Native American disease history: past, present and future directions

Ann F. Ramenofsky, Alicia K. Wilbur and Anne C. Stone

Abstract

Infectious disease introduction in the Americas has been approached in historical, not biological, terms. We believe that this historical focus has limited scholarly understanding of Native American disease experience, past and present. Our goal is to link disease contact and contemporary Native American biology. We review the historical debates, and argue that advances in evolutionary theory and molecular genetics should be incorporated into models and descriptions of Native American disease history. Our discussion highlights the model of infectious disease evolution and host-pathogen interactions in terms of the classic division between host, parasite and environment. We reference specific infectious diseases throughout and examine the question of New World tuberculosis in detail. We are hopeful that our discussion will result in new directions for investigation of disease history in the Americas.

Keywords

Native Americans; infectious disease evolution; genetics; ancient DNA; tuberculosis.

Introduction

Since the mid-twentieth century it has been widely accepted that Old World populations introduced infectious diseases to Native Americans beginning with the Columbian voyages of AD 1492. This position emphasizes the separate co-evolutionary histories for both hosts and pathogens prior to Columbus. As a result, Native Americans had no immunological memory for Old World infectious agents; upon exposure, the risks of infection, morbidity, and mortality were high.

Beyond this description lie complexity and contention. There is no consensus regarding the timing, spatial scale, and impact of introduced pathogens. Resolving these issues is made more difficult by their association with the question of the size of Native American populations in 1492 (Cook 1998; Dobyns 1966, 1983; Henige 1998; Ramenofsky 1987; Shoemaker 1999; Thornton 1987; Ubelaker 2000). Following Dobyns' lead regarding the diffusion potential of smallpox (1966, 1983), Cook (1998) has argued that the 1518 smallpox outbreak

Routledge
Taylor & Francis Group

World Archaeology Vol. 35(2): 241–257 *Epidemic and Infectious Disease*
 ISSN 0043-8243 print/1470-1375 online
DOI: 10.1080/0043824032000111407

of Hispaniola was a ten-year pandemic, spreading from the Caribbean to Mexico and south to Bolivia. Severe native mortality and, in some cases, extinction followed in the wake of this pandemic. The result: first counts of people are post-pandemic. Estimating pre-European population size requires adjusting post-disease counts upwards.

Others have been more conservative regarding the potential for massive disease diffusion. Working in particular historical settings, these scholars have argued that disease outbreaks were more localized in extent and source. This pattern created regional mosaics of demographically altered and pristine populations at the time of direct contact (Baker 1994; Baker and Kilhoefer 1996; Cook and Borah 1974; Cybulski 1994; Newson 1993; Palkovich 1994; Ramenofsky 1996). After studying skeletal populations from British Columbia, Cybulski states: 'the clearest indications of historic period change on the Northwest coast pertain to a very recent date, only a century ago' (1994: 82). If disease events were more localized, then the size of the Native American population in 1492 accordingly shrinks.

Debate also continues regarding the suite of introduced infections. There is considerable agreement that many acute viruses (smallpox, measles, yellow fever, chickenpox, influenza, and cold), some bacteria (anthrax, whooping cough, and typhus), and some parasites (malaria and schistosomes) were introduced. Because the course of most of these infections is rapid, there is no skeletal involvement (Jackes 1983; Ortner and Putschar 1981), limiting the ability of bioarchaeologists to investigate these disease agents. Accordingly, bioarchaeologists have turned their attention to documenting the changing health statuses of Native Americans following European colonization (e.g. Larsen 2001). Questions remain, however, regarding the pre-contact status of long-lived infectious agents that are characterized by a skeletal expression (tuberculosis and epidemic syphilis), or those that could have been present in the Americas (bubonic plague) prior to human entry (for review, see Merbs 1992).

