Primates, Pathogens, and Evolution: A Context for Understanding Emerging Disease

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Introduction

Nonhuman primates (NHPs) are an important source of human infectious disease, likely due to our close phylogenetic relationship (Wolfe et al. 2007). Major human diseases that appear to have originated in NHPs include malaria (Liu et al. 2010), AIDS (Chen et al. 1997; Gao et al. 1999), and perhaps even hepatitis B infection (Chen et al. 1997). In addition, NHPs serve as a reservoir for infections such as yellow fever, monkeypox, and Ebola; indeed, it has been estimated that while primates constitute only 0.5 % of all vertebrate species, they have contributed approximately 20 % of major infectious diseases among humans (Wolfe et al. 2007). Conversely, human pathogens[1] can have devastating effects on NHPs, especially the great apes, all of which are listed as endangered species and some of which, like gorillas, are critically endangered. Infectious diseases have had substantial negative impacts on

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[1]Here we use the term "pathogen" broadly, to include both microparasites (viruses, bacteria, and fungi) and macroparasites (such as worms).

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wild great ape populations, exacerbating existing threats posed by habitat loss, human encroachment, and hunting (Boesch and Boesch-Achermann 2000; Leendertz et al. 2004; Wolfe et al. 1998). Whether occurring as epidemics, small outbreaks, or single deaths, infectious diseases can negatively affect the viability of small or isolated NHP populations, due to the characteristically low reproductive rate of many NHP species, especially great apes (Boesch and Boesch-Achermann 2000; Ferber 2000; Goodall 1970, 1983; Nishida 1990; Wallis 2000; Wolfe et al. 1998).

Understanding how pathogens move between human and NHP populations and sometimes become established in a novel host requires knowledge of a pathogen's evolutionary history in its natural host, as well as the potential for transmission in both its natural and novel hosts. However, establishing these evolutionary and epidemiological relationships has been complicated by methodological missteps and conceptual pitfalls. Molecular methods allow us to construct a better picture of the past disease-scape of primates, and the past few years have witnessed a veritable explosion of information regarding major pathogen transmission events between humans and NHPs. These data have helped to elucidate pathogens' histories, though much remains to be done. In this chapter, we discuss some of the theoretical issues and methodological advances involved in reconstructing the evolutionary relationships between pathogenic organisms, humans, and NHPs. Using examples of major human diseases and their causative agents, specifically malaria (*Plasmodium* spp.) and HIV (human immunodeficiency virus), we discuss the implications for understanding emerging infectious diseases in both humans and our closest relatives. First, we explore the differentiation of the human disease-scape, attempting to reconstruct which pathogens diverged with their human hosts over evolutionary time. Next, we outline which human pathogens are believed to have resulted from cross-species transmission from NHPs. Finally, we discuss examples of cross-species parasite transmission from humans to NHPs and consider their ramifications upon conservation biology.

Differentiation of the Human Disease-Scape

We begin this chapter by exploring the differentiation of the human disease-scape from the pathogen profiles of our closest NHP relatives. We frame this discussion in terms of "heirloom" pathogens and "souvenir" species—the former representing those that we inherited from our most recent common ancestor with chimpanzees and the latter those that entered human populations via a host species switching event.

Theoretical Considerations

Studies of human disease ecology suggest that infectious diseases affecting human populations can generally be grouped into two broad categories: those with a long-standing, millennial relationship with humans and the latter those that have been

more recently acquired. Sprent (1969a, b) was the first to make this distinction, identifying two distinct classes of microbes that afflicted hunter-gatherers in the Paleolithic: "heirloom species" and "souvenir species." Heirloom species are pathogens that originated in our anthropoid ancestors and continued to infect hominins and eventually modern humans. In contrast to heirloom species, souvenir species are newer evolutionary acquisitions that are typically "picked up" via exposure to zoonotic reservoirs or vectors (Kilks 1990). These diseases are generally zoonoses, i.e., infectious diseases that can be transmitted from animals to humans. Zoonoses can be contracted through a number of routes: from sympatric reservoir host species through cross transfer, through insect or animal bites, or through the preparation and consumption of contaminated animal flesh. It appears that many of these souvenir species are capable of temporary host switches without significant levels of adaptation, as long as the novel host is sufficiently similar to the natural host in terms of resources available to the pathogen (Kellog 1896, in Brooks and Ferrao 2005, p. 1292). Thus, these microbes can remain specialized in their natural hosts while infecting multiple hosts, including humans, across a wider ecological niche. In some cases, however, a souvenir species enters the human population and stays there permanently, adapting to its novel host and becoming established; indeed, as will be discussed, this category of souvenir species includes some of the major pathogens that affect human societies.

