

Rheumatoid Arthritis at a Time of Passage

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ABSTRACT. Objective. To determine the relationship of what has been called pre-Columbian Old World rheumatoid arthritis (RA) to the RA identified in pre-Columbian North America.

Methods. All published claims of pre-Columbian Old World RA were reviewed against the established North American standard for its recognition in archeologic sites. Those characteristics included polyarticular symmetrical marginal erosions [in the absence of subchondral erosions, peripheral joint fusion, or axial skeletal involvement (C1–2 excepted)], but requiring the presence of perilesional osteopenia on radiographic examination. T test and Fisher's exact test were used to assess the significance of the extent of joint distribution and the presence of subchondral erosions, peripheral joint fusion, and axial disease in the Old World cases that some have claimed represent RA.

Results. Old World reports of alleged RA often describe isolated bones or isolated "finds" without epidemiologic consideration. Subchondral erosions were present in 95%. The 2 cases without subchondral erosions had peripheral joint fusion and axial joint disease. Peripheral joint fusion and axial joint involvement were present in almost all cases. Perilesional sclerosis was actually quite prominent, as was other evidence of reactive new bone formation, but not perilesional osteopenia.

Conclusion. As the pre-Columbian Old World erosive arthritis is clearly a different phenomenon from what has been documented in the New World, the issue appears to relate to criteria for naming RA. There clearly are 2 distinct groups that some classify under the broad banner of RA. As the Old World variety is indistinguishable from spondyloarthropathy, it is suggested that the Old World cases should be recategorized with spondyloarthropathy and that only the variety reported in archeologic sites in North America be classified as RA. (J Rheumatol 2001;28:245–50)

Key Indexing Terms:

RHEUMATOID ARTHRITIS SPONDYLOARTHROPATHY ARTHRITIS EPIDEMIOLOGY
POPULATION ANALYSIS PALEORHEUMATOLOGY ANTHROPOLOGY

The approach of the new millennium and of the "bar mitzvah" date for the first unequivocal notation of rheumatoid arthritis (RA) in the archeologic skeletal record^{1–3} stimulated reexamination of the hypothesis of its origin in the New World. This is clearly established^{2–7}. It was first detected in the west branch of the Tennessee and Green Rivers, remained geographically localized for 5000 years, and disseminated into Ohio 1000 years ago, with only relatively recent global spread⁸. While genetic or population geographic stability might explain initial localization, the time course of the subsequent spread is incompatible with the hypothesis of major genetic determination of disease occurrence. This pattern is highly suggestive that a biologic agent (i.e., microorganism or allergen) is responsible for RA.

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A residual issue is the time course of its presence in the Old World. Cases of arthritis from pre-Columbian Old World archeologic sites have been attributed to RA^{9–22}. If those Old World diagnoses were accurate/valid, the peculiar early limited distribution of RA in North America would be difficult to explain. The reports suggesting Old World cases were therefore examined more closely.

Given the established position of the North American cases as representing RA^{1–4,8}, they are utilized as standards for comparison with the Old World archeologic cases. Further validation of this approach derives from the observation that the cemetery sites containing the North American individuals with RA had no individuals with spondyloarthropathy (SpA)^{1–4,8}. Thus, RA is confidently recognized, with no confusion related to findings caused by other forms of inflammatory arthritis.

MATERIALS AND METHODS

All published claims of pre-Columbian Old World RA were reviewed against the established North American standard for its recognition in archeologic sites^{1–4,8}. Those characteristics included polyarticular symmetrical marginal erosions [in the absence of subchondral erosions, peripheral joint fusion, or axial skeletal involvement (C1–2 excepted)], but requiring the presence of perilesional osteopenia on radiographic examination^{1–4,8}. The term "subchondral" refers to the area originally covered by cartilage, in contrast to the marginal region between the cartilage and the insertion of the joint capsule.

T test and Fisher's exact test were used to assess the significance of the extent of joint distribution and presence of subchondral erosions, peripheral joint fusion, and axial disease in the purported Old World cases.

The number of affected joints (joint distribution) was calculated by treating major joints as independent groups, but counting carpals, tarsals, metacarpals, metatarsals, and phalanges only once for each component (i.e., carpal, tarsal, metacarpal, or metatarsal) on each side, independent of the number actually affected^{1-5,8,23-30}. The purpose of this arbitrary convention was to provide criteria that worked, even in the absence of complete skeletal preservation. The latter is often problematic for the small joints of the hands and feet in archeologic sites.

RESULTS

The established North American archeologic standard. Among the reviewed North American sites, 35 individuals were affected (Table 1). This represented 4% of 850 individuals (6% of women, 2% of men) in this population study⁸. Symmetrical polyarticular erosive arthritis affected an average of 14 joint groups in these individuals (Table 2).