Disease contact in the Americas and its biological and cultural consequences form a significant research area, but the historical debates have curtailed the development of new questions or new directions in research. Given that the same documentary sources are frequently employed to argue all sides of any question, current investigations are inadequate for falsifying any position or for building new knowledge. On the other hand, the emergence and spread of new and highly virulent and pathogenic viruses (HIV, Ebola, Marburg, Lassa and, at the time of this writing, West Nile virus) has stimulated the massive growth of evolutionary studies of host-pathogen interactions that range from conceptual to empirical. Mathematical models, genetic epidemiology, gene sequencing, and the construction of phylogenetic trees are rewriting our understanding of the reservoirs and histories of common human pathogens, the variation among pathogen strains, and the evolution of host resistance.

We believe that the historical problem of disease introduction and diffusion can benefit from these recent advances by recasting the problem in evolutionary and genetic terms. Ultimately, such reformulation may help explain the demographic shift in parts of the Americas from predominantly Native to predominantly European and African, or why Native American mortality rates from such viral and bacterial infections as influenza and tuberculosis continue to be approximately twice those of other populations (Indian Health Service 1999).

In the following discussion, we link Native American disease history to current evolutionary and genetic knowledge of infectious diseases. This is an enormous undertaking because none of the early post-contact historical, archaeological, or osteological records contain all the requisite information and because current Native American populations are the survivors of the evolutionary gauntlet of European contact. Consequently, how completely they represent the genetic variation of Native Americans in 1492 is unknown. Perforce, our discussion is general and abstract.

We begin with a consideration of pathogen factors relevant to the widely accepted models of infectious disease evolution and pathogen virulence. We then consider factors of environment and host that pertain to the expression of disease on local and individual scales. We conclude by discussing the controversial status of tuberculosis as endemic to the Americas at the time of European contact. We show how genetic and evolutionary knowledge could contribute to the resolution of the controversy.

Pathogen factors: infectious disease evolution

Why is there consensus that smallpox, measles, yellow fever, chickenpox, influenza, whooping cough, and typhus were introduced to the Americas (see Ramenofsky 1993 for review)? A three-stage, unilinear model, first detailed by Fenner (1971, 1980) and recently popularized by Diamond (1999) provides the theoretical support for this list.

Disease evolution results from the interaction of three parameters: hosts, parasites, and setting. The disease load of humanity changed as these parameters changed. At each stage, new infectious agents evolved without the extinction of previous infections. Consequently, disease loads at later stages were larger and more diverse than those at previous stages. Population density was the major axis Fenner employed to separate stages, including hunter-gatherer, agricultural, and urban.

The above are all crowd diseases characterized by rapid onset and short duration. Following infection, the individual either dies or recovers. With recovery, immunity to that particular strain of the virus or bacterium is long-term or permanent. According to Fenner, crowd infections evolved where human populations were dense because the nature of the infection requires continual pools of susceptibles to survive. Such conditions first evolved in Europe and Asia following the agricultural revolution when human populations developed nucleated settlements. Additional viral infections, including smallpox, measles, mumps, and rubella, evolved with the development of cities. As stressed by Diamond (1999), initial agricultural sedentism was the necessary, but not the sufficient, condition for crowd diseases. The sufficient condition was domesticated animals, especially cattle and pigs, because they were the reservoirs for many crowd infections. The ancestral strains of current crowd infections jumped the domesticated ship, colonizing and initially causing illness and death in humans who relied on these animals for milk, meat, and hides. Over time, the virulence of the pathogen declined as selection favored commensal relationships in which both hosts and pathogens survived.