Given the complexity of pathogen host specificity and adaptation, it should come as no surprise that reconstructing the history of human pathogens is a difficult endeavor. Often, in studying the origins of human pathogens, it is necessary to gather samples from our close NHP relatives to assess the presence or absence of a pathogen in a given species as well as to determine its genetic relationship to human variants. As the examples ahead will show, this process frequently represents a limiting factor in our search for disease origins due to the difficulty inherent in collecting biological samples from wild NHPs, many of which live in remote areas of the world as well as being endangered and enjoying special protections. In order to illustrate the effect that host switching and limited sampling of NHPs can have on our understanding of a pathogen's history in humans, we present the cautionary tale of malignant malaria. By beginning our discussion of human pathogen origins with this example, we hope to demonstrate the careful attention to sampling necessary when considering the evolutionary history of even intensively studied pathogens such as *Plasmodium falciparum*, never mind the myriad less-studied ones discussed in this volume (e.g., *Treponema, Toxoplasma*, *Pediculus*, and *Pthirus* lice).

Malaria: From Heirloom to Established Souvenir Species

Malignant malaria, which is caused by *P. falciparum*, is the most dangerous form of the disease, with the highest rates of complications and mortality. This species of *Plasmodium* alone is responsible for an estimated 515 million episodes of

illness (Snow et al. 2005) and nearly one million deaths annually (WHO 2010). The pathogen has exerted tremendous selective pressure upon the human genome in recent history (Hamblin et al. 2002; Sabeti et al. 2002; Tishkoff et al. 2001), but fundamental questions persist about the *Plasmodium*'s history in humans.

Early molecular studies indicated that the protozoan's closest relative was *P. reichenowi* (Escalante and Ayala 1994), a parasite species found in chimpanzees. This species was, for many years, represented by only a single strain isolated from a chimp captured in the Democratic Republic of Congo several decades ago (Collins et al. 1986). For this reason, many researchers believed that humans and chimpanzees both harbored their own distinct malaria strains; humans were infected by *P. falciparum*, while chimps carried *P. reichenowi*. This was consistent with a scenario in which each host species possessed its own heirloom *Plasmodium* species.

More intensive sampling, enabled by advances in noninvasive techniques, has recently generated a novel twist on the origins of this pathogen by suggesting that *P. falciparum* should instead be considered a souvenir species in humans. By examining blood as well as noninvasive samples collected from many wild chimpanzees, researchers identified many new *Plasmodium* isolates among chimpanzee populations (Prugnolle et al. 2010; Rich et al. 2009). Sequence analysis showed that the global genetic diversity of human *P. falciparum* was very low relative to the diversity of chimpanzee *P. reichenowi* strains, indicating that the human species had diverged more recently than the chimpanzee species. This finding was inconsistent with *P. falciparum* being an heirloom pathogen in humans. Moreover, a more comprehensive study of fecal samples from nearly 3,000 wild great apes, including chimpanzees, gorillas, and bonobos from throughout Central Africa, prompted consideration of an alternative scenario regarding *P. falciparum's* original host (Liu et al. 2010). This study demonstrated that the gorilla branch of the *Plasmodium* phylogeny included the strains most closely related genetically to human *falciparum* strains. Thus, it would appear that all circulating *P. falciparum* strains might be the result of a single, very successful cross-species transmission event from gorillas to humans.

Given the propensity of *Plasmodium* to switch primate hosts (Garamszegi 2009) and the numerous twists and turns in the history of malaria thus far, it has been noted that only further in-depth sampling of wild animals will confirm that no still-closer relative is going undetected and that the current story is the correct one (Prugnolle et al. 2011). Even with regard to a well-studied disease such as malaria, our understanding may well change with future developments, which hinge on sample availability. As Wolfe et al. (2007) note, while resolving the debate surrounding the origin of malaria will not necessarily assist with global eradication of the disease, it may contribute to our broader understanding of the dynamics of disease emergence. With the potential importance of such knowledge in mind, as well as the complexity involved in determining a pathogen's history, we now turn to a discussion of which human infections appear to be due to heirloom pathogens and which appear to be caused by souvenir species instead.