Erosive lesions with smooth, rounded lesional edges and smooth trabeculae were uniformly noted in joints in the North American sites^{1-4,8}. Involvement of diarthrodial joints was extensive, with hands and feet predominantly and symmetrically affected. Involvement was most severe at the metacarpal phalangeal (MCP), metatarsal phalangeal (MTP), and proximal interphalangeal (PIP) joints, with the least severe lesions at the distal interphalangeal (DIP) joints. Syndesmophytes, zygapophyseal, costovertebral and sacroiliac (SI) joint lesions, reactive new bone formation, periosteal reaction, and joint fusion were notably absent (Table 2).

Radiologic examination of affected joints revealed marginal erosions, limited to the bare area of bone within the synovial membrane-lined space, but extrinsic to cartilage-covered (subchondral) bone^{1-4,8,31}. Little or no sclerotic reactive bone could be detected at their borders. Even lytic lesions with nearly continuous bony floors did not show

significant radiologic evidence of condensation or sclerosis of bone (Table 2). This slight degree of bone deposition is below the radiologic threshold for visualization, which requires a change (gain) of 30–50% in bone density³². Periarticular/perilesional osteopenia was uniformly present on radiologic examination.

Old World reports. Let us now compare this North American archeologic standard for RA with what has been reported in the Old World. Arcini⁹ described subchondral cysts, severe fragmentation of periarticular bone, osseous ankylosis of joints, and eburnation. That is more characteristic of osteoarthritis and SpA. Several cases¹⁶⁻¹⁸ had misdiagnosed infectious arthritis/osteomyelitis and osteoarthritis as rheumatoid, because of the polyarticular nature of disease in those individuals. Bennike¹⁰ has now revised her diagnosis, recognizing that the isolated bones on which she made her diagnosis are not sufficiently diagnostic. Bourke¹² (p. 357) described “punched out areas at two interphalangeal joints and one distal interphalangeal joint.” That pauciarticular phenomenon certainly does not fulfill diagnostic criteria for RA. The punched out nature of the lesions actually raises the alternative likelihood of gout. It is the cases with multijoint erosive arthritis that are truly pertinent to the question — what disease is actually represented by the pre-Columbian Old World cases.

Most Old World reports of alleged RA describe isolated “finds” without epidemiologic consideration. Those revealing the denominator [size of the group in which the skeleton(s) were found] identify frequencies of 0.2–0.7% (Table 1).

Subchondral erosions were present in all but Ortner's cases (Table 2). Ortner's cases without subchondral erosions had peripheral joint fusion and axial joint (syndesmophyte, zygapophyseal, and sacroiliac) joint disease. Peripheral joint fusion was present in almost all cases of reported Old World polyarticular erosive arthritis, with the exception of one reported by Ortner²¹ and one by Blondiaux¹¹. Axial joint involvement was absent (when assessable) in only May's¹⁹ and Campillo's¹³ cases.

Those reports⁹⁻²² in which radiographs are reported or illustrated lack periarticular osteopenia. Perilesional sclerosis was actually quite prominent, as was other evidence of reactive new bone formation.

DISCUSSION

Analysis. None of the Old World cases is comparable to what has been recognized as RA in pre-Columbian North America^{1-4,8}. Publication of the characteristics of RA^{1,2} stimulated evaluation for its presence in other sites. As the epidemiologic approach was relatively new, there was a tendency to still report isolated cases. Review of Kilgore's suggestion of an isolated case is most informative^{15,23}. SpA was not in the considered differential diagnosis, indicating lack of realization that there was more than one form of

Table 1. Frequencies in other than isolated reports^{1-4,8,9,11,21,22}.

Site	Date (ybp)	Frequency	Percentage Affected
New World			
Libben	1200–850	9/210	4.3
Fort Ancient	1100–800	2/73	2.7
Carlston Annis	4300–4100	7/138	5.1
Eva	6500–6000	5/134	3.7
Averbuch	450	2/89	2.2
Seven Mile Island	4300	6/129	4.6
Koger's Island	450	4/77	5.2
Old World			
Clavel	1400	4/1193	0.3
Blondiaux	1000	1/150	0.7
	1600	1/239	0.4
Arcini	1100–800	4/2500	0.2
Thould	Medieval	1/416	0.2

ybp: Years before present.

Table 2. Characteristics of alleged Old World cases of RA.

