Unified Theory of the Origins of Erosive Arthritis: Conditioning as a Protective/Directing Mechanism?

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ABSTRACT. ***Objective.*** To validate the western Tennessee River limits of the originally described rheumatoid arthritis (RA) catchment area and to assess the possibility that absence of tuberculosis allowed the original development of RA. The hypothesis that RA was related to tuberculosis was once a driving force in treatment approach. RA initially was very limited in geographic distribution, in contrast to tuberculosis. Classical tubercular lesions were not observed in the rheumatoid catchment area in ancient times. Similarities between clinical and radiologic manifestations of spondyloarthropathy (SpA) and adjuvant arthritis raised the possibility of a potential conditioning role for occurrence of nonrheumatoid erosive arthritis.

Methods. Skeletal samples from ancient RA catchment and non-catchment areas were compared for frequency of tubercular-relatable pathologies.

Results. Tubercular-relatable osseous pathologies were found only outside the rheumatoid catchment area ($p < 0.0001$). The original RA catchment area was confirmed not to extend beyond the western portion of the Tennessee River.

Conclusion. There is an inverse relationship between occurrence of tuberculosis and RA in the Archaic and Early Woodland periods of North America. The virtually universal presence of tuberculosis in contiguous Amerindian populations contrasts dramatically with its absence in the ancient catchment area for RA. Conversely, SpA and tuberculosis do occur in the same populations. Tuberculosis may represent a conditioning agent for development of SpA, but at least potentially provides protection against development of RA. (J Rheumatol 2003;30:2095–102)

Key Indexing Terms:
SPONDYLOARTHROPATHY RHEUMATOID ARTHRITIS TUBERCULOSIS
PALEOEPIDEMIOLOGY EROSIVE ARTHRITIS

The origin of rheumatoid arthritis (RA) has been the subject of conjecture from both timeline and etiological perspectives[1-13]. Establishment of a timeline perhaps provides an opportunity to identify its etiology[10]. The timeline question actually proved resolvable. Six thousand five hundred years ago, only one area in the world contained individuals with a polyarticular symmetrical erosive arthritis, sparing sacroiliac joints and post-cervical vertebrae[10,14-17]. The female predominant (3:1) pattern in those populations is indistinguishable from that in RA today. Archaic occurrence of the disease was, however, very limited geographically. The western portion of the Tennessee and Green rivers of the USA hosted afflicted populations for over 6000 years (Figure 1). That zone also seemed to limit the geographic distribution of the disease[10,18]. No evidence of RA was found outside that catchment area (50 miles wide and 400 miles long) until 1000 years ago, when it was identified in a limited area of Ohio[10,18]. Even that remained quite focal in distribution until 200 to 300 years ago, when essentially worldwide distribution became manifest.

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What is not rheumatoid arthritis?

As the spectrum of another form of erosive arthritis, spondyloarthropathy (SpA), has been clarified[19-26], so too has the nature of RA. SpA is a disease characterized by vertebral and sacroiliac erosion and fusion, peripheral joint fusion, and peripheral joint erosion[20-26]. While peripheral joint erosions are found in both RA and SpA, examination of joint distribution can distinguish between them. Marginal erosions are found in both diseases[16,22]. Subchondral erosions are limited to SpA[20-26].

Subsequent to identification of RA in North America, there have been many attempts to identify ancient RA outside the original catchment area[27-41].

Examination of over 30,000 human skeletons outside the RA catchment area has not revealed any additional cases[10,18]. Examination of the purported European/African cases[27-41] reveals only SpA, osteoarthritis, or even infection, but no RA[10,18].

What is rheumatoid arthritis?

A disease geographically limited for 5000 years, increasing

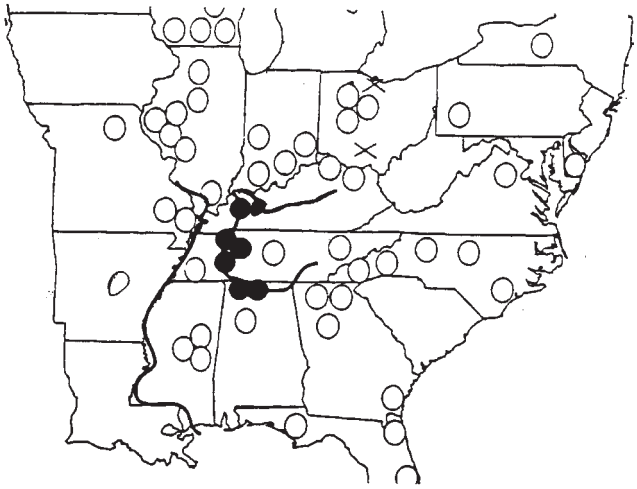


Figure 1. The initial RA catchment area, indicating location of documented sites.

in range 1000 years ago to subsequently manifest worldwide spread 200 to 300 years ago, RA presents a timeline incompatible with a primary genetic explanation for its distribution. Twin and other studies support that contention[42-44]. The staccato nature of the spread suggests the role of an allergen, or more likely, an infectious agent, that is responsible for the osteoclastic-type bone resorption characteristic of RA[45-47].

Etiology of rheumatoid arthritis

Efforts to identify such an agent, however, have not provided reproducible evidence[1,2,4-6,12]. While mycoplasma and L-forms have been considered[1,2,4-9,12], the etiologic agent(s) of RA is (are) still not identified. Part of the early confusion may have derived from misdiagnosis. Brown, *et al*[48] isolated mycoplasma (and reported therapeutic response) in gorillas they diagnosed as having RA. Subsequent investigation revealed that the gorillas actually had SpA[49], perhaps even reactive arthritis or Reiter's syndrome, secondary to infectious agent diarrhea[50]. Studies of patients with RA have not reproducibly identified a responsible agent. Perhaps there is another way of looking at the question.

