009). A complete physical examination is utilized to assess for synovitis, including the presence and distribution of swollen or tender joints and limited joint motion (St. Clair et al. 2004). Additionally, repeated serologic analysis for anti-cyclic citrullinated peptide (anti-CCP) antibodies and rheumatoid factor (RF) are conducted (St. Clair et al. 2004). In a majority of patients, the presence of these blood markers is required

before a diagnosis of RA is established (Schumacher, 1998; Hochberg, 2009). Even in the modern clinical environment of today, diagnoses of RA are incredibly difficult. Since a clinical diagnosis of RA relies so heavily on serological analysis, it is understandable that diagnosing RA in skeletal remains, where these types of analyses are impossible, is complex and problematic.

Issues with Differential Diagnosis

One of the major issues surrounding paleopathological work lies in the fact that researchers are attempting to reconstruct the health conditions and life-pathways of individuals in past populations using inherently biased samples of skeletal remains (DeWitte and Stojanowski, 2015; Wood et al. 1992). This section will focus on the inherent difficulties that lie in attempting to differentially diagnose RA in an archaeological context, including the osteological paradox, the presence of non-specific lesions, issues with preservation, as well as gender, age, and social biases.

Osteological Paradox

In 1992, Wood et al. published “The Osteological Paradox: Problems of Inferring Prehistoric Health from Skeletal Samples”. This revolutionary work challenged bioarchaeologists to consider the impact of heterogeneous frailty, selective mortality, and demographic nonstationarity in their work when making “health” inferences of past populations (DeWitte and Stojanowski, 2015; Wood et al. 1992). For the purposes of this article, I place emphasis on two of the three determinations of the Osteological Paradox. First, heterogeneity in frailty, which is the suggestion that individuals are unequal concerning their susceptibility to different disease and stressors and their risks of death (Wood et al. 1992). This becomes an important consideration when discussing the differences in disease development in males and females, with females being diagnosed with RA three times more than males. By this

principle, the hidden heterogeneity of frailty would suggest that the higher chance of disease development in females will directly affect the rate of disease prevalence in the archaeological record. The heterogeneity of frailty must also be considered when discussing the age of disease onset. In females, the common disease onset lies between thirty and forty years of age, while males are typically diagnosed between forty five and fifty years of age. By this principle, the hidden heterogeneity of frailty would indicate that all individuals who develop RA in life would have lived long enough to first develop the disease, and secondly, lived long enough with the disease to exhibit the more significant lesions that would readily survive in a burial context.

The second determination of the Osteological Paradox can be applied when discussing the lack of RA diagnoses in the archaeological record is selective mortality. This is the suggestion that our data comes from samples of those who are already dead and are therefore biased representatives of the once-living populations (Wood et al. 1992). For example, the individuals bioarchaeologists observe in the archaeological record with RA are those who died at a stage of the disease that is visible on skeletal remains, therefore neglecting those who died in the early stages of the disease, and inherently erasing them from any research sample. By this standard, the examples of RA found in the archaeological record are inherently biased, and subsequently flawed. These two determinations put forth in the Osteological Paradox highlight some of the many reasons that data on the paleoepidemiology of RA in antiquity is incompletely understood.

Preservation

Taphonomic processes can mimic RA lesions or joint deformation, which contributes to the lack of differential diagnoses in the archaeological record (Waldron, 2008). Varying bone densities among men and women, the old and the young, and those with various

diseases directly influences the rates and severity in which taphonomic processes affect the individual's skeletal preservation. The burial conditions, including temperature, humidity, and soil context must be taken into account when observing skeletal degeneration in an archaeological context (Roberts and Manchester, 2005). Due to the chronic inflammatory processes that accompany RA, bones become more brittle and osteoporotic over a life course. This creates an environment wherein bones become more susceptible to different taphonomic process after death and burial. Even in cases where the bones are recovered correctly, their fragility before burial will only hasten the process of taphonomic destruction and negatively affect the preservation of the bones in a particular skeletal sample (Roberts and Manchester, 2005).

Biological Sex and Social Biases

Biological sex is critical in the discussion of RA prevalence in antiquity. As previously discussed, RA is three times more prevalent among females than males. Biologically, female bones are more gracile than their male counterparts (Waldron, 2008). This gracility is important to consider as this may account for the fact that before the 1800s, RA was rare in the clinical literature and non-existent in the archaeological record (Bašić et al. 2017). It can be argued that RA was just as prevalent in antiquity as it is today (i.e. approximately one percent of the general population), but the relative obscurity of the condition in the archaeological record is likely a result of the remains of those afflicted with the disease preserving less readily. This is due to gracility, bias in mortuary practice, and females being more likely to have metabolic issues that affect the density of bones.

