Published in final edited form as:

Hand Clin. 2011 February ; 27(1): 1–10. doi:10.1016/j.hcl.2010.09.006.

Historical Perspective on the Etiology of Rheumatoid Arthritis

Pouya Entezami, BS¹, David A. Fox, MD², Philip J. Clapham, BS¹, and Kevin C. Chung, MD, MS³

¹Research Assistant, Section of Plastic Surgery, University of Michigan Health System

²Professor of Internal Medicine, Division Chief of Rheumatology, University of Michigan Medical School

³Professor of Surgery, Section of Plastic Surgery, Assistant Dean for Faculty Affairs, University of Michigan Medical School

INTRODUCTION

Modern advances in the medical treatment of rheumatoid arthritis (RA) have greatly alleviated patients' symptoms. Development of even more effective remedies could be spurred by discovery of the disease's etiology, but the cause of RA remains poorly understood and may involve a combination of genetic, environmental and stochastic factors. Clues to the etiology of a disease can potentially be obtained from consideration of its evolution during the development of human civilization. From a historical perspective evidence for the existence of RA in various eras and locations has come from analyses of ancient texts, Renaissance artwork and, more recently, post-mortem remains of hundreds of exhumed skeletons. Unfortunately much of this research has lacked the rigor of investigative scientific principles and its findings remain very controversial. Contributions of historical analyses to the development of a cogent etiological theory of RA have been limited to date.

From this variety of research methodologies several competing theories concerning the genesis of RA have emerged. One school of thought is that RA is a disease of the modern era and that its pathogenesis is a result of an environmental or genetic stimulus that did not exist in ancient times. A second theory posits that RA existed amongst our ancient ancestors but had never been definitively characterized. Most recently, a hybrid theory has arisen which holds that RA originally developed in indigenous populations in North America and spread to European populations through the travel of persons and/or goods. We have found that most of the literature on the history of RA can be organized into one of three categories according to which theory it supports, which we have named: the Recent Origin, Ancient Origin, and New World to Old World views.

Our aims are to analyze this literature with respect to the types and conclusions of the research that has been conducted, to present the major points of evidence and the conclusions that have been drawn, and to trace the evolution of the three historical theories of RA. We combine a comprehensive overview of paintings and paleopathological investigations (the study of ancient diseases through fossilized remains) with consideration of contemporary immunological and genetic studies.

THE HISTORY OF CLINICAL DESCRIPTIONS OF RHEUMATOID ARTHRITIS

The first description of RA acknowledged by modern medicine is found in the dissertation of Augustin Jacob Landré-Beauvais from the year 1800. Landré-Beauvais was only 28 years old and a resident physician at the Salpêtrière asylum in France when he first noticed the symptoms and signs of what we now know to be RA. He examined and treated a handful of patients with severe joint pain that could not be explained by other known maladies at the time (such as “rheumatism” or osteoarthritis).¹ Unlike gout, this condition mainly affected the poor, affected women more often than men, and had previously been ignored by other physicians who – concerned with earning acclaim and compensation for their work – usually chose to treat more affluent patients.² He hypothesized that these patients were suffering from a previously uncharacterized condition, which he named *Goutte Asthénique Primitive*, or “Primary Asthenic Gout.”¹ Though Landré-Beauvais’ classification of RA as a relative of gout was inaccurate, his dissertation encouraged other researchers in the field of bone and joint disorders to further study this disease.

The next important contributor to the study of RA was Alfred Garrod, an English physician during the mid to late 19th century.^{3–5} Alfred Garrod was the first to distinguish gout from other arthritic conditions. He found an excess of uric acid in the blood of patients suffering from gout, but not in the blood of patients with other forms of arthritis.^{3, 5} In 1859, Alfred Garrod wrote his *Treatise on Nature of Gout and Rheumatic Gout*, wherein he describes these observations. This work differentiated arthritis from gout and also categorized RA as a distinct condition, which he referred to as “Rheumatic Gout.” Alfred Garrod’s discoveries laid the groundwork for research on the etiology of RA (Rheumatic Gout). If this condition could be differentiated from both gout and other forms of arthritis, then a distinct etiology must exist.

Archibald Garrod, the fourth son of Alfred Garrod, also conducted research on RA. In 1890 he authored the extensive *Treatise on Rheumatism and Rheumatoid Arthritis*. In this book he coined the term “Rheumatoid Arthritis” to refer to the disease first discovered by Landré-Beauvais and later referred to as “Rheumatic Gout” by his father. In the ninety years that had passed since its discovery, more than a dozen terms had been used to describe the same disease. Archibald Garrod chose “Rheumatoid Arthritis” because it more accurately described the disease’s action on the human body. Furthermore, his treatise also delved into the history of RA.⁶ Archibald Garrod wrote:

...[when some] undifferentiated morbid condition is first described, the characters of which are so striking that it seems well-nigh impossible that they should have been long overlooked it is often suggested that the malady is one of recent development, a new disease which owes its origin to some alteration in the conditions of life...**in the case of the disease now to be considered, there is no room for suggestions of this kind**, for the evidence of its antiquity is derived, not from mere written descriptions, but from the impress which it has left upon the bones of its victims...