The search for an animal model

Perhaps a clue to the etiology of RA lies not with what organisms can be associated, but rather with what has not? The search for an animal model provides perspective. While the collagen-arthritis model does not resemble (in character or pattern of involvement) any known form of human arthritis[51,52], the adjuvant arthritis model does — but not RA[52]. The adjuvant arthritis model actually mimics SpA in character and distribution quite closely — subchondral erosions, peripheral joint fusion, and predominantly wrist/ankle localization of erosions[22,52], and that may be an important clue.

SpA has been documented as essentially a worldwide disease[23,24,53], sparing only the catchment area for RA[10]. The 2 diseases have proven to be mutually exclusive in the ancient human skeletal populations examined to date[10,18].

Conditioning?

Perhaps we have been asking the wrong question. Asking what causes RA is the standard question. Perhaps we should ask what conditions are necessary for SpA to occur: Not what bacterial agents actually cause SpA, but rather, what allows them to cause SpA. One such conditioning factor relates to HLA-B27[50]. However, there may be an even more basic issue.

The tuberculosis-adjuvant consideration

Does similarity to adjuvant arthritis provide a clue? Recall that adjuvant arthritis is induced by a tuberculosis fragment-driven process (e.g., Freund's adjuvant)[54]. Could something related to tuberculosis or its biochemical constituents be a necessary factor that conditions immune response to certain stressors (e.g., *Salmonella*, *Shigella*) to produce SpA? Could absence of tuberculosis or of the pertinent biochemical constituent from the individual or the environment prevent occurrence of SpA or allow another disease (i.e., RA) to develop? Pacheco-Tena and colleagues[55] identified tubercular DNA in synovial fluid of people with SpA who had no evidence of active tuberculosis. Conditioning by *Mycobacterium tuberculosis* produces T cells that are nonresponsive to cartilage proteoglycans[56]. Such a conditioned animal would be susceptible to any insult/injury that releases proteoglycans. Said insult (e.g., *Salmonella*) could precipitate SpA. Could absence of that conditioning factor have been responsible for the original development of RA, rather than SpA?

Presence of tuberculosis in North American fauna

Polymerase chain reaction-amplified DNA evidence documents that *M. tuberculosis* was pandemic in bison and mastodons in North America, for at least 38,000 years[57]. Why is that pertinent? One in 4 bison and one of every 2 mastodons have pathognomonic bone erosions, undermining the articular surface[57,58]. As not all affected individuals with tuberculosis have bone erosions, the implication of this frequency in bison and mastodons is that the entire population was affected. Rather than immediately killing its host, tuberculosis revealed an accommodation (as it does in humans[59]), probably becoming walled off and inactive until some stressful event produces reactivation.

Tuberculosis in Amerindians

The story in humans is more complex. As the anthropologic record in North America is predominantly limited to skeletal material, only study of skeletal disease "imprints" allows epidemiologically meaningful diagnosis. Polymerase chain reaction of extracted DNA may some day allow identifica-

tion of *M. tuberculosis* in unaffected bone, but that has not yet been convincingly/reproducibly documented, and attempts at isolation from affected ancient bone have only limited success[57]. Most human skeletal manifestations of tuberculosis are nonspecific. Perhaps pathognomonic for tuberculosis in humans is the spinal lesion — destruction of the vertebral body with collapse and fusion, but not destroying posterior elements (gibbus phenomenon)[60]. The latter occurs in 1–2% of humans with untreated tuberculosis[60].

The corollary is that discovery of a 1–2% frequency of gibbus phenomenon in any group of individuals suggests that the whole group is affected — perhaps universal, rather than even pandemic disease, as Naegeli suggested[61]. Examination of skeletons from Amerindian cemeteries/ossuaries (across what is now the United States) reveals a 1–2% frequency (Table 1) of gibbus formation across the continent[62-65], with one possible exception.

There are sites in North America where no tuberculosis is found. With the exception of the western portion of the Tennessee and Green rivers (the original catchment site for RA), these sites are quite small. Indeed, combining sites from these negative areas still reveals too few skeletons to assess the question statistically.

The statistical question

An explanation of the statistical problem is required. If the frequency of an event (e.g., gibbus) in 2 populations is 0 in one population and even as high as 2% in the second, those population events will not be distinguishable — unless the population size exceeds several thousand in each group — even if one settles for being wrong (beta error) 20% of the time[66-68]. The number of individuals required to rule out the presence of tubercular gibbus phenomenon would be 2484 for a power of 80% and 3727 for 90%[68].

Table 1. Sites with gibbus reaction (derived from references 95–106).

Date	Locale
5000–3000 BC	Black Earth Site, Carrier Mills, IL
2250–750 BC	ALA-307, Bay Area, CA
1000–600 BC	Hatten Mound, 23MN275, Northeast MO
1000–100 BC	SON-299, Central CA
100 AD	AP530, Seneca Co., NY
200–1000	Hopewell Mound, IL
500–1200	AP529, Monroe Co., NY
650–1330	32GF1, Northwest MN
875–975	AZ-J-54-9, Kayenta Anasazi, Northeast AZ
900–1300	Tocito Burial 4A, Tocito, NM
1050–1550	Moundville, AL
1125–1425	Turpin Site, Central OH
1200	40WM1, Arnold Site, Williamson Co., TN
1200–1400	AP526, Seneca Co., NY
130–1500	San Cristobal, Tano Site, Galisteo Basin
1300–1500	Hawikku, Zuni Village, Western NM
1325–1521	Subway Route 2, Tram D, Mexico City

As reported North American populations/samples lacking the gibbus are smaller than 1000 individuals, tuberculosis (on the basis of pathognomonic gibbus formation) cannot be ruled out in the areas these represent. Although classic gibbus lesions were not recognized during the original evaluation of the catchment area for RA, more confident assessment of the actual freedom of those skeletons from tubercular bone lesions also requires examination of populations in those Tennessee (western portion) and Green River (western portion) sites for nonspecific changes.