Mortuary treatment as it relates to gender and social standing must also be considered when the preservation of skeletal remains is considered. Differences in mortuary treatments for males and females, children or adults,

the rich or the poor, and across cultures are likely to impact the likelihood of preservation for skeletal remains (Agarwal et al. 2011). It is also important to consider the fact that those who suffered from RA in antiquity would have been without the modern medical treatments populations have today, which help to slow degeneration and make life more bearable for those burdened with the disease. This lack of medical intervention makes the likelihood of a high mortality rate convincing (Rogers, 2000). Those who would have survived long enough to show more severe forms of degeneration would have likely been more affluent or prestigious members of society, wherein compassionate care seems more likely (Bašić et al. 2017). The notion of social stratification makes well-preserved skeletons part of a select number of individuals who can be accurately diagnosed with RA in antiquity (Agarwal et al. 2011), effectively rendering the “others” in society less visible.

PALEOPATHOLOGICAL EVIDENCE/LITERATURE

To properly consider RA in antiquity, one must delve into the paleopathological literature. The origin of RA in antiquity is heavily debated, with some researchers suggesting that RA originated in the New World (Rothschild, 2001), and others arguing that RA was present in the Old World, long before Columbus ventured to the New World in 1492 (Ciranni et al. 2002). Although there are difficulties that come with trying to accurately diagnose RA in archaeological populations, there have been probable or likely diagnoses made using lesion characteristics to distinguish RA from the more typically diagnosed OA and AS (Bašić et al. 2017; Ciranni et al. 2002; Rothschild 2001; Kilgore, 1989). This section is a brief literature review of known and presumptive cases of RA in antiquity based on the aforementioned diagnostic criteria. This will include four specific occurrences of highly probable RA in antiquity

as well as the inclusion of date ranges and locations for several other presumptive cases of RA in antiquity (Table 1). These specific examples allow for a discussion of prevalence of RA in the archaeological record,

which has historically been underrepresented in the paleopathological literature.

Name of Reported Case	Modern Location	Date	Age of Individual	Sex	Diagnostic Criteria
The “Braids Lady”	Tuscany, Italy	1550–1650 AD	50–55	Female	Symmetric lesions Marginal joint erosions Joint lesions of the hands Prox. Interphalangeal joint lesions Ulnar deviation Lesions of the feet Shoulder joint lesions Osteoporosis Marginal erosion
Kodiak Isle Woman	Alaska, USA	1200 AD	30–35	Female	Symmetrical Lesions Marginal Joint Erosion Possible case of JIA
Wood and Rothschild Late Woodlands Population	Ohio, USA	800–1100 AD	Various	2 females, 7 males	Symmetric lesions Proximal interphalangeal joint lesions Distal interphalangeal joint lesions Joint lesions of the carpus Joint metatarso-phalangeal lesions Detection of osteoporosis at x-ray examination Marginal erosion at x-ray examination
Kulubnarti’s Woman	Sudan	700–1450 AD	50+	Female	Distal interphalangeal joint lesions Joint lesions of the carpus Marginal erosion at x-ray examination
Bennike’s “Danish Man”	Denmark	400–800 AD	40–50	Male	Marginal joint erosions Distal interphalangeal joint lesions
Roman Period Man	Croatia	400–500 AD	30–50	Male	Complete ankylosis Highly osteoporotic Erosion of the joint surfaces Ankylosed hands and feet

					No new bone formation
Leden and Pearson — “Swedish Man A”	Sweden	2500–1900 BC	50+	Male	Symmetric lesions Joint lesions of the carpus Lesions of the elbows Lesions of the knees Shoulder joint lesions Detection of osteoporosis at x-ray examination Ankylosis
Leden and Pearson — “Swedish Man B”	Sweden	2500–1900 BC	30–50	Male	Lesions of the elbows Lesions of the feet Ankylosis
Rothschilds Tennessee population	Alabama, USA	3000–1000 BC	Various	6 females, 2 males	Symmetric lesions Joint lesions of the hand Proximal interphalangeal joint lesions Distal interphalangeal joint lesions Joint lesions of the carpus Lesions of the feet Joint metatarso-phalangeal lesions Joint atlanto-occiput lesions Detections of osteoporosis at x-ray examination Marginal erosion at x-ray examination

Table 1—*Examples of known and presumptive cases of RA in the paleopathological literature: (Modified from Ciranni et al. 2002)*

The “Braids Lady”

The first, and potentially the oldest, definitive case of RA is colloquially known as “The Braids Lady”. This case involves the mummified remains of a sixteenth century female found in the church of San Francesco in Arezzo (Tuscany). The completeness of these mummified remains allowed for the preservation of hand and foot bones, which showcased many diagnostic criteria for RA

(Ciranni and Fornaciari, 2000). The left hand revealed large erosions of the metacarpophalangeal joints of both the third and fourth fingers, metacarpophalangeal subluxation of both the third and fourth fingers and lateral deviation of all the fingers. The carpal bones showed marginal erosions, and the bases of the proximal phalanges were slightly flared (Ciranni and Fornaciari, 2000). The toes showed partially overlapped fibular deflection. Additionally, the body showed no involvement of the sacroiliac articulation (Ciranni and Fornaciari, 2000).