The bones he refers to are ancient skeletal findings from around the world. He discusses bones unearthed in the ruins of Pompeii, skeletons found in a graveyard in Pomerania (near the border of Poland and Germany), bones from ancient Egypt, and even the remains of a Norse Viking found inside his warship, all of which he claimed display skeletal damage indicative of RA.⁶ Unfortunately, Archibald Garrod’s book only mentions these claims and does not elaborate on the specific supporting evidence. Based on his paleopathological claims, Archibald Garrod proposed that RA was not a disease of the modern era, but was present and problematic for our ancestors. His treatise serves as the backbone for the *Ancient Origin* school of thought regarding the etiology of RA.

In the 20th century, the American physician Charles Short challenged Archibald Garrod's paleopathological claims and sought to discredit the *Ancient Origin* hypothesis as presented by Archibald Garrod in his *Treatise*. Upon examination of the original paleontological reports cited by Archibald Garrod's *Treatise*, Short noticed that diagnoses of ankylosing spondylitis, osteoarthritis, and gout had been all confirmed in the skeletal samples. On the other hand he could not find a definitive diagnosis of RA, but rather only claims of RA which he deemed to be unconvincing. Claiming that Archibald Garrod's ideas were spurious, Short hypothesized that, due to the lack of evidence demonstrating otherwise, RA was actually a disease of modern origins.⁷ Though others had made similar conjectures in the past, it was Short's work that is most often credited as the basis of the *Recent Origins* view of RA. The *Ancient Origins* vs. *Recent Origins* debate persists even today as both sides of the argument continue to develop evidence to support their claims.

EVIDENCE FROM LITERATURE AND ART

Although Landré-Beauvais' dissertation is considered to be the first accepted medical report of RA, some researchers have suggested that earlier descriptions are available in ancient texts. The Greek philosopher Hippocrates wrote:

In the arthritis which generally shows itself about the age of thirty-five there is frequently no great interval between the affection of the hands and feet; both these becoming similar in nature, slender, with little flesh...For the most part their arthritis passeth from the feet to the hands, next the elbows and knees, after these the hip joint. It is incredible how fast the mischief spreads.³

It seems very possible that Hippocrates was describing a patient with RA. Similar descriptions can be found in the writings of the Greek physician Arataeus, Caesar's physician Scribonius, the Byzantine physician Soranus, Emperor Constantine IX's adviser Michael Psellus, and various other ancient physicians.^{3, 6, 8, 9} Many experts consider these texts to be evidence of RA's existence in ancient times because the writings describe symptoms that closely resemble the signs and symptoms of RA. These researchers believe these ancient writings to be evidence in favor of the *Ancient Origins* view of RA etiology. However, opponents claim that these texts offer insufficient support for the prevalence of RA because the vague descriptions do not meet the rigorous scientific standard for making such a claim.^{7, 10} The role of ancient literature in the etiological puzzle generally remains anecdotal.

Although archaic, inconsistent terminology makes it difficult to decipher exact diagnoses in pre-modern writings, artwork may be more successful in displaying a robust demonstration of RA.^{11–20} One such painting is Peter Paul Rubens' *The Three Graces* (1638), which – despite great debate^{21, 22} – remains as one of the most pronounced pieces of artistic evidence for the existence of RA before Landré-Beauvais' thesis (Figure 1a).^{15, 23} At a quick glance, the right hand of the left-most "Grace" seems disfigured and poorly represented by the artist. Yet the work of a master painter such as Rubens suggests a different reason. Exploring Rubens' history as an artist reveals that he usually adhered to realism and depicted his models in a realistic way. From an anatomical perspective, the fingers are positioned in an unnatural way. The fingers on the right hand are both flexed and in hyperextension (Figure 1b). Though this finger position is possible if a digit has suffered some injury, an injury of every finger is unlikely. This makes a diagnosis of RA much more believable. Figure 1c shows an RA patient with a hand deformity similar to that seen in the hand of the woman in Rubens' painting. It is possible that the model Rubens used for this painting suffered from RA.

The most convincing case of RA in Renaissance is a depiction of *The Temptation of St. Anthony* by an anonymous painter (mid-15th to early 16th century) from the Flemish Dutch School, as reported by Drs. Dequeker and Rico in 1992 (Figure 2a).¹² The beggar in the left-hand corner is the subject in question (Figure 2b). Particularly striking is the deformity of the beggar's right hand showing wrist luxation, ulnar deviation, and finger contractures (Figure 2c). This pattern is very similar to that seen in many RA patients (Figures 2d–e). Table 1 lists paintings by other artists who experts have claimed to show signs of RA induced deformities.

