The Antiquity of Rheumatoid Arthritis: A Reappraisal

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ABSTRACT. ***Objective***. To demonstrate the existence of rheumatoid arthritis (RA) before the 19th century.
Methods. Survey of primary and secondary references on the history of rheumatic diseases.
Results. Paleopathological evidence suggests the existence of RA in America since 8000 BC and in Europe since the 7th century. Descriptions and representations of a symmetric chronic polyarthritis producing characteristic deformities can be found in Rome since 100 BC and India since 500 BC. The first clinical distinction between RA and gout was published in Mexico in 1578. Different historical conditions contributed to lack of recognition of RA by official medicine before 1800. The recognition of RA as a distinct entity in the 19th century was influenced by socioeconomic circumstances.
Conclusion. RA is not a recent disease. Historical investigation can provide useful clues on its pathogeny. (J Rheumatol 2001;28:751–7)

Key Indexing Terms:
RHEUMATOID ARTHRITIS CHRONIC DISEASES HISTORY
PALEOPATHOLOGY CAUSE

Rheumatoid arthritis (RA) is a chronic disease, of which no cause has been identified, and as yet lacks an effective treatment. RA has been proposed as a "new" disease, not found in Europe before 1800. Buchanan proposed a viral etiology, and suggested the eventual disappearance of the disease as the inciting agent loses pathogenic power[1]. No general agreement has been achieved on these opinions. To date, it is debatable if RA in populations is losing severity[2].

The possible role of individual antigens as the "cause" of RA is partially sustained by the belief of an original geographic area from which the disease spread worldwide, thus supporting a possible infectious origin. So far, the existing evidence is not definite, but it poses serious doubts concerning the current unicausal model of chronic conditions[3,4].

We review the existing written, pictorial and paleopathological evidence on the antiquity of RA, and discuss it as a general frame on the possible causes of RA and in a less constrained perspective, on the causes of chronic conditions. Predisposition to disease should not be considered just a property of the individual, but as the result of the interaction with social groups and the environment[5,6].

WRITTEN AND PICTORIAL EVIDENCE

The absence of a convincing description of the disease has been continuously argued as firm evidence against the existence of RA before the 18th century in European populations[7,8]. The existence of systemic lupus erythematosus and Sjögren's syndrome before the 19th century is not questioned[9], despite the lack of written evidence. The technology required to define such conditions would not have been possible without a radical change in the philosophical thought on which the comprehension of man and nature was based before the 18th century[10]. Man was considered as a mixture of 4 basic humors, and an adequate blend of them was a healthy state. Most diseases were defined as an abnormal predominance of a humor in a specific place[11].

Not only the theoretical baggage of medicine has changed with time. The way we perceive pathologic conditions has also changed. The power of observation and the importance of physical signs needed to define a specific condition have also varied with time[12]. This is the most important difference to account for the supposed lack of descriptions of RA in medical literature.

It is easier to find evidence of a disease such as RA in human skeletal remains, since we are judging objective damage in bones by modern standards[13]. On the contrary, when judging ancient medical texts, we must understand what the original author had in mind while writing his description. We are always at risk of misinterpreting the texts. Similar risks have been recognized in the interpretation of disease in art[14]. With these caveats in mind, we present the evidence of the existence of RA in chronological order (Tables 1 and 2).

The oldest proposed written account of a disease that could be RA is generally ascribed to Scribonius Largus[15], who wrote about a polyarthritis occurring mainly in elderly women. A Roman woman was considered an elder between 35 and 45 years because general life expectancy was around 40 years[16,17]. Then, Scribonius Largus was probably describing a polyarthritis found in women between 30 and 40 years old, much like our modern RA.

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Table 1. Written evidence on the existence of chronic polyarthritis before the 19th century. These are the most convincing descriptions of a chronic polyarthritis before 1800.

Source	Place	Time
Caraka Samhita	India	500 BC–AD 100
Scribonius Largus	Rome	Circa 100 BC
Michael Psellus	Rome	Circa AD 1000
Alonso López de Hinojosos	México	AD 1578
Thomas Sydenham	England	AD 1676
William Heberden the Elder	England	AD 1710–1801
Jon Pétursson	Iceland	AD 1782

Table 2. Pictorial evidence of the existence of chronic symmetric polyarthritis before the 19th century. All the artistic representations are from Europe. If the lack of written evidence is assumed as a proof of absence of a condition, the reverse could also be argued: that the lack of pictorial evidence after 1500 is an indirect proof of the absence of RA in the New World, an illogical premise.