This particular work by Rosalba Ciranni and Gino Fornaciari (2000) utilized imaging techniques such as normal x-ray, x-ray by mammography, total body CT, and high-resolution CT. Microscopic examination and stereomicroscopy were also used to conclude that the “Braids Lady” was affected by RA. Many of the aforementioned diagnostic criteria supported a differential diagnosis of RA. The death of this individual occurred at the end of the sixteenth century, 200 years before the first clinical diagnosis by Landré Beauvais in the early 1800s (Ciranni and Fornaciari, 2000).

In addition to this research, Fontecchio and colleagues reconsidered the “Braids Lady” in 2012. Although, the macro and microscopic evaluation of the “Braids Lady” showcased numerous diagnostic criteria for RA, some researchers have since proposed AS as a more likely diagnosis. RA and AS are human leukocyte antigen (HLA)-linked autoimmune rheumatic diseases (ARDs). Their manifestations are associated with different susceptibility genes: specifically, HLA-DRB1 alleles for RA and HLA-B27 for AS. Genotype testing was done on DNA extracted and amplified from the mummified remains of the “Braids Lady”, and this genomic testing was able to completely exclude the HLA-B27 allele, and consequently the risk of this individual developing AS (Fontecchio et al. 2012). This investigation further confirms that RA existed, at least in Europe, 200 years before its first clinical description.

Kodiak Isle Woman

This example of a thirty to thirty five-year-old female from Kodiak Island, Alaska and dated to 1200 A.D. exhibits skeletal lesions that are strongly suggestive of RA. The skeletal lesions associated with the joints included porosity and destruction of joint surfaces, peri-articular cystic erosion, and hypertrophic bone formation (Ortner and Uthermole, 1981). The most severe manifestations occur in the knee, ankle, elbow, hand and foot bones. However,

there is minimal involvement of the spine. Interestingly, this case is postulated to be that of “juvenile rheumatoid arthritis” (JRA), often referred to clinically today as juvenile idiopathic arthritis (JIA) (Ortner and Uthermole, 1981). It is important to note that there is evidence of secondary OA found in some joints, notably the right shoulder and left knee of this individual.

This example from Kodiak Island provides additional support to the likelihood that rheumatoid arthritis has considerable antiquity. JIA is argued to be the most probable diagnosis of the skeletal lesions found in the skeletal remains (Ortner and Uthermole, 1981). A childhood age of onset would provide adequate time for the well-developed skeletal pathology seen in this case. However, the overlapping skeletal manifestations of secondary OA make a diagnosis of RA probable rather than certain (Ortner and Uthermole, 1981). Nonetheless, the Kodiak Isle Woman provides an important piece in the understanding of RA in the paleopathological literature.

Kulubnarti’s Woman

The second case is that of a possible case of RA in Sudanese Nubia. This research by Kilgore (1989) revolves around a case of erosive arthritis reported in a skeleton from Kulubnarti, Republic of Sudan (c. 100–1450 A.D.). This particular burial was exhumed in 1979 and included the skeleton of a female with an age of death estimated at fifty years or older (Kilgore, 1989). It is important to mention that in addition to suspected RA, this individual also exhibits moderate to severe osteoarthritis, specifically at the shoulders, elbows, hips, and knees. Erosion is present primarily in the metacarpophalangeal joints of the wrists (Kilgore, 1989). All the metacarpophalangeal joints of both hands show arthritis involvement and lesions were present on both the distal metacarpal and proximal phalangeal articular surfaces. Additional radi-

ographs revealed the presence of marked osteoporosis and erosions of the underlying trabecular bone of the second and third metacarpals, marginal to the joint surfaces on both the right and left hands (Kilgore, 1989). The involvement of the carpals also manifested as pitting and lytic lesions with some evidence of proliferative change. Erosive lesions were also noted bilaterally at the temporomandibular joint and on the trochlear surface of the right distal humerus (Kilgore, 1989). Both mandibular condyles exhibited complete destruction of the posterior half of the articular surface.