Conclusions derived from paintings must be considered carefully because art pieces are not necessarily scientifically sound evidence. It is important to remember that what an artist depicts in his or her work reflects personal stylistic choices.¹² It goes without saying that artists do not always set out to document their surroundings. Rather they may be more focused on creating dramatic, expressive, and beautiful results. Inferences made from paintings are typically met by critics who have – often correctly – shown that some physical features depicted in paintings are purely artistic convention and hold no medical importance.^{10, 24, 25}

Furthermore, some researchers attribute the conditions portrayed in these paintings as evidence of other rheumatic diseases (such as rheumatic fever or gout) and not necessarily RA. Though these diseases may manifest themselves similarly to RA, their onsets, pathologies, and treatments are very distinct. For example, rheumatic fever generally affects young children and is caused by a streptococcal infection, yet its physical manifestations may resemble RA in certain patients. Due to these complexities, it is generally difficult to affirm an artistic depiction of a medical condition as being RA from paintings. Moreover, the deformities depicted by Rubens and others do not correspond to the most severe and mutilating deformities that RA can produce. If RA existed in Rubens' milieu, one might expect that its most severe and spectacular changes would have attracted the attention of artists.

Nevertheless visual arts have been used in previous etiological research for various other medical conditions^{14, 23, 25} For example, the figures from Michelangelo di Lodovico Buonarroti Simoni's (1475–1564) paintings on the ceiling of the Sistine Chapel show signs of goiter, which endocrinologists have used as evidence pertinent to the historical epidemiology of thyroid disease.²³ Paintings analyzed by both medical experts and art historians can offer reliable information that other methods of research may not be able to provide. In the case of RA, paintings may suggest the presence of the disease in ancient times and are cited by some experts in support the *Ancient Origin* view of the disease. Unfortunately, a definitive diagnosis of RA is impossible for these paintings because of similarities between the presentation of RA and other rheumatic diseases.

PALEOPATHOLOGICAL EVIDENCE

In addition to analyses of historical medical writings and paintings, post-mortem investigations provide a venue for gathering scientific data about a disease's historical prevalence. The lack of widely accepted ancient medical texts regarding RA has forced researchers to turn to paleopathological studies. Due to the nature of buried skeletal remains, which generally lack soft tissues, bone and joint diseases (including RA) are typically easy to study on post-mortem specimens.

Two preliminary paleopathological studies independently carried out by Professor Flinders Petrie and Sir Armand Ruffer in the late 19th and early 20th centuries discuss human remains from Egypt that demonstrate skeletal damage similar to RA.^{26–31} Ruffer was given skeletal samples from seven different burial sites in Egypt that included Egyptian, Greek, and

Macedonian remains. Upon examination of the skeletons, he noticed severe lesions and eburnation of the joints that he concluded were suggestive of RA. Professor Petrie's discoveries utilized a similar approach and found comparable results. Unfortunately these pioneering studies were done before the development of modern paleopathological methods. Furthermore, it was not until the 1970s that RA and ankylosing spondylitis (AS) were conclusively differentiated through genetic studies.³² Close inspection of Ruffer's work reveals many potential cases of AS, but not one definitive case of RA. Ruffer and Petrie's works are generally not considered to be convincing evidence for RA in ancient times. However, their work demonstrated that evidence of rheumatic diseases could be identified in ancient human remains.

Since the work of Ruffer and Petrie, more than a dozen paleopathological studies of RA have been conducted. These recent studies have employed better defined criteria for establishing RA in archeological samples to counter the criticisms of the preliminary studies. In the earlier studies, researchers had compared what they saw in paleontological samples (which had endured the elements for centuries) to damage they had seen in fresh cadavers. This meant that a diagnosis was being made without considering the condition or preservation of the skeleton. This proved problematic as some signs of RA described in these first studies could be attributed to post-mortem erosion, a concern that led to the discrediting of many of the early studies. During the mid 20th century, researchers began using x-rays as the common method of comparing skeletal remains to living patients. Unfortunately this also entailed that their observations were dependent on the nature of soft tissue found in a living patient (i.e. the effect of soft tissue on x-rays used for radiological imaging).^{33, 34} Thus it was proposed that the signs indicative of RA damage seen on dry skeletons may not have been caused by RA. These methods and criteria have changed significantly over the last few decades. Pre-requisites proposed for diagnosing RA in skeletons include the presence of the following features:^{35–39}

1. Subchondral cysts
2. Erosions/peri-articular sinuses in affected joints
3. Rebuilding and or presence of osteophytes
4. Severe peri-articular bone fragmentation or sinuses
5. Ulnar deviation of the metacarpophalangeal joints (MCP)
6. Traces in cartilage-supporting bone tissues of a multi-articular joint, as evidence of the disease's effect on all the articular facets of the joint (distinguishing it from osteoarthritis)
7. Osseous ankylosis of joints (especially carpal and metacarpal)
8. Eburnation
9. Multiple joints which are bilaterally effected

This list is a compilation of the most utilized criteria for diagnosing RA in paleopathological studies. However, subchondral cysts, eburnation and ankylosis are seen in other forms of arthritis, such as osteoarthritis and ankylosing spondylitis, whereas osteophytes are rarely seen in RA but are typical of osteoarthritis. Thus, this list of radiographic abnormalities lacks specificity for RA. It is important to note that most samples judged to suggest RA display only a few of these criteria, which some researchers nonetheless deem to be sufficient evidence for making a diagnosis of RA.