Most researchers argue that, despite the settlement density of Native populations in Central America and the Andes, absence of the conditions that promoted evolution of crowd infections in the Old World accounts for why Native Americans were at risk for

these diseases (Diamond 1999; Ramenofsky 1987 for review; Ramenofsky 1990). Old World, pathogenic, microbial evolution presumably post-dated human migration into the Americas. Agriculture and nucleated settlements evolved later in the Americas than in the Old World, and there were large areas that were neither agricultural nor densely populated. The result was that population density varied greatly in 1492. Finally, the suite of domesticated animals in the Americas was small, including turkey, muscovy duck, guinea pig, llama, alpaca, and dog. Consequently, before 1492, Native Americans suffered from such chronic diseases as chagas, leishmaniasis, and amoebic dysentery, diseases more typically found among dispersed or hunter-gatherer populations, but Native Americans were virgin soil for Old World pathogens. These diseases, once introduced, severely winnowed Native American populations.

The stage sequence of infectious disease evolution is the cornerstone of the Fenner and Diamond model. Reliance on this sequence to explain disease introductions into the Americas is causally efficacious. It accounts for what was absent prior to Europeans, and why it was absent. The cornerstones of evolutionary change, however, are variation and selection. Reliance on these principles opens up the possibility of numerous avenues of disease evolution.

Because domesticated pigs, for example, are traditionally thought to be the reservoir for all human influenza viruses, it follows that this disease was a European introduction. The source of epidemic influenza, however, is currently under investigation (Reid et al. 1999; Webster 1999; Webster et al. 1992). Gene sequencing of the pandemic influenza virus (Influenza A) has suggested that wild, migrating water fowl (ducks especially) are the reservoir for all influenza viruses in domesticated fowl, horses, whales, pigs, and humans (Webster et al. 1992). Although there is transmission of influenza viruses between humans and pigs, this form tends not to result in epidemics.

The relationship between wild avian populations and epidemic outbreaks of influenza has implications for the history of influenza pandemics and its introduction into the Americas. The 1918 pandemic of influenza was the most severe of the twentieth-century outbreaks, killing between 20 and 40 million individuals (Crosby 1989). While most influenza pandemics cause excess deaths among the very young and old, the 1918 strain disproportionately affected young adults (Cox and Subbarao 2000). This unusual pattern may have been partly due to resistance in older adults who lived through the 1840–60 pandemic, although it does not explain why the very young were not as affected (Brownlee and Fodor 2001; Taubenberger et al. 2001). The analyses of genes in the 1918 flu virus that were isolated from victims of the epidemic support the hypothesis that the 1918 subtypes have similarities to avian strains and had not circulated widely within the human or swine population prior to the human pandemic. Despite having the sequence data, clear causes of the virulence of the 1918 pandemic have yet to be discovered (Reid et al. 1999, 2000).

If continuing research supports the avian water-fowl hypothesis regarding influenza, it is possible that migrating fowl carried the virus to the Americas, and infected human populations at any time. The occasional pre-contact outbreak of epidemic influenza, however, does not mean that influenza A was an endemic Native American disease before Europeans, or that this strain was the only one introduced by Europeans. What it does suggest is that avenues of disease transmission are more diverse than that predicted by the unilinear model.

A more compelling challenge to the unilinear model is the recent gene sequencing and evolutionary analysis of *Shigella*, a dysentery-causing bacterium closely related to *E. coli*. According to Fenner (1980: 15), *Shigella* became part of the human disease load sometime after agriculture and sedentism, roughly 10,000 years ago, because it is unique to humans and is a short-lived pathogenic infection. However, after sequencing forty-six strains of Shigella and eight strains of non-pathogenic *E. coli*, Pupo et al. (2000) showed that Shigella is not a separate genus, but simply varieties of *E. coli*. The bacterial diversity of Shigella clustered into three main strains that evolved as the ancestral bacteria acquired genetic material that facilitated invasion of intestinal walls. Using synonymous nucleotide sites, Pupo et al. calculated mean distance between Shigella strains to estimate time of divergence from a common ancestor, suggesting that two of the strains evolved between 50,000 and 270,000 years ago. The third strain dated to approximately 35,000 years ago. Even if the mathematics of biological distance is off by millennia, Shigella is clearly older than the Neolithic. The researchers recognized the importance of this, stating:

> The estimated time of origin of Shigella forms ... correlates with the origin and expansion of *Homo sapiens* rather than with the development of agriculture. It is not clear what this correlation means. It may be that Shigella strains had a greater capacity to survive in small hunter gatherer bands in the paleolithic than currently assumed ... [or] that we have underestimated the complexity of human populations at 50,000 or 200,000 years ago.
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> (Pupo et al. 2000: 10571)

Besides raising questions about the age and transmission pathways of human infectious diseases, evolutionary studies are calling into question the long-held assumption that virulence, or the rate of host mortality, decreases over time. Because pathogens that kill their hosts are also biasing their own chances of survival, it is commonly believed that the most virulent expressions of microbial infections occur only with emergent diseases or in virgin soil populations. Over time, the most virulent strains will be selected against, and, as documented in their study of the myxoma virus among Australian rabbits (Fenner and Ratliffe 1966), less virulent strains will persist.

The assumption of decreasing virulence with time is a double-edged sword in Native American disease history. Recent Native Americans have extreme susceptibility to often acute infections such as influenza and tuberculosis (Indian Health Service 1999; Koenig 1921; Matthews 1886). Although, as detailed later in this paper, many factors, including socio-economic conditions, diet, and other concurrent infections, could be contributing to this incidence, these factors seem to pale by comparison with disease history. Essentially, current incidence rates account for the absence of crowd infections prior to Columbus and absence explains the present incidence rates.

Time, however, is only one variable determining changing patterns of virulence, and 'benign coexistence' (Ewald 1993: 86) is only one outcome. For example, the interaction between nematodes, *Pegascaspus* spp., and Panamanian fig wasps, *Tetrapus* sp., is several million years old, and, under appropriate conditions, the nematodes continue to consume the body of their hosts (Herre 1993). In this dramatic case, despite the time depth of the interaction, virulence has not been replaced by commensalism between parasites and

their wasps. Many variables, including selection, pathogen mode of transmission, and natural polymorphisms of pathogen and host, determine co-evolutionary paths that range from extreme virulence and pathogenicity to commensalism (Anderson and May 1982; Bergstrom et al. 1999; Bonhoeffer and Nowak 1994; Nowak and May 1994).

Understanding patterns of virulence can be greatly aided by the genome revolution which has resulted in the availability of the complete or partial genome sequences of numerous human pathogens including tuberculosis (*Mycobacterium tuberculosis*), leprosy (*M. leprae*), epidemic syphilis (*Treponema pallidum*), bubonic plague (*Yersinia pestis*) (Cole et al. 1998, 2001; Fraser et al. 1998; Parkhill et al. 2001), influenza (Orthomyxoviridae) (Buckler-White and Murphy 1986), HIV (Muesing et al. 1985; Ratner et al. 1985; Wain-Hobson et al. 1985), and malaria (*Plasmodium falciparum*) (Bowman et al. 1999; Gardner et al. 1998). These data can contribute to knowledge about pathogen mutation rates, the relationships between different strains, and how pathogens resist host defenses, in addition to why some strains of a virus or bacterium are more virulent than others.

Changing conceptions of pathogen evolution or virulence do not invalidate the historical premise that Europeans introduced infectious agents that were new to Native Americans. On the other hand, these conceptions certainly point to a process that was more complex than we have assumed. Some infections, like shigellosis and perhaps tuberculosis and syphilis, may have been present in both hemispheres, but the subspecies or strains could certainly have been different. Contact between Native Americans and Europeans may have resulted in an exchange of pathogens with equally severe morbidity on both sides of the Atlantic.