This case of suspected RA was suggested based on the involvement of the skeletal elements most frequently associated with RA, particularly the symmetrical involvement of the hands and feet, the lytic lesions on the articular surfaces of the affected joints, the presence of a thin fragile cortex and loss of subchondral bone, radiographic evidence of bone porosity, and ankylosis of two or more elements (Kilgore, 1989). The mixed pattern of proliferative and erosive joints change in this Nubian skeleton is interesting. While this analysis in no-way provides a conclusive diagnosis of RA, the pattern of involvement indicates RA as a possible diagnosis, especially given the involvement of the hands and wrists.

Roman Period Man

The final presumptive case of RA is that of an adult male skeleton in a Roman period burial, located in modern Croatia and dated to 400–500 AD. This individual was found to have one of the most severe presumptive cases of RA known in the medical or paleopathological literature (Bašić et al. 2017). Moreover, the remains were found in an upper-class burial chamber, allowing for the excellent preservation. The age at death was estimated at 30–50 years. Most of the bones had ankylosed, but those which had not fused showed complete erosion of the joint surfaces. RA was definitively diagnosed based on the erosion of the odontoid process, mandibular condyles,

distal humerus, proximal and distal ulna, as well as the highly ankylosed hand and foot bones (Bašić et al. 2017). There were notable ankyloses of the vertebrae and sacroiliac joint, which could point towards AS, but the lack of “typical” vertebral ankylosis, lack of typical “bamboo spine” appearance and new bone formation ultimately led to its exclusion (Bašić et al. 2017). This specific case is an example of a complete skeleton, excellently preserved and sheds light on the possible antiquity of RA. The severity of disease in this case further highlights the extensive care that would have been necessary for this individual to survive and offers evidence of differential care depending on social status, as mentioned previously.

CONCLUSION

Joint disease (arthropathy) is the most common post-cranial pathological skeletal change found in past and current populations. However, regardless of the prevalence of joint disease in skeletal remains, rheumatoid arthritis (RA) is historically underrepresented in the archaeological record. RA has many different skeletal manifestations, which can overlap with other conditions making diagnosis difficult. In addition, the recognition of RA in skeletal samples is hampered by issues of poor preservation of human remains in archaeological contexts, contributing to the underrepresentation in archaeological samples. Ultimately, the understanding of RA in antiquity is incomplete and continues to require more research to identify diagnostic criteria that can be used consistently in bioarchaeological research to better differentiate RA from other arthropathies. Future research should focus on identifying RA in modern surgical populations of known disease, to highlight the similarities between lesion types in modern and archaeological populations, building off previous work done by Rothschild et al. (1992), Scott (2019), and Rogers et al. (1990).

REFERENCES

- Aceves-Avila, F., S. Báez-Molgado., F. Medina., and A. Fraga. 1998. "Paleopathology in Osseous Remains from the 16th Century. A Survey of Rheumatic Diseases." *The Journal of Rheumatology* 25, no. 4: 776–782.
- Agarwal, Sabrina C. and Bonnie A. Glencross, eds. 2011. *Social Bioarchaeology*. 1st ed. Chichester, West Sussex: Wiley-Blackwell.
- Landré-Beauvais, Augustine Jacob. 1800. "Doit-on Admettre une Nouvelle Espèce de Goutte sous la Denomination Goutte Asthénique Primitive." MD Thesis, University of Paris.
- Arnett, Frank C., Steven M. Edworthy, Daniel A. Bloch, Dennis J. Mcshane, James F. Fries, Norman S. Cooper, Louis A. Healey et al. 1988. "The American Rheumatism Association 1987 Revised Criteria for the Classification of Rheumatoid Arthritis". *Arthritis and Rheumatism* 31, no. 3: 315–324.
- Aufderheide, Arthur, and Conrado Rodriguez-Martin. 1998. *The Cambridge Encyclopedia of Human Paleopathology*. 1st ed. Cambridge: Cambridge University Press.
- Bašić, Zeljana, Ivan Jerković, Ivana Kružić, and Simun Anđelinović. 2017. "Rich but Poor: Life in the Roman Period with Extreme Rheumatoid Arthritis." *Clinical Rheumatology* 36, no. 1: 235–238.
- Bennike, Pia. 1985. *Paleopathology of Danish Skeletons: A Comparative Study of Demography Disease and Injury*. Copenhagen: Akademisk Forlag..
- Black, Michael T., Pieter A. Folkens, and Tim D. White. 2012. *Human Osteology*, 3rd ed. Amsterdam: Elsevier/Academic Press.
- Blondiaux, Joël, Anne Cotten, Christian Fontaine, Catherine Hänni, Anne Bera, and René-Marc Flipo. 1997. "Two Roman and Medieval Cases of Symmetrical Erosive Polyarthropathy from Normandy: Anatomico-Pathological and Radiological Evidence for Rheumatoid Arthritis." *International Journal of Osteoarchaeology* 7, no. 5: 451–466.
- Boule, Marcellin, and Henri V. Vallois. 1957. *Fossil Men*. New York: Dryden Press.
- Bromley, Michael, and David E. Woolley. 1984. "Histopathology of the rheumatoid lesion." *Arthritis and Rheumatism* 27, no. 8: 857–863.
- Caroll, Matthew B. 2016. "The QuickDASH in the Assessment of Rheumatoid Arthritis Disease Activity." *Osteology and Rheumatology — Open Journal*, no. 1: 23–29.
- Cammisa, Mario, Antonio De Serio., and Giuseppe Guglielmi. 1998. "Diffuse Idiopathic Skeletal Hyperostosis." *European Journal of Radiology* 27, suppl. 1: S7–S11.
- Capuano, R., M. Chimenti, F. Dini, A. Domakoski, E. Martinelli, P. Conigliaro, R. Paolesse, C.D. Natale, R. Perricone, and A. Bergamini. 2017. "FRI0012 Role of Volatile Compounds Released by Synovial Fluid in the Diagnosis of Osteoarthritis and Rheumatoid Arthritis of the Knee Joint." *Annals of the Rheumatic Diseases* 76, no. S2: 484–484.
- Chhem, Rethy K., Pierre Schmit, and Clement Faurè. 2004. "Did Rameses II really have ankylosing spondylitis? A reappraisal." *Canadian Association of Radiologists' Journal* 55, no. 4: 211–217.