Notwithstanding these limitations, a few reports of RA in ancient remains hold up under scrutiny. The most striking case of RA found in paleopathological samples was described by

Arcini in 1992.³⁶ Figure 3 shows the right hand from a skeleton found in Europe displaying both ulnar deviation and damage of the index finger. This pattern of damage makes these remains the most likely case of RA found in Europe before Landré-Beauvais' description.

One deficiency of paleontological studies is that the samples were not always ideally preserved and it is difficult to construct complete skeletal sets. Given that RA most prominently affects the hands and feet, which are usually difficult to find, skeletons with the potential to show signs of RA are particularly hard to come by.⁴⁰ Another perplexing issue for paleontological researchers is distinguishing RA from other erosive arthropathies. Similar to the problems that arise when considering artistic representations, other diseases sometimes result in a similar pattern of skeletal damage. Hence, disease-specific diagnoses must be justified by the level of detail preserved in the remains.^{29, 37, 41} Some critics disagree with the results of these studies due to disparities in the methods used to infer RA in skeletal samples.^{41–43} Still others object based on their own research having found no indications of RA.⁴⁴

Nonetheless the development of rigorous scientific techniques within paleopathology (a medical anthropology specialty field) has uncovered samples from around the world that demonstrate skeletal damage that may be suggestive of RA. By taking into consideration the expertise of anthropologists, physicians can distinguish skeletal damage caused by diseases from that caused by the elements. This has greatly increased the validity of more recent studies. Table 2 includes a comprehensive list of all paleopathological studies that claim the presence of skeletal damage indicative of RA. Reviewing the figures and text from each study reveals that many of the cases listed in Table 2 are ambiguous and generally not specific for RA. Still, there are some convincing cases from around the world to that demonstrate signs of RA preceding Landré-Beauvais' description of RA by several hundred years, thereby favoring the *Ancient Origin* view of RA etiology.⁴⁵

Different interpretations of the findings in Table 2 by various experts have led to the development of a third school of thought regarding the etiology of RA: the *New World to Old World* transfer concept.^{46, 47} Proponents of this view argue that because some of the oldest paleopathological specimens displaying RA were found in the Americas, RA must have been transmitted to the Old World through an unspecified vector after Columbus' initial discovery of the Americas.^{38, 48, 49} However, studies that have found the presence of RA in the Old World before Columbus' voyage in 1492 may potentially discredit this theory. Undeterred, the *New World to Old World* idea has recently gained momentum, especially since contact between the New World and the Old World certainly preceded the voyages of Columbus by several centuries.

CONTEMPORARY RESEARCH

Recent research on the origins and etiology of RA has begun to approach the issue from a molecular perspective.^{41, 50} It has long been hypothesized that some genetic component plays a role in the onset of RA. For example, it has been known since the first descriptions of RA that women are more likely to be affected than men by a ratio of 3:1.^{1, 27, 40} Research over the past 35 years has shown an association between RA and a group of major histocompatibility complex (MHC class II) cell surface receptors encoded by alleles of the HLA-DR locus on chromosome 6.^{41, 51–53} The MHC locus is highly polymorphic and different populations differ in allele frequency. The particular set of alleles that an individual carries is highly predictive of their potential to develop RA, and susceptibility alleles are found in individuals within every population. Although many other genes contribute to RA susceptibility, the most important contribution comes from the MHC locus.

Other studies have shown that genetics is not the sole determinant of RA.^{50, 53} Microbial pathogens including bacteria, as well as various viruses (retroviruses, parvovirus B19, rubella, Epstein-Barr and other herpes viruses) have been implicated as potential triggers of RA.^{50, 52–55} The mechanism of action of these events is still unclear and it is plausible that infections are not causative, rather that RA patients may just be more prone to infections. Thus, the suggested pathogens have only been circumstantially implicated as playing a triggering role. Hypotheses made correlating the onset of RA to an infections trigger will remain speculative until a discrete pathogen has been found. Determining what – if any – role bacterial and viral infections play in the onset of RA is still a developing area of research.