Author	Date (ybp)	Periarticular Osteopenia	Subchondral Erosions	No. of Affected Joints	Peripheral Joint Fusion	Syndesmophytes/SI or Zygapophyseal Lesions	Current Diagnosis
New World^{1-4,8}							
Libben	1200–850	Present	Absent	20	Absent	Absent	RA
Fort Ancient	1100–800	Present	Absent	12	Absent	Absent	RA
Carlston Annis	4300–4100	Present	Absent	15	Absent	Absent	RA
Eva	6500–6000	Present	Absent	12	Absent	Absent	RA
Averbuch	450	Present	Absent	12	Absent	Absent	RA
Seven Mile Island	4300	Present	Absent	13	Absent	Absent	RA
Koger's Island	450	Present	Absent	14	Absent	Absent	RA
Old World⁹⁻²²							
Isolated bones							
Bennike	1600–4500	Absent	Present	1	Absent	Absent, incomplete*	Probably infected
Skeletons							
Klepinger	2200	—	Osteophytes	2	Absent	Absent	OA
Leden	4500–2100	Absent	Multifocal sequestra	?6	Present		Osteomyelitis Infectious arthritis Possible gout
Bourke	1300	—	—	3	Absent	—	
Arcini	1100–800	Absent	Present	5	Present	Absent, incomplete*	SpA
Hacking	1300	Absent	Present	10	Present	Present	SpA
Clavel	1400	Absent	Present	6	Present	Absent, incomplete*	SpA
Blondiaux	1000	Absent	Present	10	Present	Present	SpA
	1400	Absent	Present	12	Absent	Present	SpA
Thould	Medieval	Absent	Present	4	Present	Absent	SpA
Ortner	1400	—	Absent	6	Present	Present	SpA
	600	Absent	Absent	10	Absent	Present	SpA
May	5000	—	Present	9	Present	Absent	SpA
Campillo	1500–1800	Absent	Present	7	Present	Absent	SpA
Kilgore	600–1300	Absent	Present	6	Absent	Present	SpA

*Insufficient skeletal preservation to confidently rule out presence of lesions.

ybp: Years before present. RA: rheumatoid arthritis, OA: osteoarthritis, SpA: spondyloarthropathy.

multiarticular erosive arthritis. Once the existence of other forms of erosive arthritis (e.g., SpA) was recognized, Kilgore (personal communication, 1998) accepted that this case represented SpA, not RA.

Is there validity to any of the other cases? Despite the various authors' nomenclature, they are clearly different from what was found in North America^{1-4,8}. The population frequency, relatively limited multiarticular extent, presence of reactive new bone, peripheral joint fusion and axial skeleton involvement, and frequently subchondral distribution of the erosions⁹⁻²³ (Tables 1, 2) are at variance with what was found in the North American RA^{1-4,8}. T test comparison of the number of afflicted joints revealed a value of 4.799 (18 degrees of freedom), for a probability < 0.001 that they represent the same disease. Subjecting the cases to Fisher's exact test revealed probabilities < 0.0001 that the findings (absence of periarticular osteopenia and presence of subchondral erosions or peripheral joint fusion) are relatable to the documented North American cases of RA. Those characteristics, however, are typical of SpA²⁴⁻²⁶. The latter is characterized by specific patterns of marginal and subchondral erosive joint disease, and zygapophyseal and sacroiliac fusion and/or erosion^{28,30,32-35}.

Although 40% of SpA may have a polyarticular pattern^{28-30,36}, presence of peripheral or central ankylosis and sacroiliac joint erosions is pathognomonic^{28,30,32-35}. The presence of subchondral, as well as marginal erosions is characteristic of SpA^{28,30,32}. The subchondral localization of wrist erosions is at variance with observations in RA^{1,2,29,30,32}. Absence of periarticular loss of bony density is also characteristic of SpA^{28,30,32-34,37-39}. Postcervical spine and sacroiliac joints are unaffected in RA^{1-4,8,29}. Squaring, syndesmophytes, reactive enthesial remodeling, and zygapophyseal and sacroiliac joint erosion or fusion are notably absent in RA^{1,2,4,8,29,30,32,34}. Ankylosis is also absent in definitive populations with RA (prior to the advent of corticosteroid therapy)^{1,2,4,29}. The presence of such phenomena in the Old World cases cited in Table 2 eliminates RA as a possible cause^{1,2,8,29,30,32,34,38,39}.

RA (on a population basis) tends to affect almost every appendicular joint, with predilection especially for carpal, ulnar styloid, MCP, MTP, and PIP joints. The mean number of peripheral joints involved in RA is 14^{8,29,32,34}. This contrasts with the generally more limited involvement delineated in the Old World cases (Table 2). Such limited erosive disease would be highly unusual in RA, but is quite charac-

teristic of SpA^{8,25-28,30,32,39}. While slight variation in manifestation of different diseases may allow a single individual with one disease to mimic the “classic” appearance of another, the presence of sacroiliac erosions, zygapophyseal joint fusion, and peripheral joint fusion make a diagnosis of RA entirely untenable^{30,32-39}.