Heirloom Pathogens and Human Paleolithic Ecology

During the Paleolithic, small human population sizes and, to a lesser extent, low population density would have limited the diversity of possible heirloom species affecting human and hominin populations by preventing sustained transmission of many viruses and bacteria (Dunn et al. 2010, p. 2590). However, some species of parasites and bacteria appear to have thrived in this setting. Characteristically, heirloom pathogens are organisms that are able to persist in small, dispersed populations; generate incomplete or short-lived immunity; or have a chronic course, enabling prolonged transmission to new hosts. Several potential heirloom species have been identified, including macroparasites such as head and body lice (*Pediculus humanus*) (Reed et al. 2004) and pinworms (*Enterobius vermicularis*) (Hugot et al. 1999) as well as Staphylococci (Cockburn 1967, 1971; Sprent 1962, 1969a). Other possible heirloom pathogens include the causative agents of yaws (*Treponema pallidum* subsp. *pertenue*) (Harper et al. 2008) and typhoid (*Salmonella typhi*) (Roumagnac et al. 2006).

The identification of extant pathogen species that belong to heirloom lineages has been controversial, however, as the example of *P. falciparum*, above, illustrates. Novel genetic data have assisted in this process, helping to clarify which species most likely belong in the heirloom category by providing information on pathogen divergence times and host histories. In addition, studies of host specificity in pathogens that infect wild NHP populations suggest that some major classes of parasites, such as helminths, are more likely to be heirlooms due to their species specificity than are protozoa and viruses, which are typically able to infect a wider swathe of hosts (Pedersen et al. 2005).

Unique patterns of human behavior have no doubt guided the adaptation of heirloom pathogens. Weiss and Wrangham (1999), for example, note that while chimpanzees and humans share 95–99 % of their DNA (Olson and Varki 2003), we only share approximately 50 % of our pathogens. More specifically, pathogens and parasites affecting wild NHP species primarily include helminths, viruses, and protozoa, while pathogens affecting humans are dominated by fungi and bacteria (Pedersen et al. 2005) (Fig. 1). The reasons for these differences are poorly understood but likely reflect divergent characteristics of host ecology and behavior.

The evolution of human herpesviruses may offer one example of an heirloom pathogen molded over time by uniquely human behaviors. Phylogenetic studies indicate that all eight members of the human herpesvirus family (Herpesviridae) likely derive from an ancestral viral genome which infected the last common ancestor of hominins and great apes (Gentry et al. 1988). Herpes simplex virus (HSV) spreads from sites of initial infection in skin or mucosal surfaces to neuronal cell bodies in order to establish latent infection, forming a long-term relationship with its host. This long latency would have allowed HSV to persist in small, low-density Paleolithic populations. There are two types of herpes simplex: HSV-1 primarily produces oral herpes infection, while HSV-2 primarily produces genital infection. HSV-2 appears to be the only type of herpesvirus among primates that is
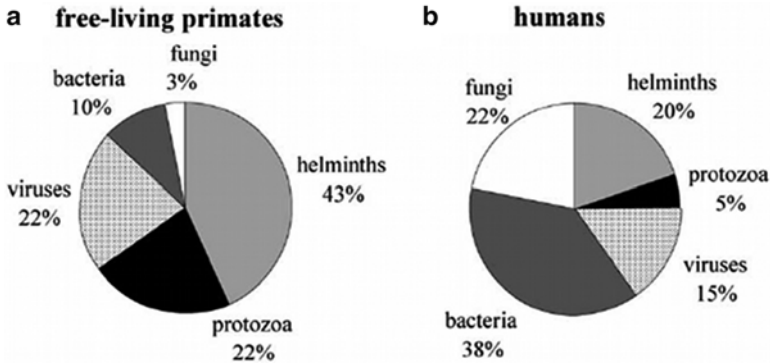
Fig. 1 Comparison of the taxonomic distribution of parasites in (**a**) free-living nonhuman primates and (**b**) humans. This data was based on a survey of 369 nonhuman primates and 1,415 humans (Figure reproduced from Pedersen et al. (2005))