Smoking has been implicated as yet another potential environmental trigger. In particular, smoking has been linked to the incidence of RA in individuals with the HLA susceptibility allele, termed the shared epitope (SE).⁵⁶ In the context of this discussion, the influence of smoking on RA heavily favors the *New World to Old World* view because smoking was introduced to Europe only after Columbus' discovery of the Americas. Unfortunately, this correlation is not perfect as about 1/3 of RA patients do not have the HLA-DR SE gene. Also not all people with RA smoke, although effects of second-hand smoke or similar environmental toxins could potentially be important in non-smoker RA subjects. Thus, smoking may not necessarily be a uniform cause of RA, but instead one of several environmental triggers involved in the genesis of RA. A possible mechanism for the effect of smoking in RA may be through induction of the formation of citrullinated autoantigens, the most specific target of immune autoreactivity yet identified in RA. As it stands this concept is still under development. To develop a more definitive conclusion, stronger evidence is needed to flesh out an immunopathogenic pathway that connects smoking, RA and autoimmune responses.

It has been suggested by that the aforementioned causes (smoking, infectious triggers, etc.) are not actually causes, but rather risk factors.⁵⁰ This would imply that RA could have been present in the populations of both the ancient New and Old Worlds, albeit very rare in the Old World in the absence of important environmental triggers. After the opening of trade routes between the hemispheres, certain risk factors (especially tobacco) could have been introduced to Europe that contributed to the eventual appearance of RA as a more common disease in the Old World. This model is attractive and is consistent with current hypotheses regarding the etiology of RA. However, as with the other suggested models, this one must be explored much further.

CURRENT HYPOTHESIS

RA generally begins to manifest in individuals between the ages of 30 and 65.⁵⁷ The estimated average life expectancy was just under 30 years when RA was first described in the year 1800.⁵⁸ Therefore it is possible that individuals who would have developed RA in ancient times died before the onset of the disease. This could partly explain why RA may have been much less common in previous centuries. Combined with the aforementioned paleopathological evidence showing the prevalence of RA in antiquity, a reasonable conclusion seems to be that RA was problematic for our ancestors in ancient times, but likely for very few of them.

One unresolved question is which generation of ancestors we are talking about. The *New World to Old World* concept proposes that an infectious trigger was transferred from the New World to Europe via trade goods (e.g. smoking tobacco), contaminated supplies, or travelers who picked up RA-inducing bacteria or viruses. Despite the plausibility of many of these arguments, discoveries of skeletons demonstrating RA in the Old World prior to the

discovery of the Americas suggests that these transferred environmental (and perhaps also genetic) factors were not absolute prerequisites for the development of RA.

By combining the conclusions from paleopathological studies with those from advanced immunological and genetic analyses, a modified and updated version of the *Ancient Origin* view now stands as the best-supported theory concerning the historical epidemiology of RA. The current hypothesis consists of the following principles:

1. RA is not a disease of recent origin, and was both present and problematic hundreds, possibly thousands of years ago, potentially with a geographic distribution distinct from its current profile.
2. RA occurs as a response to an environmental stimulus or stimuli experienced by genetically susceptible individuals.
3. The identities and origins of these stimuli or inciting events are still incompletely known, although tantalizing clues have emerged.
4. Distinct environmental triggers may be important in subsets of patients with RA. For example, smoking may be a more important risk factor in RA patients who carry an MHC allele that encodes the shared-epitope and who have autoantibodies to citrulline-containing proteins. Thus, the historical analysis of RA needs to incorporate the likely possibility that what we currently define as RA is more than one disease.

This framework allows research to be directed towards a more expanded set of possible etiological causes that may have been overlooked if one adheres strictly to any of the three previously held hypotheses concerning the history of RA. Potentially, an integration of molecular insights and historical epidemiology may provide new clues for identifying the etiology of RA.

Acknowledgments

Supported in part by a grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01 AR047328) and a Midcareer Investigator Award in Patient-Oriented Research (K24 AR053120) (to Dr. Kevin C. Chung).

References

1. Landré-Beauvais AJ. The First Description of Rheumatoid Arthritis. Unabridged Text of the Doctoral Dissertation Presented in 1800. *Joint Bone Spine*. 2001; 68:130–142. [PubMed: 11324929]
2. Kahn MF, Landré-Beauvais AJ. *Joint Bone Spine*. 2001; 68:143.
3. Copeman, WSC. A Short History of Gout. Berkeley and Los Angeles: University of California Press; 1964.
4. Storey GD. Alfred Baring Garrod (1819–1907). *Rheumatology*. 2001; 40:1189–1190. [PubMed: 11600751]
5. Garrod, AB. Treatise on Nature of Gout and Rheumatic Gout. London: Walton and Maberly; 1859.
6. Garrod, AE. A Treatise on Rheumatism and Rheumatoid Arthritis. London: Charles Griffin and Company; 1890.
7. Short CL. The Antiquity of Rheumatoid Arthritis. *Arthritis and Rheumatism*. 1974; 17(3):193–205. [PubMed: 4596668]
8. Caughey DE. The Arthritis of Constantine IX. *Annals of the Rheumatic Diseases*. 1974; 33:77–80. [PubMed: 18623888]
9. Soranus of Ephesus: On Acute Diseases and on Chronic Diseases, translated into Latin by Caelius Aurelianus (Fifth Century AD). English translation by IE Drabkin. Chicago: University of Chicago Press; 1950.

