Commentary

Early human settlements as an opportunity for infectious microorganisms

1. Introduction

Emergence of new infectious diseases has been observed and documented in the 20th century, but the phenomenon must have occurred throughout history. The study of the factors that may be involved in this process is in its early stages (May *et al* 2001; Woolhouse and Dye 2001). Nevertheless, it is worth thinking of the possible implications of new theories in this young field to our understanding of historical events. Textbooks in history of medicine tend to highlight the importance of the emergence of infectious disease in humans as coinciding with the formation of settlements in the historical era (Fiennes 1978; Kiple 1993; Crosby 1994). It is believed that as humans gradually formed larger groups, settled down, and assumed more control over the growth of foodgrains, they also began to domesticate some animals. Thus they were exposed to an increased risk of acquiring animal-based infections (zoonotic infections). Close and persistent contacts between humans and domesticated animals, as well as changes in human diet, are generally considered central to the acquisition of new infections and diseases. This line of explanation is focused on humans, and the impact of the new ecology on animals and infective microorganisms tends to be left unexplored. I wish to argue in favour of a conceptual shift from the traditional point of view to one that is less anthropocentric and is focused more on the impact of human settlements on the infectious agents. This approach is justified because it places both humans and microorganisms in a much more encompassing natural environment and allows us to consider how both may have been subjected to natural selection during the period of early domestication. This approach is also supported by recent theories of the emergence of infectious disease.

2. Infectious agents and humans

The arguments presented in this paper are based on characteristics of infective microorganisms and humans and the interaction between them. Excellent discussions of several aspects of this interaction as well as historical and current examples are available (Dobson and Foufopoulos 2001; Baum and Bar-Gal 2003; Ewald 2003). Most infectious microorganisms are thought to be host-specific or limited to a few hosts. The restriction of an infection to a certain host is part of the evolutionary adaptation process that the host and the infective agent have undergone over a long period of time. A change in the 'habitat' for an infectious agent implies changes in the host or the infectious agent, or the introduction of a third party facilitator (e.g. a phage). A change in the host that is not detrimental to that host, that is, a permissive change, may take a huge number of generations. Given the vastly longer generation time of humans compared to microorganisms, it is more likely that such a change would occur in the infective component rather then in it human, or animal host.

3. The historical setting

Changing conditions resulting from early human settlements would have impacted those involved in that ecology – humans, domesticated animals and microorganisms. In the pampas or prairies of our ancestors, the most likely contact between species was on the feeding chain. Humans and animals had

nomadic life styles, thereby minimising the chances of cross contamination. Apes or hunter-gatherer humanoids are likely to have harboured about the same number of infections as any other large migratory animal (Kiple 1993; Martin 2003). But each species would have acquired its own infectious agents and diseases; an immune system with a different vocabulary and skills, as it were. The exposure of members of a species to a new infection could have had a fatal outcome as happened in the case of the massive epidemic that followed the exposure of native North Americans to infections that were, up to that time, limited to the European population (Kiple 1993).

As humans domesticated animals and became settled, they continued to improve their ability to control the growth of food in their immediate surrounding and maintain a supply of food throughout the year. This persistent, close contact of humans and animals gave rise to a new situation: infectious agents could be transferred and shared among animals of different species and humans. This period constituted a crucial step in the development of human societies, and it was accompanied by a noticeable alteration in the diseases that affect humans (Kiple 1993). Nevertheless, the relevant ecological changes would have been of more significance for the infective agents rather than for the humans. With their rapid generation turnover, the infectious agents were much better equipped to take advantage of this new ecology by using animals and humans as their explorative 'laboratory'.

Studies of ancient infections are limited by the degradation of biological material, but recent technologies promise some insights (Cohen and Crane-Kramer 2003; Rothschild 2003). Nevertheless, the possible outcome of this historical change in human habitat remains speculative. It is likely that in this process, and over time, there have been infectious agents that successfully adapted and moved from humans to animals and vice versa. There must have been infectious agents that successfully moved from one animal to another and, later, with further modification, 'jumped' to humans. Some domesticated or partially domesticated animals must have come in contact with their wild relatives, thus allowing for the transmission of newly modified infectious agents from the human habitat to the virgin wild habitats in forests or savannahs. In parallel to known human history (epidemics following the European explorations in the New World), the re-introduction of such modified infectious agents to the wild habitat may have had disastrous consequences to infected animals. Furthermore, some of the animal infections that were contracted originally from humans could act as reservoirs in the wild that could come back later and infect future human generations.

4. Recent perspectives

Some of the claims made in the previous section can be supported by observations. Rapid changes in microbial or viral flora in response to antibiotic therapy are well documented in current medical practice. Familiar examples include changes that result from the evolution of drug resistance. Such changes are usually facilitated via the acquisition (importation) of foreign genetic material from other infectious agents in their immediate environment. The likelihood of this happening is enhanced if the antibiotic fails to eradicate the whole stock of bacteria, or when there are many bacteria in the environment that already carry the resistant factor. The former situation corresponds to sub-optimal therapy; the latter is often seen in hospitals where, via plasmid exchange, generations of bacteria come to possess the information of which antibiotics are present in the environment. Another example comes from bacteria that can alter their life cycle and form a more resistant stage under hostile environmental conditions (physical, chemical, or biological); for example, L-form or cell wall deficient bacteria (Domingue and Woody 1997). The relation of these altered forms to disease is not well understood but it has been speculated that the alteration may result in altered disease processes and manifestations (Domingue and Woody 1997). We do not know what, if any, the consequences of such processes may have been for human history.

"[Most] ecological literature has paid little attention to invading microorganisms, including viral, bacterial, and protozoan agents of infectious disease. Studies of 'emerging disease' are relatively

et al 2001). The studies alluded to emphasize that pathogens can cross the species barrier, but this does not necessarily imply a successful establishment of an ongoing infection. Many factors influence the probability of success. They involve, among other things, the presence of other infections in the host (cross-immunity), the size of the susceptible population (measles virus requires

a population over 300,000 to avoid fading out), and the availability of an alternative reservoir for the microorganism (May *et al* 2001). Out of 1415 species of microorganisms pathogenic to humans, 868 (61%) are zoonotic infections. Interestingly, the majority (75%) of emerging diseases are of zoonotic origin (Taylor *et al* 2001). While direct transmission from animals is important for some zoonotic pathogens, the majority of humans are infected by other humans (Taylor *et al* 2001). Multi-host pathogens are prevalent among human pathogens and even more so among domestic mammal pathogens (Cleaveland *et al* 2001). An understanding of the dynamics of infectious disease in complex multi-host communities may help to mitigate the threat of infectious diseases to both humans and animals.

Current molecular biology technologies allow scientists to reconstruct the evolution of micro-organisms. The reconstruction process offers challenges and remains somewhat speculative but can yield interesting insights (Simmonds 2001; Rothschild 2003). Several examples are now available for the reconstruction of the evolution of microorganisms over time, their migration through different species and over different geographical areas. These include recent emerging diseases such as HIV and hepatitis as well as tuberculosis and syphilis, diseases that had their emergence much earlier in our past.

5. Summing up

The purpose of this commentary was to expand the traditional anthropocentric view of human infections and consider the possible implications of such a conceptual shift. I have tried to point out that the settlement of humans (and domestication of animals) could have resulted in the emergence of new diseases of animal populations. The diseases could then have spread from the domesticated animals to the 'wild' animal reservoir. This line of argument reflects the fact that human history is an integral and interdependent component of natural history.

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