If one includes nondiagnostic findings, one can make a stronger statement of exclusion[69]. El-Najjar reported[70] osseous lesions in 8% of 20th century tubercular skeletons. It therefore seemed appropriate to apply more liberal standards to populations from the western portion of the Tennessee and Green rivers to answer the question more fully. The numbers required for the latter are 241 for a power of 80%, and 313 for a power of 90%. Given the challenges to contemporary epidemiology related to subsequent occurrence of tuberculosis in individuals with established RA[71], and to avoid the potentially confounding factors of greater social interactions in the later Mississippian periods of North America[72], analysis of the confirmed RA catchment area was restricted to the Early Woodland and Archaic periods of North America. Verification that the catchment area was limited to the western portion of the Tennessee and Green rivers was also attempted by seeking more eastern sites along those rivers.

MATERIALS AND METHODS

Archaic sites examined. Archaic populations examined included Cherry (84BN74), Kay's Landing (15HY13), and Big Sandy (25HY18) from the RA catchment area and Seven Mile Island (LU25), Carlston Annis (15BT5), and Eva (6BN12), previously identified as having RA[10]. These were compared with Carrier Mills (11SA87), Hatten Mound (23MN275), and Ala-307, documented as having SpA[24].

Sites along the eastern portion of Tennessee and Green rivers. A search for well documented sites with adequate skeletal preservation along the eastern portion of the Tennessee and Green rivers revealed none in the Archaic or Woodland periods. The earliest site of sufficient size with adequate skeletal preservation from that area was Dallas (7HA1). Dallas is a Mississippian site (900 years before the present) located on the eastern portion of the Tennessee River, outside the previously identified RA catchment area[10].

Technique. Each skeletal element of all individuals was carefully observed by at least 2 authors, with concurrence as to the observation representing an erosion and ruling out artifact, such as animal gnawing or post-mortem trauma.

Identification of possible tuberculosis. Identification of possible tuberculosis in skeletons was predicated upon the presence of any of a variety of lesions: these included bone erosion and destruction of vertebral endplates, eventually leading to vertebral body collapse, fusion, and formation of the classic gibbus (although with general sparing of posterior vertebral elements)[60]. Peripheral joint involvement with erosion, trabecular disorganization, and joint fusion[60] was also sought. Trabecular disorganization and bone destruction with minimal reactive new bone formation were sought to distinguish tubercular arthritis from SpA[22,60]. Tubercular osteomyelitis was recognized as ill defined lytic areas. Surface manifestations include smooth, macroscopic zones of resorption (in contrast to the osteoclastic

fronts of resorption noted with RA or SpA)[22,60,73,74]. As nonarticular involvement is predominantly diaphyseal, in contrast to metaphyseal involvement in fungal disease[60], this attribute was also considered. While the gibbus is considered relatively specific for the diagnosis of tuberculosis[60] and the other findings noted above are nonspecific, all were sought to maximize the opportunity to recognize any potential tuberculosis in that population.

Rheumatoid arthritis. Diagnosis of RA was predicated upon presence of polyarticular erosive arthritis, compatibility of all the findings with our current understanding of that disease, and identity of skeletal pathologic changes with those noted in unequivocally diagnosed individuals[74]. The latter included periarticular osteopenia, marginally distributed erosions, axial skeleton (atlantoaxial junction excepted) sparing, and absent joint fusion[60,75].

Spondyloarthropathy. Diagnosis of SpA was predicated upon the presence of axial joint disease or peripheral arthritis and identity of skeletal pathologic changes with those noted in clinically unequivocally diagnosed individuals[22]. Specific identifying characteristics included joint fusion, erosions with subchondral distribution, reactive new bone formation, and variable perilesional bone density[60,75].

To achieve a statistical power of at least 90% (beta error < 10%) with alpha error < 5%, 315 individuals were needed in each study group. Statistical comparison of the frequency of possible tubercular lesions in the rheumatoid catchment and non-catchment areas was by chi-square and Fisher exact tests.

RESULTS

There was no osseous evidence for existence of tuberculosis in any of the examined Archaic sites in which RA was present (Table 2). This contrasted with sites with SpA, in which tuberculosis was clearly present (Table 2).

Examination of the Dallas site (the eastern portion of the Tennessee River) revealed 2 cases of SpA (Figure 2A), but no evidence of RA. Among the 4 cases of tuberculosis in that population, classic gibbus (Figure 2B) was present in one individual. The anulus fibrosus fusion in SpA (Figure 2A) is clearly distinguishable from the central vertebral body destruction, collapse, and angulation of tuberculosis (Figure 2B).

The absence of osseous signs compatible with tuberculosis was statistically significant in the Archaic and Early Woodland catchment area for RA, contrasted with outlying areas (chi-square = 12.4, p <0.0001; Fisher exact test < 0.0001).

DISCUSSION

It is ironic that one of the major pharmaceuticals (gold salts) in the history of RA suppression was actually first used because of the hypothesis that RA was caused by tuberculosis[76,77]. Now we examine the converse. Was it the absence of tuberculosis that allowed the original development of RA? The worldwide distribution of tuberculosis[78-82] may have spared the RA catchment area. The major questions are if and why.