10. Snorrason E. Landre Beauvais and his "Goutte Asthenique Primitive". *Acta Medica Scandinavica*. 1952; 142 Supplement 256:115–118. [PubMed: 14902361]
11. Alarcón-Segovia D, Laffón A, Alcocer-Varela J. Probable Depiction of Juvenile Arthritis by Sandro Botticelli. *Arthritis & Rheumatism*. 1983; 26(10):1266–1268. [PubMed: 6354195]
12. Dequeker J, Rico H. Rheumatoid Arthritis-like Deformities in an Early 16th-Century Painting of the Flemish-Dutch School. *JAMA*. 1992; 268(2):249–251. [PubMed: 1608144]
13. Hayakawa S, Komine-Aizawa S, Osaka S, Iida T, Hayakawa J, Nishinarita S, Nemoto N. Rembrandt's Maria Bockenolle has a Butterfly Rash and Digital Deformities: Overlapping syndrome of Rheumatoid Arthritis and Systemic Lupus Erythematosus. *Medical Hypotheses*. 2007; 68:906–909. [PubMed: 17113236]
14. Dequeker J. Medicine and the Artist. *Age and Ageing*. 2008; 37:4–5. [PubMed: 17993649]
15. Appelboom T. Hypothesis: Rubens - One of the First Victims of an Epidemic of Rheumatoid Arthritis that started in the 16th-17th century? *Rheumatology*. 2004; 44:681–683. [PubMed: 15840609]
16. Rubinstein HM, Blair SJ. The Hand in Art. *J Hand Surg Am*. 1985; 10A(4):589. [PubMed: 3894493]
17. Levine H. Art, Artists, and Arthritis. *Maryland Medicine*. 2002 Spring;3(2):40. [PubMed: 12056227]
18. Levine H. Art, Artists, and Arthritis. *Maryland Medicine*. 2002 Summer;3(3):45. [PubMed: 12214496]
19. Rubens: The Artist and Arthritis. *Science News*. 1981; 119(8):117.
20. Boonen A, Rest J, Dequeker J, Linden S. How Renoir Coped with Rheumatoid Arthritis. *British Medical Journal*. 1997; 315:1704–1708. [PubMed: 9448547]
21. Appelboom T. Style Versus Substance in Artistic Depiction: Reply. *Rheumatology*. 2005; 44(11):1465. [PubMed: 16159945]
22. Rothschild B. Style Versus Substance in Artistic Depiction. *Rheumatology*. 2005; 44(11):1464. [PubMed: 16143632]
23. Slater V, Ramachandran M. Medical Conditions in Works of Art. *British Medical Journal*. 2008; 315:1704–1708.
24. Leden I. Doubts About Sandro Boticelli's Depiction of Juvenile Rheumatoid Arthritis. *Arthritis and Rheumatism*. 1984; 27(10):1197–1198. [PubMed: 6386006]
25. Weisman M, R-J P, Steinberg L, Ehrlich G, Philippot P, Bywaters E. International Symposium: Art, History, and Antiquity of Rheumatic Diseases. *Clinical Rheumatology*. 1986; 5:278–294. [PubMed: 3524972]
26. Bridges PS. Prehistoric Arthritis in the Americas. *Annual Review of Anthropology*. 1922; 21:67–91.
27. Barr J. An Address on Rheumatoid Arthritis. *The British Medical Journal*. 1913:733–735.
28. Ruffer A. Arthritis Deformans and Spondylitis in Ancient Egypt. *J. Pathology*. 1918; 22:152–196.
29. Karsh RS, McCarthy JD. Archaeology and Arthritis. *Archives of Internal Medicine*. 1960; 105:640–644.
30. May WP. Rheumatoid Arthritis (Osteitis Deformans) Affecting Bones 5,500 Years Old. *The British Medical Journal*. 1897; 2(1927):1631–1632.
31. Domen RE. Paleopathological Evidence of Rheumatoid Arthritis. *JAMA*. 1981; 246(17):1899. [PubMed: 7026807]
32. Schlosstein L, Terasaki PI, Bluestone R, Pearson CM. High Association of an HL-A Antigen, W27, with Ankylosing Spondylitis. *New England Journal of Medicine*. 1973; 288:704–706. [PubMed: 4688372]
33. Ortner DJ, Utermohle CJ. Polyarticular Inflammatory Arthritis in a Pre-Columbian Skeleton from Kodiak Island, Alaska, U.S.A. *American Journal of Physical Anthropology*. 1981; 56:23–31.
34. Rothschild BM. Paleopathology, its Character and Contribution to Understanding and Distinguishing Among Rheumatologic Diseases: Perspectives on Rheumatoid Arthritis and Spondyloarthropathy. *Clinical and Experimental Rheumatology*. 1995; 13:652–662.