transmitted primarily via sexual contact, and some have suggested that it may owe its existence to uniquely human sexual practices. The divergence of HSV-1 and HSV-2 dates back approximately 8–10 million years (McGeouch et al. 1995) and presumably reflects the development of species-specific tropisms for the epithelium of the oropharynx and the urogenital tract, respectively. For HSV-1 and HSV-2 to take on these distinct tropisms, oral and genital sites had to become microbiologically isolated from each other, while oral–oral and genital–genital contact between the hosts had to be maintained. McGeouch et al. (1995) have suggested that the evolution of continual sexual attractiveness of hominin females throughout the entire menstrual cycle, with an expected attendant increase in the frequency of sexual intercourse, and the adoption of close face-to-face mating among hominins, which may have facilitated the practice of kissing, provided the necessary conditions for the evolutionary divergence of HSV-1 and HSV-2. This hypothesis, of course, awaits rigorous testing, and more generally, the issue of how the behaviors of particular primate species provide niches conducive to sexual transmission remains a subject for further study.

Even absent the unique behavioral practices that characterize humans, however, millions of years of evolution in different hosts ensures divergence among the microbes that inhabit the bodies of humans and NHPs. For instance, the gut microbial communities of the great apes, including humans, have evolved independently with their hosts, diverging over the years in a manner consistent with host speciation patterns (Ochman et al. 2010). Common shared ancestors are hypothesized to exist between gut microflora species of humans and chimpanzees (Ushida et al. 2010) and also strepsirrhines (Bo et al. 2010). This suggests that some of the symbiotic microbes in human and NHP guts could be heirlooms. Understanding the intersecting roles of physiological similarity, behavioral divergence, environmental context, and microbial colonization is therefore crucial when reconstructing the evolutionary histories of heirloom microbes, both beneficial and pathogenic, in humans and NHPs.

Souvenir Species and Changing Human Ecology

Hominins, particularly the genus *Homo*, became increasingly generalized as they evolved new strategies for inhabiting and manipulating new environments. Modern humans, in particular, have increased the scope of their exposure to pathogens via the environmental modification and plant and animal domestication associated with the adoption and intensification of agropastoralism. Numerous souvenir pathogens have come to infect human populations, some of which have their origins among NHPs. Many of these primarily remain residents of their reservoir animal hosts. For example, though limited human-to-human transfer may occur in pathogens such as SARS or Ebola, they must be considered what Weiss (2009) designates "temporary exhibits" in humans. There are cases, though, in which a souvenir species adapts to its novel host so well that it becomes established and flourishes within human populations. One example, already discussed, is *P. falciparum*. Another major example comes in the form of HIV/AIDS, which we discuss here.

HIV: A Souvenir Species with a Complicated Past

Similar to the example of malaria discussed above, investigation into the NHP origins of HIV/SIV has demonstrated that continued research on even the most well-studied disease agents can yield important and surprising insights into their origins and evolution. HIV represents the best-known example of an NHP pathogen transmitted to and then sustained within humans, and it remains one of the most serious pandemics in history. The UNAIDS *Report on the Global AIDS Epidemic 2010* estimates that 33.3 million people are infected with HIV worldwide, among them 2.6 million children. It is estimated that some 25 million people worldwide have died from HIV-/AIDS-related diseases (UNAIDS 2010). The majority of individuals with HIV live in sub-Saharan Africa (UNAIDS 2010). Adding to the disease burden in sub-Saharan Africa and other regions with high rates of HIV is the fact that this infection disproportionately affects young adults (Patton et al. 2009), leading to high morbidity and mortality among those individuals who would otherwise be among the most economically active in their societies. A result of this pattern of infection is a demographic crisis in which young children and older adults carry the burden of looking after themselves, each other, and those who are infected. The fact that a disproportionate burden of infection is found in countries with high rates of political and economic inequality compounds this crisis even further (Fox 2012).