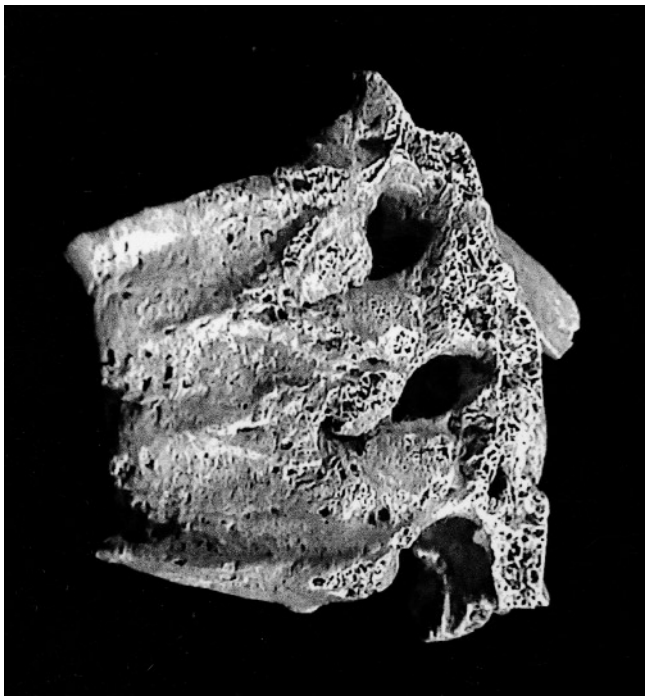
While tuberculosis is not increased in frequency among individuals with RA (compared to the general population)[71,83], the opposite question had not been fully explored. Further, modern life and transportation complicate the question of current tuberculosis exposure. It is to the ancient populations that we must turn to answer this question. The question of tuberculosis in RA has become even more complex with availability of the tumor necrosis factor antagonist infliximab[71].

Activation of tuberculosis has been noted with infliximab use in RA[84]. There is, however, one other consideration. Did those "rheumatoid"-labeled individuals with tuberculosis actually have RA? Given the common current tendency to lumping of patients with inflammatory arthritis under the umbrella of RA[85,86], it would be of interest to learn if those who developed tuberculosis actually had the symmetric erosive disease (sparing the sacroiliac and spine) and no subchondral erosions or joint fusion (in the absence of corticosteroid exposure). The latter would be considered classical RA[87]. Or did the patients who developed tuberculosis actually have what has been called a different disease[87], which many would classify as nonclassical — actually SpA[22,50]. Critical examination of such individuals and those from areas of rampant tuberculosis with inflammatory arthritis will be necessary to assess whether some really had RA or if the disease present was actually SpA.

Table 2. Tuberculosis assessment in selected American sites.

State	Site	Dates	Number	Tuberculosis Lesions	Diagnosis
AL	Seven Mile Island	4300*	129	None compatible	RA
KY	Carlson Annis	4300–4090	138	None compatible	RA
TN	Eva	6500–6000	134	None compatible	RA
TN	Cherry	4300	66	None compatible	RA
TN	Kay's Landing	4300	73	None compatible	RA
TN	Big Sandy	4300	48	None compatible	RA
IL	Carrier Mills	7000–5000	159	Present, 3%	SpA
MO	Hatten Mound	2000–2600	82	Present, 5%	SpA
CA	Cco295	2250	153	Present, 3%	SpA
TN	Dallas	900	67	Present, 8%	SpA

* years before present.



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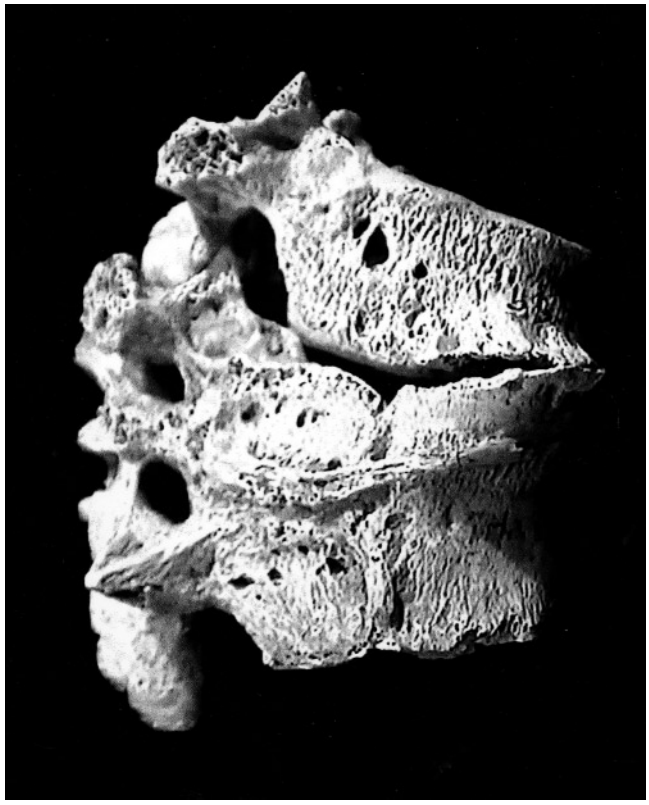

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Figure 2. Affected vertebrae in SpA and tuberculosis. A. Fusion through the anulus fibrosis in 7HA1#95, characteristic of SpA. B. Destruction of vertebral body with collapse and fusion, absent posterior element destruction, but with fusion of those elements (gibbus phenomenon) in 7HA1#89 characteristic of tuberculosis.

A dichotomy analogous to that of RA and tuberculosis also exists for tuberculosis and leprosy[88]. This is especially intriguing, as a rheumatoid-like arthritis has been reported with leprosy. As this arthritis generally resolves with treatment of the underlying leprosy[89-92], it is unclear if this is simply a rheumatoid mimic, or if it is further evidence that a form of mycobacteria (*M. leprae*), known to be protective against *M. tuberculosis* infection[88], actually (at least in the lepromatous form) "allows" the occurrence of RA.

This study supports the perspective that the original catchment area for RA was free of tuberculosis. It further documents the original perspective that RA was originally limited in distribution to the western portions of the Tennessee and Green rivers.

It is intriguing and perhaps pertinent that the catchment area for ancient RA excluded the distribution patterns (Figures 3 and 4) of the 2 large herbivores (bison and mastodon) documented to carry tuberculosis[57,58]. This contrasts with the presence in the catchment area of mammoths[93], megafauna in whom no signs of tuberculosis have been identified[58]. While bison and mastodon may have been extinct 6500 years ago in the catchment area, their environmental influence in other areas may be pertinent to conditioning to development of SpA.

