

## Arthritis through Geologic Time and its Environmental Implications

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### Abstract

The evolutionary significance of the geometric increase in prevalence of a specific disease, a form of inflammatory arthritis referred to as spondyloarthropathy, suggests either an as yet undetermined organismal benefit or an increase in environmental contamination. Recognized on the basis of sacroiliac joint pathology, the character and prevalence were assessed in Rhinocerotidae in North American, European and Asian paleontological collections. *Bemalambda* had identical pathology to that found in *Corythodon*. Sacroiliac fusion was noted in seven *Plesiaceratherium gracile* and in two *Coelodonta antiquitatis*. Miocene and Pleistocene occurrence in Europe and Asia revealed the identical trend to that noted in North America. Given the independent occurrence (Europe/Asia and North America) and parallel increase in population penetrance of spondyloarthropathy through geologic time and evidence from contaminated human sites, the results provides a window to an environmental exposure problem that has exacerbated over geologic time.

### Introduction

The geometric increase in prevalence of spondyloarthropathy through geologic [1,2] and again in recent [3] times was considered a possible indication of an as yet unknown organismal benefit. Spondyloarthropathy is a form of inflammatory arthritis characterized by sacroiliac or zygapophyseal joint erosions or fusion or vertebral bridging through the anulus fibrosus [3-6]. First observed as isolated occurrences in the Cretaceous [7], prevalences as high as 50% were noted in the North American Paleocene [8]. The affected groups in the Paleocene were evolutionary dead ends, a fate that could even be potentially attributed to this disease.

The disease surfaced again in the North American Eocene in two evolutionary lines (Equidae and Rhinocerotidae) and demonstrated increased population penetrance over geologic time. Now we find the identical scenario in Europe and Asia. Paleocene occurrence has been documented in a single individual from Asia, a member of the same family afflicted in the North American Eocene. It was therefore of interest to compare occurrence and prevalence of spondyloarthropathy in Asia and Europe with that in North America.

### Materials and Methods

The skeletal remains of fossil rhinoceros were subjected to visual examination to identify the presence of specific pathology in the collections of the Institute of Vertebrate Paleontology and Paleoanthropology, Beijing, China (IVPP); Tianyu Museum, Pingyi, Shandong, China (TN) and Ryksmuseum voor Geologie en Minearlogia (RGM), Leiden, Netherlands. The diagnosis of spondyloarthropathy was made on the basis of specific sacroiliac (SI) or zygapophyseal (ZA) joint erosions or fusion or vertebral bridging in the form of syndesmophytes [4-6]. Variation in prevalence of spondyloarthropathy according to locale was assessed by Chi square statistical analysis.

### Results

Sacroiliac joint fusion was identified in the only *Bemalambda* (IVPP V04115) for which the auricular surface (iliac-sacral junction) is preserved. *Bemalambda* dated at 58 million from Hukou, Nanxiang, Guangdong Sacroiliac fusion was noted in seven *Plesiaceratherium gracile* (TN 44-57, TN 44-47, TN 44-123, TN 44-1, TN 44-206, TN 44-8, and TN 44-2) and in two *Coelodonta antiquitatis* (IVPP V4387.45 and IVPP V4387.47 (Table 1). *Plesiaceratherium gracile* were collected from

Epoch	Locale	Genus	Afflicted/Examined	% Afflicted
Paleocene	Asia	<i>Bemalambda</i>	1/1	100
	N. America	<i>Corythodon</i>	3/18	17
Miocene	Asia	<i>Plesiaceratherium</i>	7/46	15
	N. America	<i>Teleoceras</i>	9/39	23
Pleistocene	Europe	<i>Coelodonta</i>	2/9	22

**Table 1:** Comparison of Prevalence of Spondyloarthropathy

the diatomites of the Early Miocene Shanwang Formation at the locality Xiejiahe in Linqu, Shandong of eastern China. *Coelodonta antiquitatis* dated at the Late Pleistocene from northeastern China. Miocene and Pleistocene occurrence in Europe and Asia revealed the identical trend to that noted in North America. Prevalence of spondyloarthropathy was independent of locale (Chi square = 0.853, non-significant).