Environmental and host factors

Here we highlight the roles that environment (e.g. crowding, socio-economics, diet), dosage of new infectious organisms, current disease load (as well as past disease history), and host genetics play in individual and population responses to infectious organisms. All these aspects of the disease process must have operated during the early centuries of disease contact. Although our discussion separates these components, the division between host, pathogen, and environment is not absolute but depends upon one's perspective. To a pathogenic organism, for example, available hosts are a part of the environment, while, to different potential hosts, pathogens can be viewed as environmental components. We begin with the relationship between population density, or crowding, and infectious diseases.

Population density has long been recognized as essential in the emergence, maintenance, and diffusion of infectious diseases (Anderson and May 1992; Bailey 1957, 1975). Under conditions of crowding, there are larger pools of susceptibles that can provide a home for horizontally transmitted, respiratory pathogens. Given the association between infectious disease and population density, day-care centers, airports, and huge urban complexes (Chen 1994; Fenner 1980; Garrett 1994) of the twenty-first century correspond to Fenner's initial nucleation of 10,000 years ago. Anderson and May (1992), for example, note that, in modern African populations, age-related changes in incidence of measles are

directly related to density of settlement, with a significantly lower median age of infection in dense urban populations compared to isolated rural populations.

Population density is also one of the environmental variables with implications for the differential mortality among Native Americans at the time of disease contact (Ramenofsky 1990). In the Caribbean and Mexico, where native settlements were nucleated, or where native populations were pulled into mission centers as in Spanish Florida, California, and Ecuador (Jackson 1993; Milanich 1999; Newson 1995; Worth 2001), respiratory infections could gain a foothold. However, where native populations were dispersed, as on the Plains or in parts of the Southwest, and in the far Northwest, the chances of infection were likely far lower and the chances of survival greater.

There are also direct biological effects of crowding upon the human immune system that influence a host's susceptibility to disease. Recent experimental research by Power et al. (1998) demonstrated that, at low doses of mycobacterial pathogens, hosts were able to make an appropriate immune response and avoid tuberculosis; higher doses caused a much less efficient immune response that precipitated disease. The authors speculate that '[i]t is natural to suppose that crowded living conditions will lead more often to the substantial infection required to establish disease' (1998: 5747). Thus, crowding as a result of widespread relocation and concentration of native groups was one of the most important variables in terms of susceptibility to respiratory diseases.

In addition to population factors, other environmental factors are known to contribute to a host's susceptibility to infectious disease. The association of poverty and disease is widely accepted, although the exact mechanisms by which poverty exacerbates disease susceptibility are not yet known. What is known is that general nutrition can affect the immune system's ability to resist pathogens. Dirks (1993) shows that general starvation increases susceptibility to pathogens, and, conversely, that infection increases the level of general starvation. Severe social disruption, as typically occurs in warfare, forced relocation, and/or concentration, is causal in typhus epidemics (Harden 1993; Zinsser 1935); endemic typhus routinely occurs in cold climates, where frequency of bathing is decreased, with concomitant increase of frequency of typhus-carrying lice (Harden 1993).

Consideration of host genetics, at both the individual and the population levels, is also important in developing an understanding of disease susceptibility beyond simply assuming host naiveté. At the individual scale, the interplay of host genetics with pathogens typically encountered in the environment strongly influences the immune responses to future pathogenic challenges. An excellent example is the mycobacterial disease tuberculosis (TB). One of the few studies of the impact of tuberculosis on a naive Native American population was conducted on the Yanomamo Indians of Brazil (Sousa et al. 1997). Following contact with outsiders and exposure to *M. tuberculosis*, the Yanomamo suffered high rates of infection and disease. Serological studies indicated that high percentages of individuals were producing an immune response called Th2, probably a result of high prevalence of parasitic worm infection, in contrast with other Brazilian groups who produced predominantly a Th1 response (and thus had lower rates of disease). Although all healthy humans are capable of making both the Th1 and Th2 immune responses, the two downregulate one another. In other words, if the Th1 response is dominant, then the Th2 response is repressed. The Th1 response is the most successful at preventing disease from pathogens, such as *M. tuberculosis*, that live inside cells. When

extracellular pathogens such as helminthic worms are predominantly encountered, the Th2 response is the most effective. As with the Yanomamo, the extreme susceptibility in other Native American groups may have been programmed by their history, both individual and evolutionary, with other pathogenic organisms commonly encountered in their environments.