Our initial search for the etiology of RA stimulated consideration of allergens or infectious agents that were specific to the catchment area[18]. The only factor that corresponded with this area was one aspect of habitat, termed the oak-hickory deciduum. The latter refers to a forest area in which oak and hickory trees predominate. Bison are predominantly plains animals and mastodons seem to prefer bogs (at least that is where their bones are found), in contrast to mammoths (whose bones are found in the catchment area)[107,108]. Thus it may have been an accident of forestation

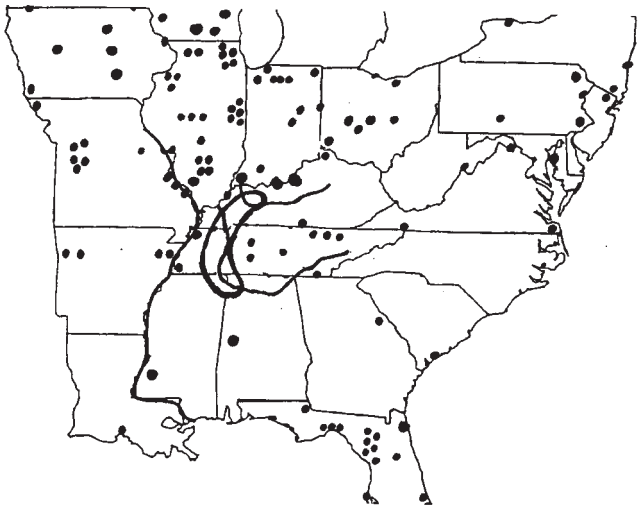

Figure 3. Distribution of bison in Eastern North America. Derived from references 93, 107.

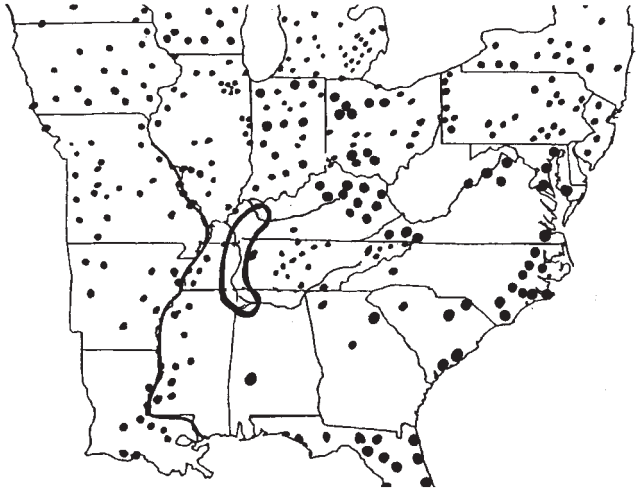

Figure 4. Distribution of mastodon in Eastern North America. Derived from references 65, 93, 107, 108.

that determined the distribution of these animals and set the scenario for the development of RA.

A possible differentiating role for tuberculosis in the development of RA or SpA seems appropriate to consider. Several questions arise: Is tuberculosis essential to this formula? Will any mycobacteria have the same effect? Why does *M. leprae* appear different? Can other organisms be substituted for mycobacteria? What component is responsible: cell wall, protein, DNA? Could the difference between mycobacterial DNA and mammalian DNA be a factor? It is apparently the unmethylated CpG dinucleotides (found in mycobacterial, but not mammalian DNA) that activate the immune system[54]. Does this give additional support to the work of Matsumoto and colleagues[94], who demonstrated precipitation of an inflammatory arthritis in mice by injection of antibodies to the enzyme glucose-6-phosphate isomerase? Another window to disease exploration seems opened.

