

Nonhuman Primate Seronegative Arthritis: Probability Values for Valuable Science in a Case Report



Among our more stochastically minded colleagues, it is fashionable to disparage the value of case reports. Still, case reports can have considerable scientific value, particularly in highlighting subjects for more extensive investigation using novel models. It is commonly known that pregnancy and many other biologic phenomena can be identified and studied with an $n = 1$. The nonhuman primate medical literature is replete with case studies¹. This reflects the scarcity of the available observations of diseases in these species and the eagerness by investigators to garner some new knowledge from these rare opportunities that might apply to human conditions. In nonhuman primate arthritis, a familiar example is the first publication of calcium pyrophosphate dihydrate (CPPD) crystal arthropathy affecting "Wilma," a Barbary ape at the Metropolitan Toronto Zoo². This publication led to the systemic study of nonhuman primate degenerative arthritis that resulted in the distinction of osteoarthritis (OA) from CPPD crystal arthropathy³⁻⁵. In turn, this led to the recognition of spontaneous OA in living nonhuman primates and its development as an appropriate model for OA in humans^{3,6-10}.

Polyarthritis in gorilla populations residing in zoo environments is well recognized¹¹⁻¹⁶. This has led to the discovery of the high frequency of HLA-B27 among gorillas and the association between HLA-B27 and spondyloarthropathy¹⁷. The successful therapeutic strategy of sulfasalazine administration for inflammatory polyarthritis in this species¹⁸ is based on these observations.

In this issue of *The Journal*, Hyrich and colleagues¹⁹ explore the characteristics and bacterial reactivity of gorilla synoviocytes derived from the left metatarsal joint of a gorilla acutely involved with seronegative arthritis. These studies revealed that the cells have surface expression of HLA-B27, that the bacterial clearances of *Salmonella typhimurium* and *Yersinia enterocolitica* were similar to clearances from synoviocytes of humans, and that the bacte-

rial clearance appears to occur by a mechanism other than nitric oxide production. Like humans, another gorilla sharing the same environment was also B27-positive, but showed no signs of disease.

Gorillas are said to have a higher incidence of reactive arthritis than humans. Gorillas live in warm, wet environments. Gorilla environments in zoos deliberately or coincidentally simulate this ecologic niche. This niche favors the propagation of the relevant enteric microorganisms. Presumably, these microorganisms are present in the gorilla environment much of the time. Indeed, enterocolitis is a major cause of morbidity and mortality in gorillas²⁰. Further, spontaneous abortion and stillbirth are common in zoo gorillas, raising the issue of relationships between fatal fetal outcomes and maternal enteric infections. This suggests that gorillas may be more susceptible to these microorganisms and, contrary to the limited findings in this case report, some mechanisms of enteric bacterial reactivity may differ from humans'.

These studies do raise stimulating questions. Why are only some of the HLA-B27 animals susceptible to polyarthritis, and why does this happen sporadically? Can we assume that the lowland gorilla, with high frequency of HLA-B27 and seronegative polyarthritis, has some biologic feature that allows joint inflammation to persist and that other B27-positive members of his cohort who do not have arthritis lack this feature? Can gorillas be studied to identify the mechanism that promotes persistence of joint inflammation? If found, will this feature be clinically relevant to the pathogenesis of human polyarthritis? While we are asking these questions, why should one bother to study occasional cases of seronegative arthritis or many other diseases in the restricted environments of zoos when large human populations with disease are available for study? This latter question has a ready answer composed of 2 parts: natural history and comparative biology. Humans with chronic dis-

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eases present almost invariably with a history of self-medication for the disease or ingestion of other drugs for intercurrent illnesses. Nonhuman primates do not have access to or capacity for self-medication, so that the presentation of arthritis reflects entirely the disease's natural history. In reactive arthritis, this provides assurance that the functional tests reflect the disease activity rather than modification by exogenous influences.

Comparative biology is important because if the disease is similar to that in humans but the human environmental conditions are different, the environmental conditions may not be pertinent to disease. For example, in CPPD crystal arthropathy and OA in nonhuman primates, studies⁷ have indicated that vegetarian versus meat diets, cold versus warm climates, and calcium content of water are not relevant for these disorders.

Returning to the specific question of polyarthritis in the lowland gorilla, this species appears to have both the HLA subtype and the appropriate environmental conditions that favor seronegative arthritis. Case reports such as the one in this issue point the way to careful systemic study of microbiologic reactivity in this species, which could yet yield the critical observation regarding biologic mechanisms underlying this condition. In this context, much more insight can be expected by studying further the naturally occurring polyarthritis in the gorilla species using advanced biologic analytical techniques.

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