That host genetics influence susceptibility to infectious pathogens became abundantly clear at the end of the twentieth century in a number of candidate gene, association, and linkage studies on several populations worldwide. Leprosy, for example, has been clearly associated with alleles of the NRAMP1 gene in Vietnam (Abel et al. 1998). In India, vitamin D receptor gene alleles are associated not only with susceptibility to leprosy, but also with the type (lepromatous or tuberculoid) developed (Roy et al. 1999). These studies confirmed animal experiments and analyses of human twins that were conducted earlier and that indicated the importance of host genetics for susceptibility to disease. In addition, these studies demonstrated the influence of host genetics on duration and severity of disease following onset. Malaria, leishmaniasis, human immunodeficiency virus and the mycobacterial diseases, tuberculosis and leprosy, have been particularly well studied in this regard (see, for reviews, Davies and Grange 2001; Hill 1998).

Within a population, genetic diversity of alleles at loci important for immunity and cellular defense can influence the ability of a pathogen to enter a population or can influence the severity of disease. In particular, homozygosity is more common among small, endogamous populations, and, thus, as noted by Black (1992), this could affect the ability of a population to fight particular diseases. Black hypothesizes that New World populations in particular are more susceptible to disease because of their relative genetic homogeneity. This homogeneity would enable a pathogen that has adapted to avoid immune defenses of one Native American to then spread easily among other Native Americans and evade their defenses. It has been hypothesized that heterozygosity for HLA class I and class II alleles is advantageous for pathogen resistance (Doherty and Zinkernagel 1975). Carrington et al. (1999) performed survival and genetic analyses of HLA class I alleles among Caucasian and African American HIV patients and found that homozygous individuals in both groups rapidly progressed to AIDS.

The previous experience of a population with a disease can also influence the diversity at genetic loci. Almost all Africans are homozygotes for the FY*O allele at the Duffy blood group locus, which provides complete resistance to malaria caused by *Plasmodium vivax* (Miller et al. 1976). Among northern Europeans, a deletion in the CCR5 receptor gene appears to prevent HIV infection in homozygous individuals and slow progression to disease in individuals heterozygous for the deletion (Dean et al. 1996). The presence of this allele in northern Europeans may be due to genetic drift or to selection by a past disease agent.

The role that host genetics, environment, and current disease load play in determining the response that individuals and populations can make to infectious organisms has not been part of models of disease spread in the Americas. Incorporating these factors into thinking about Native American disease history is important, as they may illuminate the causes of differential mortality. In the southeastern United States, for instance, Larsen et al. (2001) have shown that native health was compromised at the time of European contact. It seems likely that poor health, in addition to the mission system, which was

continually aggregating people, was significant in native catastrophic decline. On the other hand, the dispersed settlement pattern of Native Americans in much of the western United States probably contributed to their survival. Today, the Navajo are the largest Native American tribe. Since the time of first description, they have lived in small, highly dispersed family units. This dispersion may have sheltered them from many infections and contributed to their historic low incidence of tuberculosis (Hrdlička 1909). The settlement pattern that helped them survive some crowd diseases, however, put them in contact with Hanta virus infections. While the addition of environmental and pathogen factors to disease models is challenging, it promises to shed greater light on post-Columbian epidemics. Below we discuss these issues for re-evaluating the impact of tuberculosis in the Americas.