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REFERENCES

1. Albert LJ. Infection and rheumatoid arthritis: Guilt by association? J Rheumatol 2000;27:564-6.
2. Aoki S, Yoshikawa K, Yokoyama T, et al. Role of enteric bacteria in the pathogenesis of rheumatoid arthritis: Evidence for antibodies to enterobacterial common antigens in rheumatoid sera and synovial fluids. Ann Rheum Dis 1996;55:363-9.
3. Chen T, Rimpilainen M, Luukkainen R, et al. Mononuclear cell response to enterobacteria and Gram-positive cell walls of normal intestinal microbiota in early rheumatoid arthritis and other inflammatory arthritides. Clin Exp Rheumatol 2002;20:193-200.
4. Cuellar ML, Espinoza LR. Infectious agents and rheumatoid arthritis. Rheumatoid Arthritis 2000;3:3-5,15.
5. Ebringer A, Wilson C, Tiwana H. Is rheumatoid arthritis a form of reactive arthritis? J Rheumatol 2000;27:559-63.
6. Hyrich KL, Inman RD. Infectious agents in chronic rheumatic diseases. Curr Opin Rheumatol 2001;13:300-4.
7. Nakagawa K, Brusic V, McColl G, Harrison LC. Direct evidence for the expression of multiple endogenous retroviruses in the synovial compartment in rheumatoid arthritis. Arthritis Rheum 1997;40:627-38.
8. Perl A. Mechanisms of viral pathogenesis in rheumatic disease. Ann Rheum Dis 1999;58:454-61.
9. Rook GA, Lydyard PM, Stanford JL. A reappraisal of the evidence that rheumatoid arthritis and several other idiopathic diseases are slow bacterial infections. Ann Rheum Dis 1993;52:S30-S38.
10. Rothschild BM, Woods RJ, Rothschild C, Sebes JI. Geographic distribution of rheumatoid arthritis in ancient North America: Implications for pathogenesis. Semin Arthritis Rheum 1992;22:181-7.
11. Silman AJ. The changing face of rheumatoid arthritis: Why the decline in incidence? Arthritis Rheum 2002;46:579-81.
12. Stransky G, Vernon J, Aicher WK, Moreland LW, Gay RE, Gay S. Virus-like particles in synovial fluids from patients with rheumatoid arthritis. Br J Rheumatol 1993;32:1044-8.
13. Zucker-Franklin D, Pancake BA, Brown WH. Prevalence of HTLV-I Tax in a subset of patients with rheumatoid arthritis. Clin Exp Rheumatol 2002;20:161-9.
14. Rothschild BM, Woods RJ. Symmetrical erosive disease in Archaic Indians: The origin of rheumatoid arthritis in the New World. Semin Arthritis Rheum 1990;19:278-84.
15. Rothschild BM, Turner KR, DeLuca MA. Symmetrical erosive peripheral polyarthritis in the Late Archaic Period of Alabama. Science 1988;241:1498-501.
16. Rothschild BM, Woods RJ, Ortel W. Rheumatoid arthritis 'in the buff': Erosive arthritis in representative defleshed bones. Am J Phys Anthropol 1990;82:441-9.
17. Woods RJ, Rothschild BM. Population analysis of symmetrical erosive arthritis in Ohio Woodland Indians (1200 years before the present time). J Rheumatol 1988;15:1258-63.
18. Rothschild BM. Rheumatoid arthritis at a time of passage. J Rheumatol 2001;28:245-50.
19. Granfors K, Marker-Hermann E, de Keyser F, Khan MA, Veys EM, Yu DT. The cutting edge of spondyloarthropathy research in the millennium. Arthritis Rheum 2002;46:606-13.
20. Rothschild BM. Rheumatoid arthritis in a Medieval skeleton: An illogical diagnosis for a case of spondyloarthropathy. Int J Osteoarchaeol 1994;5:218-9.
21. Rothschild BM, Woods R. Old World spondyloarthropathy: The gorilla connection. Arthritis Rheum 1988;31:934-5.
22. Rothschild BM, Woods RJ. Spondyloarthropathy: Erosive arthritis in representative defleshed bones. Am J Phys Anthropol 1991;85:125-34.
23. Rothschild BM, Woods RJ. Spondyloarthropathy as an Old World phenomenon. Semin Arthritis Rheum 1992;21:306-16.
24. Rothschild BM, Woods RJ. Character of pre-Columbian North American spondyloarthropathy. J Rheumatol 1992;19:1229-35.
25. Rothschild BM. Paleopathology, its character and contribution to understanding and distinguishing among rheumatologic diseases: Perspectives on rheumatoid arthritis and spondyloarthropathy. Clin Exp Rheumatol 1995;13:657-62.
26. San Zhang C, Rothschild BM. Zygapophyseal and costotransvertebral/costovertebral joints: An anatomic assessment of arthritis impact. Br J Rheumatol 1992;32:1066-71.
27. Arcini C. Rheumatoid arthritis — rare reality as recovered among