Painting	Artist	Year
The Temptation of St. Anthony	Unknown	1500–1670
The Donators	Jan Gossaert	Possibly 1530
Portrait of Siebrandus Sixtius	Unknown	1538–1631
Various paintings	Peter Paul Rubens	1577–1640
The Painter's Family	Jacobo Jordaen	1593–1678

In Asia, there is also evidence suggesting the presence of a chronic symmetric polyarthritis in the *Caraka Samhita*, a medical text from India written between 500 BC and AD 100[18,19]. It had subcutaneous nodules and could produce contractures and atrophy of the limbs.

A Roman emperor, Constantine IX (AD 980–1055), seems to have been the first illustrious sufferer of RA. A brilliant description of his disease is found in the *Chronographia* by Michael Psellus, stressing the recurrent polyarthritis involving the joints of the limbs with severe contractures, deformities in the hands, and consequent disability[20].

There is also graphic evidence to support the existence of RA in Europe from 1500 to 1700. The most convincing examples are cited in Table 2. Ample information on them can be consulted in the original reports[21-23]. In "The Temptation of St. Anthony," now in the Escorial Museum in Spain (artist unknown), a beggar is shown with hand and wrist rheumatoid-like deformities not found in any of the other portrayed individuals. "The Painter's Family" is another interesting example (Jacobo Jordaen, 1593–1678). The hands of the serving maid portrayed are different from the hands of the 3 other individuals appearing in the scene. The symmetric inflammation of the metacarpophalangeal joints in a young woman is very suggestive of the disease.

The case of Siebrandus Sixtius (1538–1631) deserves special mention. Two portraits in which the hands are clearly visible and a contemporary report of his "nodular rheumatism" present a clinical description of RA made in the 17th century[24]. Upon close examination, these portraits reveal swelling of metacarpophalangeal and proximal interphalangeal joints, with ulnar deviations and flexion contractions of the fingers. Few conditions besides RA can produce these changes.

Thomas Sydenham (1624–1689) has until now been acknowledged with the first clinical distinction between RA and gout. In his *Observationes Medicae*, published in 1676, he described a type of rheumatism differing from gout mainly by its frequent recurrence and the possibility of crippling the patient. Observing the fingers of one of his patients, he clearly describes swan-neck deformities[25].

William Heberden the Elder (1710–1801) also recognized RA and gout as different diseases[26]. To specify the distinction, he made special emphasis on how the limbs lost their function completely and on the chronic characteristic painful joints occurring in RA as compared with gout.

In Iceland, Jón Pétursson described in 1782 a chronic symmetric and destructive polyarthritis with occasional systemic manifestations as a frequent condition in his regular practice[27]. He specified the female preponderance of the condition and the peak incidence around 40 years of age, which clearly distinguished it from gout.

In 1800, Augustin-Jacob Landré-Beauvais presented his doctoral thesis in Paris. Describing a new type of gout, he presents a remittent polyarticular chronic disease in indigent women of asthenic constitution. In it, the absence of tophi and suppuration was notorious. Each crisis left the patient with a progressive limitation in joint motion, leading to ankylosis of the afflicted joints[28]. Once again, prognosis made the difference.

In 1853, Jean Martin Charcot described the arthritis, the deformities and contractures, the muscular atrophy, and the recurrence and spontaneous remissions of RA in his doctoral thesis. He mentions the long time needed by the disease to produce deformities, but although it was not a strange condition any more, it was not accepted worldwide as an independent condition[29,30].

Finally, Sir Alfred Baring Garrod (1819–1907) in 1859 introduced the term rheumatoid arthritis to substitute for rheumatic gout, so ill defined in the medical literature of his time. It seemed impossible to him that the characteristics of the disease had been overlooked for such a long time, so he presented it as a new disease[31]. Even today, RA is still difficult to define. To avoid the confusion, different classification criteria have been designed to speak a common language[32,33].

Most of the literature discussed until now was originally written in English or translated to it. It is worth noting that medical writings in Spanish have not been systematically

surveyed for evidence on the antiquity of RA and other rheumatic conditions[34].