Investigating tuberculosis

Tuberculosis is an excellent example of an infectious disease worthy of investigation in light of recent evolutionary, epidemiological, immunological, and genetics breakthroughs. According to Diamond (1999: 212), Europeans introduced tuberculosis to the Americas. This position echoes the early twentieth-century arguments of medical doctors (most notably Cockburn 1962; Hrdlička 1909; Morse 1961) who believed that *M. tuberculosis* was introduced. The assumption of introduction was supported by the extreme susceptibility and high mortality among Native American groups (e.g. Stead 1997). This position began to change in the middle decades of the twentieth century with the discovery of tubercular-like lesions in Peruvian mummies (Allison et al. 1973, 1981). These findings, in turn, led to a re-analysis of skeletal material and resulted in the suggestion that *M. tuberculosis* was present in the Americas prior to contact (see Buikstra 1976; Ramenofsky 1987 for review; Buikstra 1999). Daniel (2000) refutes the assumption of an Old World introduction, noting the geographical and temporal distribution of probable pre-Columbian tuberculosis cases and then using epidemiological research that showed that tuberculosis epidemics typically last 300–400 years. 'A similar time period for an epidemic wave of tuberculosis, beginning in the Andean region of South America about 1500 years ago, would leave many generations for susceptibility to redevelop among native Americans' (2000: 398). The high incidence of tuberculosis seen in post-contact Native Americans is thus consistent with early pre-Columbian epidemics in small Native American populations, with subsequent loss of acquired immunity in later generations of those same populations.

Genome research, on the other hand, has prompted renewed debate regarding the specific form of New World tuberculosis. A small fragment (IS*6110*) of ancient DNA diagnostic of the *M. tuberculosis* complex has been recovered from several sets of pre-Columbian remains throughout the New World (Arriaza et al. 1995; Braun et al. 1998; Salo et al. 1994). IS*6110* is present in all five members of the *M. tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. microti*, *M. africanum*, and *M. canetti*); it has subsequently been suggested that the New World organism may, in fact, have been *M. bovis* rather than *M. tuberculosis*, and that domesticated cattle in the Old World constitute the origin of human tuberculosis from *M. tuberculosis* (Stead 1997; Stead *et al.*

1995). If, in fact, *M. bovis* was present in the pre-Columbian New World, its propensity to infect animal populations would have provided a reservoir for occasional opportunistic human infection, which might indeed resemble disseminated *M. tuberculosis* disease in skeletal populations.

The suggestion that, pre-contact, New World tuberculosis resulted from a different subspecies has recently been challenged. Rothschild et al. (2001) examined a metacarpal of an extinct long-horned bison from the Natural Trap Cave in Wyoming radiocarbon dated at 17,870 ± 230 years BP. *M. tuberculosis* complex DNA was recovered by two separate laboratories, one of which determined that the organisms are genetically more similar to the human pathogens *M. tuberculosis* and *M. africanum* than to *M. bovis*. If valid, these results indicate that *M. tuberculosis*-like organisms were indeed present in the New World long before the arrival of Columbus, despite the assertions that they could not possibly have been (Stead et al. 1995). Finally, recent work by Brosch et al. (2002) indirectly lends support to the claim of New World Paleocene *M. tuberculosis*. Examination of the distribution of twenty variable regions in the genome of modern *M. tuberculosis* complex organisms indicates an evolutionary scenario wherein the common ancestor of *M. tuberculosis* complex organisms resembled *M. tuberculosis* genetically (rather than *M. bovis*). This is in direct contrast to the previously held belief that human tuberculosis evolved from the bovine variety (Stead et al. 1995), and thus solely in the Old World with the domestication of cattle. Further, Brosch et al. (2002) suggest that the increase of tuberculosis in eighteenth-century Europe may have been due to the evolution of strains with increased virulence. Regarding the extremely high prevalence of TB in Africa and India, the authors state that:

> It seems likely that these ancestral strains predominantly originated from endemic foci, whereas modern M. tuberculosis strains that have lost TbD1 may represent epidemic M. tuberculosis strains that were introduced into the same geographical regions more recently as a consequence of the worldwide spread of the tuberculosis epidemic.
>
> (Brosch et al. 2002: 3688)