Scanian skeletal remains from Viking and Medieval times. Sydsvenska Medicinhistoriska Sallskapets Arsskrift 1992;18 Suppl:10-21.
28. Bennike P. Paleopathology of Danish skeletons. Copenhagen: Akademisk Forlag; 1985.
29. Blondiaux J, Cotten A, Fontaine C, Hanni C, Bera A, Flipo R-M. Two Roman and Medieval cases of symmetrical erosive polyarthropathy from Normandy: Anatomico-pathological and radiological evidence for rheumatoid arthritis. Int J Osteoarchaeol 1997;7:451-66.
30. Bourke JB. A review of the paleopathology of the arthritis diseases. In: Brothwell D, Sandison AT, editors. Diseases in antiquity. Springfield: Charles C. Thomas; 1967:352-70.
31. Campillo D. Etude des restes squelettiques d'un individu de l'epoque tardi-romaine, atteint de polyarthrite rhumatoide. Anthropologie et Prehistoire 1990;101:71-83.
32. Clavel G, Grados F, Viger B, et al. Was rheumatoid arthritis existing in the Middle Ages? About 4 cases [abstract]. Arthritis Rheum 1999;42 Suppl:S245.
33. Hacking P, Allen T, Rogers J. Rheumatoid arthritis in a medieval skeleton. Int J Osteoarchaeol 1994;4:251-5.
34. Inoue K, Hukuda S, Nakai M, Katayama K, Huang J. Erosive peripheral polyarthritis in ancient Japanese skeletons: A possible case of rheumatoid arthritis. Int J Osteoarchaeol 1999;9:1-7.
35. Kilgore L. Possible case of rheumatoid arthritis from Sudanese Nubia. Am J Phys Anthropol 1989;79:177-83.
36. Klepinger L. Paleopathologic evidence for the evolution of rheumatoid arthritis. Am J Phys Anthropol 1979;50:119-22.
37. Leden I, Persson E, Persson O. Peripheral polyarthritis in two neolithic skeletons. Ossa 1985-86;12:79-88.
38. Leden I, Persson E, Persson O. Aspects of the history of rheumatoid arthritis in the light of recent osteo-archaeological finds. Scand J Rheumatol 1988;17:341-52.
39. May WP. Rheumatoid arthritis (osteitis deformans) affecting bones 5,500 years old. BMJ 1897;2:1631-3.
40. Ortner DJ. Archaeological evidence of polyarticular inflammatory arthritides in North America. In: Appelboom T, editor. Archeology, history and antiquity of rheumatic disease. Brussels: Elsevier Press; 1987:6-10.
41. Thould AK, Thould ET. Arthritis in Roman Britain. BMJ 1983;287:24-31.
42. Jawaheer D, Gregersen PK. Rheumatoid arthritis: The genetic components. Rheum Dis Clin North Am 2000;28:1-16.
43. Jawaheer D, Gregersen PK. The search for rheumatoid arthritis susceptibility genes: A call for global collaboration. Arthritis Rheum 2000;46:582-4.
44. Svendsen AJ, Holm NV, Kyvik K, Petersen PH, Junker P. Relative importance of genetic effects in rheumatoid arthritis: Historical cohort study of Danish nationwide twin population. BMJ 2002;324:264-6.
45. Gravallese EM, Harada Y, Wang J-T, Gorn AH, Thornhill TS, Goldring SR. Identification of cell types responsible for bone resorption in rheumatoid arthritis and juvenile rheumatoid arthritis. Am J Pathol 1998;152:943-51.
46. Redlich K, Hayer S, Maier A, et al. Tumor necrosis factor alpha-mediated joint destruction is inhibited by targeting osteoclasts with osteoprotegerin. Arthritis Rheum 2002;46:785-92.
47. Suzuki Y, Tsutsumi Y, Nakagawa M, et al. Osteoclast-like cells in an *in vitro* model of bone destruction by rheumatoid synovium. Rheumatology 2001;40:673-82.
48. Brown TM, Clark HW, Bailey JS, Gray CW. A mechanistic approach to treatment of rheumatoid type arthritis naturally occurring in a gorilla. Trans Am Clin Climatol Assoc 1970;82:227-47.
49. Rothschild BM, Woods RJ. Spondyloarthropathy in gorillas. Semin Arthritis Rheum 1989;18:267-76.
50. Neiffer DL, Rothschild BM, Marks SK, Urvater JA, Watkins DI. Management of reactive arthritis in a juvenile gorilla (Gorilla gorilla gorilla) with long-term sulfasalazine therapy. J Zoo Wildlife Med 2000;31:539-51.
51. Rothschild BM, Woods RJ, Rothschild C. Paradox of erosive arthritis in New World monkeys: Collagen-induced versus naturally occurring spondyloarthropathy. Clin Exp Rheumatol 1994;10:92-3.
52. Rothschild BM, Hong N, Turnquist JE. Naturally occurring spondyloarthropathy in Cabo Santiago Rhesus macaques. Clin Exp Rheumatol 1997;15:45-51.
53. Rothschild BM, Arriaza B, Woods RJ, Dutour O. Spondyloarthropathy identified as the etiology of Nubian erosive arthritis. Am J Phys Anthropol 1999;109:259-67.
54. Ronaghy A, Prakken BJ, Takabayashi K, et al. Immunostimulatory DNA sequences influence the course of adjuvant arthritis. J Immunol 2002;168:51-6.
55. Pacheco-Tena C, Alvarado de la Barrera C, Lopez-Vidal Y, et al. Bacterial DNA in synovial fluid cells of patients with juvenile onset spondyloarthropathies. Rheumatology 2001;40:920-7.
56. van Eden W, Holoshitz J, Nevo Z, Frenkel A, Klajman A, Cohen IR. Arthritis induced by a T-lymphocyte clone that responds to Mycobacterium tuberculosis and to cartilage proteoglycans. Proc Natl Acad Sci USA 1985;82:5117-20.
57. Rothschild BM, Martin LD, Lev G, et al. Mycobacterium-tuberculosis-complex DNA from an extinct bison dated 17,000 years bp. Clin Infect Dis 2001;33:305-11.
58. Rothschild BM, Helbling M II. Documentation of hyperdisease in the Late Pleistocene: Validation of an early 20th century hypothesis [abstract]. J Vert Paleontol 2001;21:94A.
59. Enserink M. Driving a stake into resurgent TB. Science 2001;293:234-235.
60. Resnick D. Diagnosis of bone and joint disorders. Philadelphia: Saunders; 2002.
61. Naegeli O. Uber Haufigkeit, Lokalisation und Ausbreitung der Tuberkulose nach 500 sektionen des zuercherischen Pathologischen Institutes. Virchows Arch 1900;160:426-38.
62. Buikstra J. Prehistoric tuberculosis in the Americas. Evanston, IL: Northwestern University Archeological Program; 1981.
63. Buikstra JE. Paleoepidemiology of tuberculosis in the Americas. In: Palfi G, Dutour O, Deak J, Hutas I, editors. Tuberculosis past and present. Szeged, Hungary: Golden Book Publisher Ltd.; 1999:479-500.
64. Daniel TM. The origins and precolonial epidemiology of tuberculosis in the Americas: Can we figure them out. Int J Tuberc Lung Dis 2000;4:395-400.
65. Rothschild BM, Helbling M II. Pandemic TB or not TB [abstract]. Am J Phys Anthropol 2002;Suppl 34:134.
66. Fleiss JC. Statistical methods for rates and proportions. New York: Wiley; 1981.
67. Lupo KD, O'Connell JF. Cut and tooth mark distributions on large animal bones: Ethnoarchaeological data from the Hadza and their implications for current ideas about early human carnivory. J Archaeol Sci 2002;29:85-109.
68. Steel RG, Torrie JH. Principles and procedures of statistics: With special reference to the biological sciences. New York: McGraw-Hill; 1960:70-1,74-6.
69. Goldblatt M, Cremin BJ. Osteo-articular tuberculosis: Its presentation in coloured races. Clin Radiol 1978;29:669-77.
70. El-Najjar MY. Skeletal changes in tuberculosis: The Hamman-Todd Collection. In: Buikstra J, editor. Prehistoric tuberculosis in the Americas. Evanston, IL: Northwestern University Archeological Program; 1981:85-97.
71. Wolfe F, Flowers N, Anderson J, Urbansky K. Tuberculosis rates are not increased in rheumatoid arthritis [abstract]. Arthritis Rheum