### Discussion

The trend in North America was originally thought to indicate an advantage it provided to affected individuals [2]. Given the independent occurrence (Europe/Asia and North America) and parallel increase in population penetrance through geologic time [2], two additional explanations must be considered: Organismal and Environmental. Is there something specific to the genetic makeup of Coryphionidae and Perissodactylae that makes them more susceptible to or predetermined to spondyloarthropathy? Is there something in the environment that has evolved to be more potent or whose concentration has increased? Given the current, essentially trans-mammalian penetrance of spondyloarthropathy [1-3,9-20], the environmental hypothesis seems favored. This does not actually negate genetic effects (which may

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determine disease susceptibility), but seems to determine the prevalence with which a given animal develops the disease. Genetic drift could also be considered, but is much less likely as an explanation for parallel development in physically separate (different continents) populations.

Do experimental animal models offer potential insights to this question? The adjuvant arthritis model, although developed to model rheumatoid arthritis [21], actually appears more relevant to spondyloarthropathy [5,20]. Differential susceptibility of various rodent strains to development of adjuvant arthritis suggests genetic determination of susceptibility, while environmental exposure (to an as yet unidentified agent) determines occurrence. The adjuvant model is based on Freund's adjuvant, essentially fragment *Mycobacterium tuberculosis* [22,23]. A corollary would be to suggest that spondyloarthropathy is actually a form of adjuvant arthritis. The reactive variety of spondyloarthropathy could be considered a form of adjuvant arthritis, but with effect environmental adjuvants predominantly limited to enterobacteriaceae, *Chlamydia*, and perhaps *Yersinia* and *Campylobacter*. Thus, does Cenozoic prevalence reflect adjuvant reaction to increases in environmental stimuli?

Ankylosing spondylitis could be similarly considered adjuvant, as HLA-B27 animal studies have shown that disease does not occur in a microbiologically-sterile environment [24]. Ulcerative colitis and Crohn's disease alter intestinal permeability [25], allowing systemic exposure to antigens that would otherwise be excluded. Gastrointestinal alteration has similarly been noted in undifferentiated spondyloarthropathy [26]. The Koebner phenomenon in some individuals with psoriatic arthritis [27,28] indicates increased organismal reactivity, which may represent an additional genetic factor that alters the body's reaction to what would have otherwise been considered reactive arthritis (spondyloarthropathy). After all, the histological alterations of psoriasis and of the skin reaction in reactive arthritis are essentially indistinguishable [29].

We suggest the penultimate question is what in the environment is acting as the precipitating adjuvant. One could start by asking what "non-pathogenic" mycobacteria have the same biologic effect as Freund's adjuvant. But, why limit the question to mycobacteria? Several future courses of study are recommended: Evaluation of environmental bacteria for adjuvant function and evaluation of environments for presence of these bacteria. The latter is not straight forward. The environmental contamination in the Belleville and Rochester sites (cemeteries with identical population prevalence of spondyloarthropathy) was related to using the same carts to dump sewage in the lake (Lake Ontario) as were used to bring ice back for human consumption [30], so exposure was equivalent at both sites.

As the prevalence of spondyloarthropathy is indistinguishable in captive (e.g., zoo) and wild-caught animals [5], the problem is not simply artificial environments. That contrasts with osteoarthritis in mammals, where the effect of artificial environments is clearly documented [31,32]. As the prevalence of spondyloarthropathy was equal in lowland and mountain gorillas [12], general environmental contamination (with adjuvant-active microorganisms) is suggested, although not necessarily the same organism at the various locales. Is there a specificity to microenvironmental support of specific organisms? Do such locations correlate with increased frequency of spondyloarthropathy? Synchronous localization of spondyloarthropathy and tuberculosis in the archeologic record of North America [33] supports that hypothesis. These are questions that may be addressed by further examination of the archeologic record, related to times when population mobility was sufficiently limited as to allow identification of life history.

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