- Ciranni, Rosalba, Francesca Garbini, Emanuele Neri, L. Melai, Laura Giusti, Gino Fornaciari. 2002. "The "Braids Lady" of Arezzo: A case of rheumatoid arthritis in a 16th century mummy." *Clinical and Experimental Rheumatology* 20, no.6: 745–752.
- Cross, Marita, Emma Smith, Damian Hoy, Loreto Carmona, Frederick Wolfe, Theo Vos, Benjamin Williams et al. 2014. "The Global Burden of Rheumatoid Arthritis: Estimates from the Global Burden of Disease 2010 Study." *Annals of the Rheumatic Disease* 73, no. 7: 1316–1322.
- Crubézy, Eric, Jérôme Goulet, Bruzek Jaroslav, Jelinek Jan, Rougé Daniel, and Ludes Bertrand. 2002. "Epidemiology of Osteoarthritis and Enthesopathies in a European Population Dating Back 7700 Years." *Joint Bone Spine* 69, no. 6: 580–588.
- DeWitte, Sharon, and Chrisopher Stojanowski. 2015. "The Osteological Paradox 20 Years Later: Past Perspectives, Future Directions." *Journal of Archaeological Research* 23, no. 4: 397–450.
- Dürr, Hans, Heiner Martin, Christoph Pellengahr, Marcus Schlemmer, Markus Maier, and Volkmar Jansson. 2004. "The Cause of Subchondral Bone Cysts in Osteoarthritis." *Acta Orthopaedica Scandinavica* 75, no. 5: 554–558.
- Duyar, İzzet. 2019. "A Case of Ankylosing Spondylitis from the Excavations at Kılıçlı Necropolis (Sinope, Northern Turkey) and its Implications on the Antiquity of the Disease in Anatolia." *International Journal of Osteoarchaeology* 29, no. 6: 1100–1108.
- Elliot-Smith, Grafton., and Warren R. Dawson. 1924. *Egyptian Mummies*. New York, Dial Press.
- Entezami, Pouya, David Fox, Phillip Clapham, and Kevin Chung. 2011. "Historical Perspective on the Etiology of Rheumatoid Arthritis." *Hand Clinics* 27, no. 1: 1–10.
- Feldtkeller, Ernst, Ernst-Martin Lemmel, and Anthony S. Russell. 2003. "Ankylosing Spondylitis in the Pharaohs of Ancient Egypt." *Rheumatology International* 23: 1–5.
- Felson, David. 1988. "Epidemiology of Hip and Knee Osteoarthritis." *Epidemiologic Reviews* 10: 1–28.
- Fontecchio, Gabriella, Luca Ventura, and Maria Poma. 2012. "Further Genomic Testing and Histological Examinations Confirm the Diagnosis of Rheumatoid Arthritis in an Italian Mummy from the 16th Century." *Annals of the Rheumatic Diseases* 71, no. 4: 630.
- Freedman, Julia, Clare Milner, Songing Zhang, and Xiaopeng Zhao. 2012. "The Influence of Body Mass Index on Biomechanical Risk Factors for Osteoarthritis during Walking." *Journal of General Internal Medicine* 27: 689.
- García-Arias, Miriam, Alejandro Balsa, and Emilio Martin Mola. 2011. "Septic Arthritis." *Best Practice and Research Clinical Rheumatology* 25, no. 3: 407–421.
- Gay, Chloe, Candy Guiguet-Auclair, Charline Mourgues, Laurent Gerbaud, and Emmaniel Coudeyre. 2019. "Physical Activity Level and Association with Behavioral Factors in Knee Osteoarthritis." *Annals of Physical and Rehabilitation Medicine* 62, no. 1: 14–20.
- Gladman, Dafna, Christoff Antoni, Phillip Mease, Debroah Clegg, and Peter Nash. 2005. "Psoriatic Arthritis: Epidemiology,