2001;44 Suppl:S105.
72. Verano JW, Ubelaker DH. Disease and demography in the Americas. Washington, DC: Smithsonian Press; 1992.
73. Hershkovitz I, Rothschild BM, Dutour O, Greenwald C. Clues to recognition of fungal origin of lytic skeletal lesions. Am J Phys Anthropol 1998;106:47-60.
74. Leisen JC, Duncan H, Riddle JM, Pitchford WC. The erosive front: A topographic study of the junction between the pannus and the subchondral plate in the macerated rheumatoid metacarpal head. J Rheumatol 1987;l5:l7-22.
75. Rothschild BM, Martin L. Paleopathology: Disease in the fossil record. New York: CRC Press; 1993.
76. Forestier J. L'aurothiopie dans les rheumatisme chronique. Ann Med Interne (Paris) 1929;53:323-7.
77. Rothschild BM. Rheumatology: A primary care approach. New York: Yorke Medical Press; 1982.
78. Cave AJ. The evidence for the incidence of tuberculosis in ancient Egypt. Br J Tuberc 1939;33:142-52.
79. Daniel TM. The early history of tuberculosis in central East Africa: insights from the clinical records of the first twenty years of Mengo Hospital and review of relevant literature. Int J Tuberc Lung Dis 1998;2:784-90.
80. Daniel VS, Daniel TM. Old Testament Biblical references to tuberculosis. Clin Infect Dis 1999;29:1557-8.
81. Morse D, Brothwell DR, Ucko PJ. Tuberculosis in ancient Egypt. Am Rev Respir Dis 1964;90:524-41.
82. Zimmerman MR. Pulmonary and osseous tuberculosis in an Egyptian mummy. Bull NY Acad Med 1979;55:604-8.
83. Yun J-E, Lee S-W, Kim T-H, et al. The incidence and clinical characteristics of Mycobacterium tuberculosis infection among systemic lupus erythematosus and rheumatoid arthritis patients in Korea. Clin Exp Rheumatol 2002;20:127-32.
84. Kearne J, Gershon S, Wise RP. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001;345:1098-104.
85. Francois RJ, Eulderink F, Bywaters EG. Commented glossary for rheumatic spinal diseases, based on pathology. Ann Rheum Dis 1995;54:615-25.
86. Rogers J, Waldron T, Dieppe P, Watt I. Arthropathies in palaeopathology: The basis of classification according to most probable cause. J Archaeol Sci 1987;14:179-93.
87. Rothschild BM. Two faces of 'rheumatoid arthritis': Type A versus type B disease. J Clin Rheumatol 1997;3:334-8.
88. Jacobson RR, Krahenbuhl JL. Leprosy. Lancet 1999;353:655-60.
89. Gibson T, Ahsan Q, Hussein K. Arthritis of leprosy. Br J Rheumatol 1994;33:963-6.
90. Pernambuco JC, Cossermelli-Messina W. Rheumatic manifestations of leprosy: Clinical aspects. J Rheumatol 1993;20:897-9.
91. Modi TH, Lele RD. Acute joint manifestations in leprosy. J Assoc Phys India 1969;17:247-54.
92. Atkin SL, El-Ghobarey A, Kamel M, Owen JP, Dick WC. Clinical and laboratory studies of arthritis in leprosy. BMJ 1989;298:1423-5.
93. Corgan JX, Breitburg E. Tennessee's prehistoric vertebrates. Tenn Div Geol Bull 1996;84:1-85.
94. Matsumoto I, Maccioni M, Lee DM, et al. How antibodies to a ubiquitous cytoplasmic enzyme may provoke joint-specific autoimmune disease. Nature Immunol 2002;3:360-5.
95. Klepinger L, Henning D. The Hatten Mound A two-component burial site in Northeast Missouri. Missouri Archaeol 1976;37:92-170.
96. Roney J Jr. Palaeopathology of a California archaeological site. Bull Hist Med 1959;33:97-109.
97. Ritchie WA. Pathological evidence suggesting pre-Columbian tuberculosis in New York State [abstract]. Am J Phys Anthropol 1952;10:305.
98. Fink M. Tuberculosis and anemia in a Pueblo III (ca. AD900-1300) Anasazi child from New Mexico. In: Merbs CF, Miller RJ, editors. Health and disease in the prehistoric Southwest. Arizona State University Anthropological Research Papers 1985;34:359-79.
99. Cuesta M. La Poblacion de Mexico-Tenochtitlan Estudio de Osteologia Antropologica. Mexico City: Instituto Nacional de Antropologia e Historia; 1982:126.
100. Stodder A. Bioarchaeological investigations of protohistoric Pueblo health and demography. In: Larsen CS, Milner GR, editors. In the wake of contact. New York: Wiley-Liss; 1994:97-107.
101. Powell ML. Status and health in prehistory: a case study of the Moundville Chiefdom. Washington, DC: Smithsonian Institution Press; 1988.
102. Wells C. Bones, bodies, and disease: Evidence of disease and abnormality in early man. New York: Frederick A. Praeger; 1966.
103. Widmer L, Perzigian AJ. The ecology and etiology of skeletal lesions in Late Prehistoric populations from Eastern North America. In: Buikstra JE, editor. Prehistoric tuberculosis in the Americas. Northwestern University Archaeological Program 1981;3:99-113.
104. Sumner DR. A probable case of prehistoric tuberculosis from Northeastern Arizona. In: Merbs CF, Miller RJ, editors. Health and disease in the prehistoric Southwest. Arizona State University Anthropological Research Papers 1985;34:340-6.
105. Akins NJ. A biocultural approach to human burials from Chaco Canyon, New Mexico. Reports of the Chaco Center 1986;9:1-120.
106. Crane HR, Griffin J-B. University of Michigan radiocarbon dates IV. Am J Sci 1959; Suppl 1:173-98.
107. Graham RW, Lundelius EL Jr. Faunmap: A database documenting Late Quaternary distributions of mammal species in the United States. Ill State Mus Sci Papers 1994;25:289-92,424-5,460-1.
108. Hay OP. The Pleistocene of North America and its vertebrate animals from the states east of the Mississippi River and from Canadian provinces east of longitude 95°. Washington, DC: Carnegie Institution of Washington; 1923.