35. Thould AK, Thould BT. Arthritis in Roman Britain. *British Medical Journal*. 1983 December. 287:24–31. [PubMed: 6190533]
36. Arcini C. Rheumatoid Arthritis - Rare Reality as Recovered Among Scanian Skeletal Remains from Viking and Medieval Times. *Sydsvenska Medicinhistoriska*. 1992; 18:11–21.
37. Lagier R. Bone Eburnation in Rheumatic Diseases: A Guiding Trace in Today's Radiological Diagnosis and in Paleopathology. *Clinical Rheumatology*. 2006; 25:127–131. [PubMed: 16374573]
38. Rothschild BM, Woods RJ. Symmetrical Erosive Disease in Archaic Indians: the Origin of Rheumatoid Arthritis in the New World. *Seminars in Arthritis and Rheumatism*. 1990; 19(5):278–284. [PubMed: 2192458]
39. Giuffra V, Vitiello A, Giusiani S, Forniciari A, Caramella D, Villari N, Fornaciari G. Rheumatoid Arthritis, Klippel-Feil Syndrome and Pott's Disease in Cardinal Carlo de' Medici (1595–1666). *Clinical and Experimental Rheumatology*. 2009; 27:594–602. [PubMed: 19772790]
40. Bennike, P. Paleopathology of Danish Skeletons: A Comparative Study of Demography, Disease, and Injury. Copenhagen: Akademisk Forlag; 1985.
41. Ortner DJ, Tuross N, Stix AI. New Approaches to the Study of Disease in Archeological New World Populations. *Human Biology*. 1992; 64(3):337–360. [PubMed: 1607183]
42. Duncan H. Letter to the Editor. *Paleopathology Newsletter*. 1979; 25:10–11.
43. Klepinger L. Letter to the Editor. *Paleopathology Newsletter*. 1979; 26:6–7. [PubMed: 11610610]
44. Rothschild BM, Arriaza B, Woods RJ, Dutour O. Spondyloarthropathy Identified as the Etiology of Nubian Erosive Arthropathies. *American Journal of Physical Anthropology*. 1999; 109:259–267. [PubMed: 10378463]
45. Rogers J, Dieppe P. Skeletal Palaeopathology and the Rheumatic Diseases: Where are we now? *Annals of the Rheumatic Diseases*. 1990; 49:885–886. [PubMed: 2256733]
46. Kramar C, Lagier R, Baud CA. Rheumatic Diseases in Neolithic and Medieval Populations of Western Switzerland. *Zeitschrift fur Rheumatologie*. 1990; 49:338–345. [PubMed: 2085056]
47. Domen RE. The Antiquity and Origins of Rheumatoid Arthritis. *JAMA*. 1992; 268(19):2649. [PubMed: 1433680]
48. Rothschild BM, Turner KR, DeLuca MA. Symmetrical Erosive Polyarthritis in the Late Archaic Period of Alabama. *Science*. 1988; 241(1498–1501)
49. Woods RJ, Rothschild BM. Population Analysis of Symmetrical Erosive Arthritis in Ohio Woodland Indians (1200 Years Ago). *J Rheumatology*. 1988; 15(8):1258–1263.
50. Fox, DA. Etiology and Pathogenesis of Rheumatoid Arthritis. In: Koopman, WJ., editor. *Arthritis and Allied Conditions: A Textbook of Rheumatology*. 15th ed.. Vol. 1. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 1089–1107.
51. Reveille JD. The Genetic Contribution to the Pathogenesis of Rheumatoid Arthritis. *Current Opinion in Rheumatology*. 1998; 10:187–200. [PubMed: 9608321]
52. Condeelis JJ. The Autoimmune Diseases. *JAMA*. 1992; 268(20):2882–2892. [PubMed: 1433704]
53. Moreland, LW. *Rheumatoid Arthritis: Epidemiology, Pathogenesis, and Treatment*. London: ReMEDICA Publishing; 2001.
54. Álvarez-Lafuente R, Fernández-Gutiérrez B, Miguel S, Jover JA, Rollin R, Loza E, Clemente D, Lamas JR. Potential Relationship Between Herpes Viruses and Rheumatoid Arthritis: Analysis with a Quantitative Real Time Polymerase Chain Reaction. *Ann Rheum Dis*. 2005; 64:1357–1359. [PubMed: 16100341]
55. Balandraud N, Roudier J, Roudier C. Epstein-Barr Virus and Rheumatoid Arthritis. *Autoimmunity Reviews*. 2004; 3:362–367. [PubMed: 15288002]
56. Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, Ronnelid J, Harris HE, Ulfgren A, Rantapaa-Dahlqvist S, Eklund A, Padyukov L, Alfredsson L. the Epidemiological Investigation of Rheumatoid Arthritis Study Group. A New Model for an Etiology for Rheumatoid Arthritis: Smoking May Trigger HLA-DR (Shared Epitope) Restricted Immune Reactions to Autoantigens Modified by Citrullination. *Arthritis and Rheumatism*. 2006; 54(1):38–46. and. [PubMed: 16385494]