- Clinical Features, Course, and Outcome.” *Annals of the Rheumatic Diseases* 64, suppl. 2: ii14–ii17.
- Goldring, Steven, and Ellen Gravallesse. 2002. “Pathogenesis of Bone Lesions in Rheumatoid Arthritis.” *Current Rheumatology Reports* 4, no. 3: 226–231.
- Gregory Tsoucalas, and Markos Sgantzos. 2017. “Primary Asthenic Gout by Augustin-Jacob Landre-Beauvais in 1800: Is this the First Description of Rheumatoid Arthritis?” *Mediterranean Journal of Rheumatology* 28, no. 4: 223–226.
- Hacking, Peter, Tim Allen, and Juliet Rogers. 1994. “Rheumatoid Arthritis in a Medieval Skeleton.” *International Journal of Osteoarchaeology* 4: 251–255.
- Hochberg, Marc. 2009. *Rheumatoid Arthritis*. Philadelphia, PA: Mosby/Elsevier.
- Horak, Zdenek, Petr Kubovy, Martin Stupka, and Jitka Horakova. 2011. “Biomechanical Factors Influencing the Beginning and Development of Osteoarthritis in the Hip Joint.” *Wiener Medizinische Wochenschrift* 161, no. 19–20: 486–492.
- Hunter, Theresa, Natalie Boytsov, Xiang Zhang, Krista Schroeder, Kaleb Michaud, and Andre Araujo. 2017. “Prevalence of Rheumatoid Arthritis in the United States Adult Population in Healthcare Claims Databases, 2004–2014.” *Rheumatology International* 37, no. 9: 1551–1557.
- Inoue, Koji., Wataru Takigawa, M. Sato, M. Kumagai, Yukio Dodo, and K. Katayama. 2005. “A Possible Case of Spondyloarthropathy in a Prehistoric Japanese Skeleton.” *International Journal of Osteoarchaeology* 15, no. 3: 186–195.
- Jurmain, Robert D., and Lynn Kilgore. 1995. “Skeletal Evidence of Osteoarthritis: a Palaeopathological Perspective.” *Annals of the rheumatic diseases* 54, no. 6: 443.
- Keat, Andrew. 2010. “Ankylosing Spondylitis.” *Medicine* 38, no. 4: 185–189.
- Khan, Abdul Qayyum, Keshav Gupta, Javed Jameel, and MKA Sherwani. 2010. “Diffuse Idiopathic Skeletal Hyperostosis.” *Journal of Clinical Orthopaedics and Trauma* 1, no. 1: 47–48.
- Kilgore, Lynn. 1989. “Possible Case of Rheumatoid Arthritis from Sudanese Nubia.” *American Journal of Physical Anthropology* 79, no. 2: 177–183.
- Landré-Beauvais, Augustine Jacob. 2001. “The First Description of Rheumatoid Arthritis. Unabridged Text of the Doctoral Dissertation Presented in 1800.” *Joint Bone Spine* 68, no. 2: 130–143.
- Leden, I., E Pearson and O Persson. 1986. “Aspects of the History of Rheumatoid Arthritis in the Light of Recent Osteo-Archaeological Finds.” *Scandinavian Journal of Rheumatology* 17, no. 5: 341–352.
- Lieverse, Angela, Andrzej Weber, Vladimir Ivanovich Bazaliiskiy, Olga Ivanova Gorionova, and Nikolai Aleksandrovich Savel’ev. 2007. “Osteoarthritis in Siberia’s Cis-Baikal: Skeletal Indicators of Hunter-Gatherer Adaptation and Cultural Change.” *American Journal of Physical Anthropology* 132, no. 1: 1–16.
- Lieverse, Angela, Brianna Mack, Vladimir Ivanovich Bazaliisky, and Andrzej Weber. 2016. “Revisiting osteoarthritis in the Cis-Baikal: Understanding Behavioral Variability and Adaptation Among Middle Holocene Foragers.” *Quaternary International* 405, part. B: 160–171.
- Mcgonagle, Dennis, Phillip Conaghan, Phillip