Alonso López de Hinojosos published the *Suma y recopilación de cirugía, con un arte para sangrar muy útil y provechosa* in 1578. He was one of 4 physicians ascribed to the Hospital Real de San José de los Naturales, in México City[35]. His book is divided into 7 treatises. In the fifth treatise, dealing with the "mal de bubas," one of many different designations employed at the time for venereal diseases, he deals with various joint diseases. In chapter IV, among other rheumatic syndromes[36], he distinguished at least 2 different types of gout. Even now, we can recognize in his descriptions classical gout, with arthritis regularly seen in hands or feet, sporadic attacks, and no joint pain or limitation through intercritical periods in the first years of the disease. He described tophi as hard nodules, "pieces of lime or gypsum" ["pedazos de cal y yeso"], which made hands and feet "ugly and monstrous" ["feos y monstruosos"] and could open spontaneously[37].

There was yet another type of gout. It was chronic and always attacked the same joints. Not accompanied by tophi, it disabled patients by severe contractures in joints. López de Hinojosos also made a clear description of severe muscular atrophy as the most frequent evolution seen in his patients ["...quedar los hombres tullidos, porque como a los nervios se les consume la humedad, quedan tan secos como pergamino que con el fuego se secó, y encoge"]. Although no mention is made of how frequent the condition was in his regular practice, composed of Spaniards and Amerindians, he leaves us with the conviction that it was a common problem.

European physicians writing medical books in New Spain always emphasized new conditions with uncommon signs or symptoms[38]. López de Hinojosos described the expected evolution of a common disease in his regular practice, not a new disease. López de Hinojosos made his career in Spain, and was already a practicing physician when he crossed the Atlantic Ocean. He did not describe a new disease or an alarming new evolution of a previously known condition. Such a crippling disease would have been more notorious than it apparently was had it never been seen in Europe before 1492. His description was published more than 100 years before Sydenham's and it should be acknowledged as the first clinical distinction between gout and what we now identify as RA.

PALEOPATHOLOGICAL EVIDENCE

RA is hard to find in skeletal remains. In ancient burials and medical museums, bones of hands and feet expected to present the characteristic erosions are usually the least preserved[39]. Another serious difficulty is the different definitions of RA found in anthropological and rheumatological literature. To correct this, the usual recommendation is that physical anthropologists and rheumatologists must be part of the team evaluating the bones to be reported, to ensure the best diagnosis possible. Unilateral approaches have led to doubtful diagnoses[40].

An example of this is the mention of RA in Egyptian mummies. Spondyloarthropathies and other conditions were not distinguished from RA in the early years of the 20th century[41]. This led to the misclassification of some cases of spondyloarthropathies and severe osteophytosis as RA[42]. This mistake is still repeated in some reference books on the history of medicine[43].

Rothschild has described more than 900 skeletons with a polyarticular erosive symmetrical affliction that cannot be distinguished from modern RA[44-46]. These skeletons belong to different historical periods, ranging from 6500 to 450 BC. Ankylosing spondylitis, osteoarthrosis, and gout can confidently be excluded because of the erosions' anatomic distribution, their specific situation within each joint, and the lack of syndesmophytes. These characteristics make other reports of RA dubious because of the presence of ligamentous calcifications and other features suggestive of diverse spondyloarthropathies[47-49].

Rothschild, *et al* proposed this condition as originating on the west branch of the Tennessee River in the United States because they concentrate around a precise geographic region in what now corresponds to the states of Tennessee, Kentucky, Alabama, and Ohio. This supports a local factor as a cause of the disease we now identify as RA[50]. Rothschild has emphasized the absence of a similar condition elsewhere, although incomplete mention is made of evidence from the rest of the US and from other regions of the world[51]. Rogers and Dieppe[52] and Leden and Arcini[53] have made a point by stressing that negative evidence cannot be used as a proof of certainty.

Fraga, *et al* describe 21 cases of an erosive condition similar to modern RA in the collection of Mesoamerican human skeletal remains preserved at the National Museum of Anthropology of Mexico[54], 8 skeletons of the Preclassic era (Tlatilco, 1400–600 BC), 5 of the Classic era (Teotihuacan, 200 BC to AD 650), and 8 of the Postclassic era (AD 800–1550). Erosions were found in the articular surface, the edges of the articular surface, and the capsule insertion in carpal metacarpophalangeal, tarsal, and metatarsophalangeal joints. Macroscopically, the lesions were symmetrical, similar in appearance and age, and clearly distinguishable from the flaky eroded bone produced by the passage of time. We are unaware of similar reports in Central and South American cultures.