There are two types of HIV: HIV-1 and HIV-2. Scholars have understood for some time that both types evolved from the simian immunodeficiency viruses (SIVs), with HIV-1 deriving from the SIV variant of chimps (SIVcpz) and HIV-2 from the SIV of sooty mangabeys (SIVsmm) (Gao et al. 1999; Hahn et al. 2000; Hirsch et al. 1995; Peeters et al. 2002; Weiss and Wrangham 1999). SIV infection is quite common in NHPs over 40 species-specific SIV variants have been documented in

African monkeys (Sharp and Hahn 2010). Moreover, cross-species transmission of SIV has been postulated from African green monkeys to both patas monkeys (Bibollet-Ruche et al. 1996) and yellow baboons (Jin et al. 1994). In a survey of 788 wild-caught NHPs from Cameroon, serological evidence of SIV infection was present in 13 of the 16 primate species tested, with about 20 % of total samples testing seropositive (Peeters et al. 2002). SIV has also been demonstrated in sooty mangabey bushmeat samples from rural Sierra Leone, underscoring how the initial transfer of HIV-2 may have occurred (Apetrei et al. 2005). Therefore, NHPs represent a substantial potential reservoir of continued SIV transmission to humans.

Our understanding of where human HIV strains originated has become more nuanced with time. For example, it has long been understood that the HIV-1 lineage, as a whole, originated from chimpanzees; however, one group within the lineage may have a slightly different history than the others. HIV-1 group O (named for its "outlier" status) accounts for a relatively small proportion of HIV cases and is rarely found outside of Cameroon. Intensive sampling of wild chimpanzees and gorillas has demonstrated that HIV-1 group O appears to be most closely related to an SIV strain circulating in gorillas (SIVgor) (Van Heuverswyn et al. 2006). Thus, it is possible either that humans initially contracted the group O virus from gorillas or that chimpanzees independently transmitted the virus to both gorillas and humans.

How often does SIV take hold in humans, establishing sustained infection in its new host and spreading to other people? Determining the answer to this question requires extensive and sensitive surveillance of a sort that has yet to be conducted, but it appears that SIV infection in humans in close contact with NHPs is relatively common. In Cameroon, one man was found to be infected with a virus serologically related to SIVmnd, a version of the virus found in mandrills (Souquière et al. 2001), demonstrating that NHPs other than the great apes and sooty mangabeys are capable of transmitting SIV to humans. In another instance, a Cameroonian woman who reported no contact with great apes or bushmeat was found to harbor a novel HIV virus closely related to SIVgor (Plantier et al. 2009). The virus's high replication rate in this patient and the ease of its isolation in culture suggest that this novel variant had adapted to human cells and may have spread from human to human at some low level. Finally, 23 individuals out of a sample of 2,436 people at high risk for exposure through poaching and bushmeat consumption tested seropositive for SIV, though no active infections were demonstrated in this group (Djoko et al. 2012). Thus, it appears that SIV transmission to humans may not be a rare event, and a low level of human-to-human transmission may even occur at times.

What is the fate of individuals infected with SIV? Strains of SIV that infect mangabeys and macaques appear to be very closely related to HIV-2, which is less virulent than HIV-1. Accidental infection of two different laboratory workers with these SIV strains did not result in AIDS-like symptoms, despite the presence of SIV and HIV-2 antibodies (Khabbaz et al. 1994). This suggests that SIV infections in humans may not necessarily be harmful, which could prove lifesaving for individuals in Central Africa who have tested seropositive. However, Peeters et al. (2002)

have noted that recombination between SIVs and circulating HIVs may pose a threat to human health if it results in novel strains with an increased ability to exploit our species.

In conclusion, though the sequence of events that allowed for permanent establishment and spread of HIV-1 and HIV-2 in humans remains uncertain (Pepin 2011), molecular and epidemiological studies are providing a richer context for understanding these souvenir pathogens. As discussed, it has been known for some time that at least two host switches, one from chimpanzees and one from sooty mangabeys, resulted in HIV-1 and HIV-2, respectively. Recent research, though, has demonstrated that a third host switch from gorillas may have resulted in one rare HIV subtype (HIV-1 group O) (Van Heuverswyn et al. 2006). Additionally, molecular epidemiological studies have demonstrated that cross-species exposure to SIV is ongoing (Djoko et al. 2012) and may at times even result in low-level transmission among humans (Plantier et al. 2009). Thus, the potential for novel forms of HIV to take root in humans appears to be present, though most SIV transmission events seem to fizzle out quickly.