- O'Connor, Wayne Gibbon, Michael Green, Richard Wakefield, et al. 1999. "The Relationship Between Synovitis and Bone Changes in Early Untreated Rheumatoid Arthritis: A Controlled Magnetic Resonance Imaging Study." *Arthritis and Rheumatism* 42, no. 8: 1706–1711.
- Messerli, Franz, Harikrishna Makani, and Dan Halpern. 2011. "Gout." *The New England Journal of Medicine* 364, no.19: 1876–1877.
- Myasoedova, Elena, Cynthia Crowson, Hilal Maradit Kremers, Terry M. Therneau, and Sherine Gabriel. 2010. "Is the Incidence of Rheumatoid Arthritis Rising?: Results from Olmsted County, Minnesota, 1955–2007." *Arthritis & Rheumatism* 62, no. 6 :1576–1582.
- Neogi, Tuhina. 2011. "Gout: Disease/Disorder Overview." *The New England Journal of Medicine* 364, no. 5: 443–452.
- Nuki, George, and Peter Simkin. 2006. "A Concise History of Gout and Hyperuricemia and their Treatment." *Arthritis Research and Therapy* 8, no. 1: S1.
- Oelzner, Peter, Antje Schwabe, Gabriele Lehmann, Thorsten Eidner, Sybille Franke, Gunter Wolf, and Gert Hein. 2008. "Significance of Risk Factors for Osteoporosis is Dependent on Gender and Menopause in Rheumatoid Arthritis." *Rheumatology International* 28, no. 11: 1143–1150.
- Ortner, Donald, and Charles Utermohle. 1981. "Polyarticular Inflammatory Arthritis in a Pre-Columbian Skeleton from Kodiak Island, Alaska, U.S.A." *American Journal of Physical Anthropology* 56, no. 1: 23–31.
- Pasero, Giampiero, and Piero Marson. 2006. "The Antiquity of Psoriatic arthritis." *Clinical and Experimental Rheumatology* 24, no. 4: 351–353.
- Rajić Šikanjić, Petra, and Dejana Vlak. 2010. "Autoimmune Joint Diseases in Late Medieval Skeletal Sample from Croatia." *Rheumatology International* 30, no. 3: 349–356.
- Resch, Heinrich. 2008. "Pathophysiology of Rheumatoid Arthritis and Other Disorders." In *Radiology of Osteoporosis*, edited by Stephan Grampp, 25–33. Berlin: Springer.
- Roberts, Charlotte, and Kieth Manchester. 2005. *The Archaeology of Disease*. 3rd ed., New York: Cornell University Press.
- Rogers, Juliet, and Paul Dieppe. 1990. "Skeletal Paleopathology and the Rheumatic Diseases—Where are we Now?" *Annals Of The Rheumatic Diseases* 49, no. 11: 885–886.
- Rogers, Juliet, Iain Watt, and Paul Dieppe. 1990. "Comparison of Visual and Radiographic Detection of Bony Changes at the Knee Joint." *British Medical Journal* 300, no. 6721: 367–368.
- Rogers, Juliet and, Tony Waldron. 1995. *A Field Guide to Joint Disease in Archaeology*. John Wiley and Sons, Inc, New York.
- Rogers, Juliet, Tony Waldron, Paul Dieppe, and I Watt. 1987. "Arthropathies in Palaeopathology: The Basis of Classification According to Most Probable Cause." *Journal of Archaeological Science* 14, no. 2: 179–193.
- Rogers, Juliet, and Tony Waldron. 2001. "DISH and the Monastic Way of Life." *International. Journal of Osteoarchaeology* 11, no. 5: 357–65.

