

could well be the limited number of well-preserved skeletons dating from before AD 300 is just too small for us to have randomly encountered one with classic lesions. This reminds us once again of the difficulties in studying the past prevalence of a disease in which only a small fraction of infected individuals develop skeletal lesions we can confidently diagnose today.

Ekaterina A. Pechenkina

Department of Anthropology, Queens College of the City University of New York, Powdermaker Hall, 314 65-30 Kissena Boulevard, Flushing, NY 11367, U.S.A. (ekaterina.pechenkina@qc.cuny.edu). 2 IX 08

Mycobacterium tuberculosis is a curious pathogen. It is neither as old as some tropical pathogens that have circulated among primates for tens of millions of years (Martin 2003) nor as recent as pathogens acquired during the Holocene from domesticated animals. Members of the human lineage first encountered pathogens of the tuberculosis complex as early as 2.5 million years ago, when our ancestors spread into open habitats harboring abundant reservoirs of mycobacteria (Gutierrez et al. 2005). Surprisingly, tuberculosis remained invisible in the paleopathological record for almost the entirety of its coexistence with humans. Except for a single case of *Lep-tomeningitis tuberculosa* reported for a *Homo erectus* cranium from Turkey by Kappelman et al. (2008), no skeletal manifestations of tuberculosis have been found on human remains dating to before 8,000 years ago. Thereafter, tuberculosis-related lesions became fairly common, although with considerable interpopulation variation in their location and frequency.

Wilbur et al.'s paper is a thought-provoking meta-analysis of the effects of diet and nutrition on the epidemiology of tuberculosis in past populations. The authors propose a model linking manifestations of the disease to the levels of two dietary components: iron and protein. Their model postulates that diet-related anemia would curb the progression of tuberculosis infection, while protein deficiencies would elicit an aggressive form of the disease. Wilbur et al.'s approach has great potential. Using the known effects of dietary composition on disease progression to construct models for paleo-epidemiology ought to help resolve multiple conundrums in the human skeletal record with respect to tuberculosis, as well as to other diseases.

Their proposed model is simple by necessity: the low resolution of the paleopathological record prohibits addressing variation in individual human responses to pathogens or variations in the virulence of particular pathogens. Of greater concern is whether dietary levels of iron and protein are really the major factors affecting the progression of mycobacterial infection and whether the effects of variation in the availability of these two nutrients can be reduced to the tenets of the proposed model. The relationship between iron intake and

the progression of tuberculosis infection may not be as straightforward as the authors presume.

As Wilbur et al. suggest, extreme iron deficiency would impede the reproduction of mycobacteria. However, this shortage of iron would also compromise immune response by diminishing respiratory burst and nitrogen oxide production in macrophages, thus increasing the efficiency of initial infection (Schaible and Kaufman 2004, 948; Ekiz et al. 2005). Since low levels of dietary iron may produce such opposing effects on the progression of tuberculosis, it is not clear at what levels the benefits of dietary anemia in curbing mycobacterial reproduction would outweigh the disadvantages of compromised immune response.

Furthermore, chronic disease can cause anemia even when dietary iron is sufficient; this is probably a component of the innate response restricting pathogen proliferation (Zarychanski and Houston 2008). Patients suffering from tuberculosis often develop anemia as a result of the infection, even if their levels of dietary iron are normal. Successful treatment of these patients for tuberculosis restores their serum iron without iron supplementation (Lee et al. 2004; Sahiratmadja et al. 2007). Skeletal indicators of anemia interpreted as diet-linked could be the result of anemia due to infection instead (Stuart-Macadam 1992). It is possible that Wilbur et al. were unable to find a clear inverse relationship between skeletal manifestations of tuberculosis and anemia evidenced by porotic hyperostosis, not because porotic hyperostosis is an indicator of "limited utility" but rather because the relationship between tuberculosis epidemiology and anemia is nonlinear.

In addition, their proposed model seems to underplay the role of stress in the progression of tuberculosis. Persistent stresses in general, including physiological stress caused by malnutrition or nutrient deficiencies, result in immunosuppression by activating the hypothalamic-pituitary-adrenal axis, increasing both susceptibility to new pathogens and the reactivation of latent ones (Rhen and Cidlowski 2005, 1714). With specific respect to the progression of tuberculosis, almost any form of stress, including protein or caloric deficiency (Zachariah et al. 2002), lack of vitamins (Chan 2000), or even extreme psychological stress due to war, deprivation, migration, or natural disaster (Barr and Menzies 1994; Lerner 1996; Pavlovic et al. 1998; Ponticciello et al. 2005), correlates positively with increased morbidity and mortality.

We should acknowledge that the epidemiology of tuberculosis is an outcome of complex interactions among multiple factors having continuous variation, including levels of various nutrients, the virulence of particular strains, individual susceptibility, and so on. With all that in mind, it may well be that stress accounted for much of the recognized variation in the distribution of tuberculosis-related lesions in past populations. The transition to agriculture and population growth during the early Holocene introduced a whole series of new stressors into the human condition. One possible result was that the pathogenesis of tuberculosis became aggressive enough to cause skeletal lesions.