Brosch et al.'s findings directly contradict the hypothesis that *M. tuberculosis* evolved from *M. bovis*. Taking them together with Rothschild et al.'s recovery of ancient tuberculosis DNA infecting extinct bison over 17 kya, it seems entirely possible that *M. tuberculosis* complex organisms ancestral to or closely related to modern human tuberculosis may have indeed been present in the New World. It is intriguing to speculate that the high tuberculosis morbidity and mortality experienced by post-contact Native American populations were due to exposure to subspecies or strains with higher virulence than those endemic to the New World (Ramenofsky 1996).

The new research in the fields of epidemiology, immunology, and molecular genetics highlighted throughout this paper suggests several avenues for future work on human tuberculosis. Determination of exactly which organism was present in the pre-Columbian New World may be possible using direct sequencing of polymorphic areas specific for *M. tuberculosis* or *M. bovis* on affected ancient remains. While we appreciate the difficulties involved in ancient DNA analysis, careful laboratory work that targets sites informative about strain characteristics would aid in understanding evolution. These methods should be first tested on known samples in medical collections. It is possible that the infectious

organism causing the lesions seen in the New World remains were of an as-yet undiscovered (and now extinct?) mycobacterium closely related to the *M. tuberculosis* complex. With the complete sequence of *M. tuberculosis* now available (Cole et al. 1998), molecular biological analysis of recovered ancient tuberculosis in both the New World and the Old World may help shed light on the antiquity and evolutionary histories of bovine and human tuberculosis.

Interesting questions that may finally be answerable include the specific/subspecific and strain affiliation of organisms recovered from ancient materials and their comparison to modern organisms in the area in order to address the question of authenticity (it is highly doubtful that pre-Columbian Native Americans were infected with the exact strains causing epidemics in the same geographical locations today). Brosch et al. (2002) suggest that examination of TbD1 presence/absence in ancient tuberculosis cases from various global regions and over different time periods would be especially useful for elucidation of the epidemiological and evolutionary history of human tuberculosis. By utilizing all of the modern techniques available to us, clearer insights into the question of New World tuberculosis should emerge.

Summary and conclusion

Although there is no question that Native Americans died in significant numbers following European contact, the assumption that introduced viruses and bacteria had uniform effects everywhere strikes us as an over-simplification. When there is no immunological memory, populations are at great risk for infections by foreign pathogens. Nonetheless, actual infection varies according to a whole set of factors, including population distribution, concomitant infections, diet, individual and group genetics, as well as the strain of the pathogen itself.

We have evaluated the assumption of uniform action and consequence by first analyzing the model of disease evolution that underlies assumptions regarding what diseases were introduced. This discussion both highlighted the internal contradictions of the model and argued that present virulence patterns cannot be used to justify assumptions about introduced diseases. In an effort to broaden the discussion regarding introduced diseases, we considered environmental and host genetic variables that must be factored into historical discussions. Some factors that contribute to the probability of disease contact, such as population density or population health, are easier to assess archaeologically than the identification of particular pathogens. Nonetheless, genome research is offering insight into pathogen evolution and variability, as well as host ability to repel pathogen invasion. Taken together, we believe that building new models that incorporate recent advances in evolutionary theory and genetics can provide more complete knowledge of Native American disease history. This knowledge, however, is only a beginning. The real challenge of the integrated research advocated here is to take the insights of history into the present, using them to improve, rather than to justify, the current health problems of Native Americans.

Acknowledgements

We would like to thank Peter Mitchell for requesting this paper. Our ideas have benefited from discussions with and comments by Marilyn Ramenofsky and Jeremy Kulisheck. Jane Buikstra, Della Cook, and Elizabeth Martinson provided insightful comments that improved the paper. We, however, are responsible for conceptual errors and omissions.

The University of New Mexico, Department of Anthropology

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