- Rogers, Juliet. 2000. "The Palaeopathology of Joint Disease." In *Human Osteology in Archaeology and Forensic Science*. Edited by M. Cox and S. Mays, 163–182. London, Greenwich Medical Media.
- Rothschild, Bruce. 2001. "Rheumatoid Arthritis at a Time of Passage". *The Journal of Rheumatology* 28, no. 2: 245–250.
- Rothschild, Bruce and G. Heathcote. 1993. "Characterization of Gout in a Skeletal Population Sample: Presumptive Diagnosis of a Micronesian Sample." *American Journal of Physical Anthropology* 98: 519–25.
- Rothschild, Bruce M., Robert J. Woods, Christine Rothschild, and Jenő I. Sebes. 1992. "Geographic Distribution of Rheumatoid Arthritis in Ancient North America: Implications for Pathogenesis." *Seminars in Arthritis and Rheumatism* 22, no. 3, 181–187.
- Rothschild, Bruce, Robert Woods, and Wade Ortel. 1990. "Rheumatoid Arthritis "In the Buff": Erosive Arthritis in Defleshed Bones." *American Journal of Physical Anthropology* 82, no. 4: 441–449.
- Saffo, Zaid, and Paul Pulice. 2017. "Diffuse Idiopathic Skeletal Hyperostosis." *The Journal of the American Osteopathic Association* 117, no. 2: 138.
- Saleem, Sahar, and Zahi Hawass. 2014. "Ankylosing Spondylitis or Diffuse Idiopathic Skeletal Hyperostosis in Royal Egyptian Mummies of 18th –20th Dynasties? Computed Tomography and Archaeology Studies." *Arthritis and Rheumatology (Hoboken, N.J.)* 66, no. 12: 3311–6.
- Schett, Georg, and Gary Firestein. 2010. "Mr Outside and Mr Inside: Classic and Alternative Views on the Pathogenesis of Rheumatoid Arthritis." *Annals of the Rheumatic Diseases* 69, no. 5: 787–789.
- Schumacher, Ralph H., 1998. "Clinical Diagnosis of Rheumatoid Arthritis." *Drugs Of Today* 34, no. 3: 225–229.
- Schwartz, Stephan. 2006. "Disease of Distinction." *Explore: The Journal of Science and Healing* 2, no. 6: 515–519.
- Scott, Maryann. 2019. "The Physiopathology of Osteoarthritis: Applying Bioarchaeological Measures to a Modern Surgical Population." Masters Thesis. University of Saskatchewan.
- St. Clair, William E., David Pisetsky, and Barton Haynes. 2004. *Rheumatoid Arthritis*. Philadelphia: Lippincott Williams and Wilkins.
- Szentpetery, Agnes, Eric Heffernan, Muhammad Haroon, Mark Kilbane, Phil Gallagher, Malachi McKenna, and Oliver FitzGerald. 2016. "Striking Difference of Periarticular Bone Density Change in Early Psoriatic Arthritis and Rheumatoid Arthritis Following Anti-Rheumatic Treatment as Measured by Digital X-ray Radiogrammetry." *Rheumatology* 55, no. 5: 891–896.
- Uhlig, Till. 2011. "The History of Rheumatoid Arthritis." *European Musculoskeletal Review* 6, no. 3: 145–147.
- Valdes, Ana, and Tim Spector. 2010. "The Clinical Relevance of Genetic Susceptibility to Osteoarthritis." *Best Practice and Research Clinical Rheumatology* 24, no. 1: 3–14.
- Vis, M., W. Güler-Yüksel, and W. Lems. 2013. "Can Bone Loss in Rheumatoid Arthritis be Prevented?" *Osteoporosis International* 24, no. 10: 1–13.

- Waldron, Tony. 2008. *Palaeopathology*. Cambridge: Cambridge University Press.
- Waldron, Tony, Juliet Rogers, and Iain Watt. 1994. "Rheumatoid Arthritis in an English Post-Medieval Skeleton." *International Journal of Osteoarchaeology* 4, no. 2: 165–167.
- Wallace, Stanley. 1964. *A Short History of the Gout and the Rheumatic Diseases*. Los Angeles, University of California Press.
- Weida, Meng, Zaihua Zgu, Xia Jiang, Chun Lai Too, Steffen Uebe, Maja Jagodic, et al. 2017. "DNA Methylation Mediates Genotype and Smoking Interaction in the Development of Anti-Citrullinated Peptide Antibody-Positive Rheumatoid Arthritis." *Arthritis Research and Therapy* 19, no. 1: 71.
- Wendling, Daniel, Clément Prati, and Joachim Sieper. 2018. "Disease Activity in Ankylosing Spondylitis: The Global Therapeutic Target." *Annals of the Rheumatic Diseases* 77, no. 8: 1095–1096.
- Wood, James, and Mark Cohen. 1992. "The Osteological Paradox." *Current Anthropology* 33, no. 4: 343–370.
- Wood, Alexander MacDonald, Timothy Brock, Kieran Heil, Rachel Holmes, and Axel Weusten. 2013. "A Review on the Management of Hip and Knee Osteoarthritis." *International Journal of Chronic Diseases* 2013, no. 28: 10–20.
- Woods, Robert, and Bruce Rothschild. 1988. "Population Analysis of Symmetrical Erosive Arthritis in Ohio Woodland Indians (1200 years ago)." *The Journal of Rheumatology* 15, no. 8: 1258–1263.
- Yoo, Han-Gyul, Sang Il Lee, Han-Jung Chae, Seoung Ju Park, Yong Chul Lee, and Wan-Hee Yoo. 2011. "Prevalence of Insulin Resistance and Metabolic Syndrome in Patients with Gouty Arthritis." *Rheumatology International* 31, no. 4: 485–491.
- Zias, Joe, and Piers Mitchell. 1996. "Psoriatic Arthritis in a Fifth-Century Judean Desert Monastery." *American Journal Of Physical Anthropology* 101, no. 4: 491–502.