If these Old World cases were to be considered RA, they certainly exemplify a different RA than that described in early North America. As they are indistinguishable from SpA, continued use of the RA nomenclature does not seem supportable.

What is rheumatoid arthritis? As the pre-Columbian Old World erosive arthritis⁹⁻²² is clearly a different phenomenon from what has been documented in the New World^{1-4,8}, the issue appears to relate to criteria for identifying the RA category. The fundamental question would appear to be whether RA is a specific disease^{1,2,8,29,30,40} or simply a “catch-all” term for any inflammatory arthritis^{14,41,42} that tends to spare axial joints. Presence of axial disease in some of the purported Old World cases violates even that definition^{11,14,15,21}. If those authors were correct in diagnosing such individuals as having RA, there would seem to be little to distinguish RA and SpA.

Given the empirical nature of rheumatology and the potential benefit to disease understanding of narrowly defined groups, continued separation of RA and SpA seems meritorious. Subchondral erosions and peripheral joint fusion teleologically seem to be results of a different process than that producing marginal erosions or in which periosteal bone is lost.

Biomechanical analysis certainly reveals the 2 varieties of arthritis to be very different^{43,44}. Two very different vibration profiles were noted during electronically assessed knee motion. All individuals with lower vibration profiles had periarticular osteopenia and symmetrical polyarticular marginal erosions, but no axial disease or peripheral joint fusion. Those fulfilling the high vibration cluster had both subchondral and marginal erosions, and/or peripheral joint fusion, but no axial joint involvement. The latter vibration finding was indistinguishable from what was found in individuals with unequivocal (those with axial joint disease) SpA. The latter was recognized on the basis of axial joint disease (sacroiliac joint erosions or fusion, syndesmophytes, or zygapophyseal joint erosion or fusion).

Why were more severe cases not found? The difference between classic and typical cases may explain the rarity of severe cases in the archeologic record. While classic cases are often utilized to illustrate the disease, they are actually relatively rare even in clinical practice. Examination of over 50,000 human and animal skeletons revealed several thousand with SpA^{1-6,8,23-30,39,45-50}, but only a half dozen “severe” erosive cases. Less than 1% of rhesus macaques (20% with SpA) had severe erosive disease⁴⁶. The database for RA is an order of magnitude smaller. Severe cases of erosive disease

are rare in the archeologic, zoologic, and paleontologic record. While one could posit that severity in such cases might be so substantial that the entire bone is not preserved, that would not explain its rarity in the vast zoologic skeletal holdings^{23,27,30,39,45-50}. Severe disease is rare. Failure to recognize it yet in the archeologic record may simply be a statistical artifact, for such a rare phenomenon.

American Rheumatism Association criteria. The ancient North American cases of RA fulfilled the American Rheumatism Association (ARA) criteria³⁸ by virtue of identification of polyarticular symmetrical erosive disease. While some of the European cases may fulfill similar criteria, Silman’s critique⁴⁰ must be recalled. The 1987 criteria eliminated the exclusion categories inherent to application of the first ARA (now American College of Rheumatology, ACR) version. Those categories would have excluded a diagnosis of RA for the European pre-Columbian cases. The current analysis reinforces Silman’s concerns⁴⁰ about limitations of the ARC criteria for epidemiologic study, and suggests that the European cases represent a very different disease.

Conclusions

There clearly are 2 distinct groups that some classify under the broad banner of rheumatoid arthritis. As the Old World variety is indistinguishable from spondyloarthropathy, it is suggested that it should be recategorized with SpA and that only the variety reported in North America^{1-4,8} be classified as RA. Such classification revision would certainly be in conformity with biomechanical and archeologic findings, provide a natural categorization scheme, and perhaps allow opportunity for enhanced understanding of the pathophysiology of the disorder(s) we call RA.

While evidence of SpA abounds in the literature of human skeletal disease⁵¹⁻⁵⁶, pre-Columbian Old World RA remains elusive⁵⁷. The published, peer reviewed literature clearly still provides no credible Old World evidence of RA prior to New World contact^{5,8}. The evidence continues to support the hypothesis that a biologic agent is responsible for RA. Study of post-Columbian Old World skeletons is awaited to determine the time course of first occurrence of RA and perhaps identify the specific biologic agent.

Note added in proof: Two more cases of suggested pre-Columbian European cases of RA were presented at the 2000 European Paleopathology meeting in September in Chieti, Italy^{58,59}. Subchondral erosions of wrist and ankle fusion make the diagnosis of RA untenable and support the alternative diagnosis of spondyloarthropathy.

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