57. Majithia V, Geraci SA. Rheumatoid Arthritis: Diagnosis and Management. *The American Journal of Medicine*. 2007; 120:936–939. [PubMed: 17976416]
58. Riley JC. Estimates of Regional and Global Life Expectancy. *Population and Development Review*. 2005; 31(3):537–543.
59. Dequeker J. Siebrandus Sixtius: Evidence of Rheumatoid Arthritis of the Robust Reaction Type in a Seventeenth Century Dutch Priest. *Annals of the Rheumatic Diseases*. 1991; 51:561–562. [PubMed: 1586264]
60. Hormell RS. Notes on the History of Rheumatism and Gout. *The New England Journal of Medicine*. 1940; 223(19):754–760.
61. Klepinger LL. Paleopathologic Evidence for the Evolution of Rheumatoid Arthritis. *American Journal of Physical Anthropology*. 1979; 50:119–122. [PubMed: 367177]
62. Rogers J, Watt I, Dieppe P. Arthritis in Saxon and mediaeval skeletons. *British Medical Journal*. 1981 December; 283:19–26. [PubMed: 6788246]
63. Leden I, Persson E, Persson O. Aspects of the History of Rheumatoid Arthritis in the Light of Recent Osteo-archeological Finds. *Scandinavian Journal of Rheumatology*. 1988; 17:341–352. [PubMed: 3062766]
64. Kilgore L. Possible Case of Rheumatoid Arthritis from Sudanese Nubia. *American Journal of Physical Anthropology*. 1989; 79:177–183. [PubMed: 2662779]
65. Ciranni R, Garbini F, Neri E, Melai L, Giusti L, Fornaciari G. The "Braids Lady" of Arezzo: A Case of Rheumatoid Arthritis in a 16th Century Mummy. *Clinical and Experimental Rheumatology*. 2002; 20:745–752. [PubMed: 12508764]

Figure 1.
(a) Peter Paul Rubens' *The Three Graces*, (b) closeup of the left-most figure's hand, (c) patient with similar pattern of RA damage.

Figure 2. (a) An anonymous Flemish painter's depiction of *The Temptation of St. Anthony*, (b) the beggar, (c) close-up of the beggar's deformed hand showing slight ulnar deviation, finger contractures, and wrist luxation. From Dequeker J, Rico H. Rheumatoid Arthritis-like Deformities in an Early 16th-Century Painting of the Flemish-Dutch School. *JAMA* 1992;265(2):249–51, with permission. (d & e) patient with a similar pattern of RA damage.

Figure 3.

Right hand of skeleton found by Arcini, showing ulnar deviation and damage of the second finger indicative of RA. *From Arcini, C. Rheumatoid Arthritis – rare reality as recovered among Scanian skeletal remains from Viking and Medieval times. Sydsvenska Medicinhistoriska Sallskapet 1992;18:11–21, with permission.*

Table 1

Paintings that include human figures with characteristics suggested of being caused by Rheumatoid Arthritis^{12–16, 19, 59}

Artist	Title	Year Painted
Anonymous	The Temptation of St. Anthony	15 th –16 th Century CE
Guiseppe Maria Crespi	The Holy Family	17 th –18 th Century CE
Jacob Jordaens	The Painter's Family	1620
Cornelisz Moeyaert	Portrait of Siebrandus Sixtius	1631
Rembrandt Harmenszoon van Rijn	Portrait of Maria Brockenolle	1634
Peter Paul Rubens	Rubens' final self-portrait	17 th Century CE
Peter Paul Rubens	The Three Graces	1638

Table 2Published paleopathological studies of Rheumatoid Arthritis^{28, 30, 35, 36, 38–40, 48, 49, 60–65}

Date of Samples	Year Published	Location	Hypothesis Supported
4000-1000 BCE	1917	Egypt	Ancient Origin
3000-1000 BCE	1988	Alabama	New World to Old World
2750-2625 BCE	1897	Egypt	Ancient Origin
2500-1900 BCE	1988	Sweden	Ancient Origin
2290-2040 BCE	1990	Kentucky	New World to Old World
1300 BCE	1940	Lower Egypt	Ancient Origin
800 BCE	1988	Ohio	New World to Old World
400-1 BCE	1985	Denmark	Ancient Origin
339-210 BCE	1979	Sicily	Ancient Origin
100 BCE	1983	England	Ancient Origin
700-1450 CE	1989	Sudan	Ancient Origin
900-1536 CE	1992	Denmark/Sweden	Ancient Origin
1400 CE	1981	England	Ancient Origin
1500 CE	2002	Italy	Ancient Origin
1666 CE	2009	Italy	Ancient Origin