There are at least 5 cases of possible RA in Europe before 1492. The first, a woman who lived between AD 70 and 470 in Poundbury, England, showing erosions in carpus and metacarpal heads. No age at death is mentioned in the original report[55]. Three additional cases from a cemetery in Amiens, France, are promising (7th to 9th century). The skeletal remains of 2 men and a woman present carpitis and

tarsitis along with marginal erosions of metacarpophalangeal joints. The same authors discussed a 15th century skeleton of a man with bilateral erosions of metacarpophalangeal joints and carpus. None of these had sacroiliac or spinal changes[56].

IS RA A NEW DISEASE?

The existing evidence sustains the presence of RA worldwide long before 1492. Until now, no studies have investigated a modification in the prevalence of the disease in Europe after 1492, to support a possible vector introduced through the transoceanic exchange established after Columbus.

Thinking of RA as born in one place with a subsequent worldwide spread is tempting but hard to sustain[57]. An infectious cause depends on a physical transport to disseminate the disease. If the condition was originated in the zone proposed by Rothschild, *et al*, we should have evidence of physical transport such as migrations or commercial routes to explain the presence of a similar condition in Mexico.

To explain the worldwide presence of the disease, multiple catchment areas are a tempting possibility. In our view, the real problem is not to decide which continent has the dubious honor of having the first cases of a condition but to define the different original catchment areas. In this way, we could probably define the antigens and environmental influences responsible for the disease, such as food-borne or vector-associated antigens[58]. Rothschild has even proposed an allergen as the transmitting vector, probably originating in caves[59]. Experimental data from molecular analysis of tissue-infiltrating T cells in modern disease do not support the concept that a single antigen drives synovial inflammation[60].

The most tempting possibility is to consider the disease as caused by a yet unidentified pathogen, as Buchanan and Murdoch suggested[1]. They made an analogy based on the unicausal model of disease, successful in infectious diseases since the 19th century. In regard to RA, the unicausal model does not explain some crucial points. It assumes the existence of a new pathogen, possibly present in the zone defined by Rothschild in Tennessee[50]. If it did exist, there was no previous knowledge of it by the immune system of any of the inhabitants of the ports of entrance of the ships sent from the New World to Europe[61]. Other contagious conditions, such as smallpox, typhus, and syphilis became prevalent in a few years in the same way, with great alarm among contemporary physicians[62,63]. This is the expected behavior of a pathogen introduced in a previously virgin population[64]. In consequence, we do not have adequate historical evidence to suggest an infectious origin of RA. Modern epidemiological data do not support an infectious cause: there is no clustering in time and space, and no confirmed cases of direct transmission[65].

We face another problem. Although we define RA as a single disease, we may be embracing many conditions under this diagnosis[66]. RA can be considered as a syndrome: a common pathway of damage produced by the immune system. A single cause can induce different clinical syndromes, depending on environmental influences and the host's specific characteristics, as described for other infectious conditions[67,68]. We have epidemiological evidence suggesting that the incidence of RA depends on presently ill defined host–environment interactions[69,70]. Diet and environmental modifications in experimental arthritis models influence the presence and severity of the disease[71,72]. These conditions could also have played a part in the proposed and not yet confirmed increased incidence of the disease in the Old World after 1492. In consequence, RA could also possibly arise from diverse antigens (or arrays of antigens) in diverse latitudes and historical periods. This possibility has not been taken into account until now when explaining the disease's historical evolution.

A new disease is not always one that has never been seen before, as Garrod stated. It is in most cases a previously present but unrecognized condition, of which acquired immune deficiency syndrome gives us a painful example[73]. Levins, *et al* proposed a set of conditions under which a new disease is recognized[74]. "New" diseases are old conditions that either had no previous chance of manifesting their complete natural history because of a short lifespan of the population, or prevalent conditions in populations with no previous voice in the medical establishment.

Based on Levins' premises, it seems that RA was identified as a "new" disease in the 19th century because of the longer lifespan found in European populations since then, and because health services examined a new population. Landré-Beauvais assisted low income patients. Scribonuis Largus was a military physician who accompanied Julius Caesar on some of his campaigns. Roman soldiers were often poor, since their payment was irregular in amount and in constancy[75]. Most of the ancient authorities cited in the English literature as evidence of the nonexistence of a convincing description of RA dealt with wealthy patients. López de Hinojosos treated patients of all incomes, from aborigines to wealthy Spaniards[76].

Since the Middle Ages, the lifespan of the general population has increased[77]. RA needs at least 10 years to leave the imprint by which it was recognized by all the cited authors: crippling deformities. When the average lifespan was around 40 years, it must have been difficult to find cases as severe as those needed to differentiate gout from RA by the criteria employed by physicians in those days. Few cases must have been available to study and recognize the evolution as clearly distinctive. Thus, an increase in lifespan was essential to allow a slow disease to develop. This is also the case for other chronic conditions, such as atherosclerosis[78].

AN INTEGRATIVE HYPOTHESIS

It is generally agreed that RA is the consequence of a sustained immune response probably triggered by an external antigen in a susceptible host[79]. The nature of this antigen is still a matter of debate, and it is possible that different antigens will produce the disease in different cases[80]. The biomedical model is the philosophical basis to explain disease. It depends upon the existence of a unique cause, capable of being integrated in a pathophysiological chain for each disease. This does not seem to be the case in most chronic conditions.

RA depends of the conjunction of a genetic predisposition and a supportive environment[81-83] — not only HLA genes, but also a genetically determined threshold at which the cytokine-hypothalamo-pituitary-adrenal system is evoked through inflammation[84,85].

As in animal models of autoimmunity, environmental factors could be fine tuners of the host's response[86]. In animal models, cell mediated autoimmune diseases like diabetes and adjuvant arthritis can be attenuated and totally prevented in their hosts by modifying intestinal flora. Normal flora protect them from the disease, while a germ-free environment aggravates it[87,88]. It seems a normal intestinal flora assures an ample range of antigenic stimulus for the individual, which diversifies the T cell repertoire and suppresses cell mediated immunity for antigens encountered this way.

RA seems to need the right person in the right place and, we should add, at the right time. It requires a susceptible host and a specific environment. The modification of any of these conditions should modify the presence of the disease in populations. It has been proposed that current increases of certain autoimmune conditions are a consequence of the high levels of hygiene found in developed countries[89]. There is some evidence pointing to a low prevalence of RA in underdeveloped countries[90]. An historical survey searching for evidence of an increase in suspected cases paralleling the economic development of a restricted geographical zone should give interesting results.

New models should be proposed to explain causality in chronic diseases. Ideally, we need a model to assess the specific weight of the environmental modifications induced by the Columbian exchange — for example, modification in European diet and customs by products from the New World[91]. One interesting example now under scrutiny is tobacco. Unknown in Europe before 1492[92], it has been proposed in recent years as an independent risk factor for RA[93-96]. The physiopathogenic mechanisms proposed are endothelial damage and increased production of rheumatoid factors[97].

Precise identification of the environmental determinants of the disease, if they are finally proven as individual antigens, would allow us to design specific vaccines for every important antigen in a specific geographic zone or to modify hazardous environmental conditions. With this proposal we intend to increase our knowledge of the etiologic factors of RA. The pragmatic benefit would be a rational design of treatments and a possible preventive strategy for RA.

The available written, pictorial, and paleopathological evidence clearly shows the existence of a chronic disabling polyarthritis well before AD 1700 that could not be modified by treatment. Women were more frequently affected, with a clinical onset before 40 years of age. Not accompanied by tophi, it disabled patients after years of pain. It existed in Europe and Asia well before 1492, and is referred to as a common condition.

By studying circumscribed geographic zones, like those reported by Rothschild, *et al*, it should be possible to define the environmental factors and potential antigens that can sustain a chronic immune response such as RA.

With the existence of osseous remains showing a polyarticular erosive disease similar to RA in diverse zones and historical periods worldwide, an exhaustive review of multiple burial sites could disclose similar specific geographic zones. A multidisciplinary approach to studying these zones will disclose ample information on the influence of the potential variables on the development of RA, by defining the environment to which the sufferers were exposed, their diet, and their genotype.

This is no new proposal. This is "two-dimensional epidemiology" as originally proposed by Dieppe and Rogers[98], applied to the study of RA.

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