Major Factors Facilitating Adaptation of NHP Pathogens to Humans

Malaria and HIV, both discussed extensively in this chapter, are examples of pathogens that originally came from NHPs but found a permanent home in humans. There are multiple reasons why a given NHP host species may or may not become an established source of infection for humans. Phylogenetic relatedness and physical and environmental proximity are two primary—and tightly interwoven—factors which are likely to affect this dynamic. In an assessment of the animal origins of 25 major human infectious human diseases, Wolfe et al. (2007) partially attributed the finding that the majority of tropical infectious diseases arose in the Old World rather than the New World to the greater genetic distance separating New World monkeys and humans. It represents roughly twice the genetic distance between Old World monkeys and humans and many times that between humans and Old World apes. At the same time, physical proximity and shared habitats are likely to play a substantial role. For example, Wolfe et al. (2007) partially attributed the high number of souvenir infections arising in the Old World to the greater evolutionary time available for transfers between primates and humans there (c. 7–8 million years) as compared to the New World (c. < 14,000 years).

On a regional level, some populations have maintained fairly frequent exposure to NHPs. In Africa, South America, and Asia, in particular, communities living in close proximity to NHPs often become involved in activities associated with a high risk of exposure to NHP pathogens. Bushmeat handling and consumption provides one of the most effective means for the spread of pathogens from NHPs to humans

Fig. 2 Nonhuman primate bushmeat confiscated in the Lomako Forest of the Equateur province in the Democratic Republic of Congo. (**a**) Fresh remains of the lower half of a black mangabey (*Lophocebus aterrimus*) found at the Iyema study site in 2010. It lies atop a pile of leaves that were used to wrap it for easier carrying. (**b**) A pile of smoked bushmeat confiscated in 2007 by the members of the Institut Congolais pour la Conservation de la Nature, who work as park guards. The pile includes bonobos, monkeys, antelope, crocodiles, and red river hogs. (**c**) Close-up of a skewered and smoked monkey from the pile, most likely a black mangabey (Photo Credits: Amy Cobden)

(Fig. 2). Almost 100 % of villagers in rural forested areas of Cameroon have reported eating NHPs, with over 70 % involved in hunting and 30 % active in butchering (Wolfe et al. 2004a). Both activities involve repeated contact with potentially infective body fluids and tissues. They also generate opportunities for pathogen transmission to other individuals and communities linked by the bushmeat trade. A market survey of two cities in Equatorial Guinea recorded 4,222 primate carcasses on sale over 424 days (Fa et al. 1995), illustrating the great importance of NHP hunting to local economies.

The prevalence of human infections derived from NHPs suggests that these pathogens are able to exploit between-species interactions effectively. For example, Wolfe et al. (2005) found that bushmeat hunters in rural Cameroon are infected with a wide variety of human T-lymphotropic viruses (HTLVs), which are linked to leukemia, lymphoma, and HTLV-associated myelopathy, as well as multiple simian T-lymphotropic virus (STLV)-1-like viruses. The high diversity of these viruses in Cameroon indicates ongoing cross-species transmission from NHPs to humans. Similarly, at least three independent examples of NHP-to-human transmission of simian foamy virus (SFV), which to date has not been linked to any signs of disease in humans, have been confirmed in hunters (Wolfe et al. 2004b). Each event derived from distinct NHP lineages—De Brazza's guenons, mandrills, and gorillas—indicating that many species can potentially infect humans. Bites and scratches by NHPs, in particular, appear to be a very efficient means of transmitting viruses. In one study, over 35 % of hunters reporting such wounds were seropositive for SFV infection, and almost 2 % of serum samples belonging to adults from Cameroon were found to be seropositive as well, underscoring the high prevalence of cross-species transmission opportunities (Calattini et al. 2007).

While the factors leading to introduction of NHP pathogens into human populations are increasingly well characterized, the conditions that facilitate their establishment in our species are poorly understood. For example, though studies of Cameroonian hunters suggest that exposure to STLVs via NHP blood contributes to a greater diversity of HTLVs than is found in other populations (Wolfe et al. 2005), only HTLV-1 and HTLV-2 appear to have established themselves worldwide. Similarly, reports of the presence of dual HIV-1 and SFV infections in a commercial sex worker from the Democratic Republic of Congo and in a blood donor from Cameroon suggest the potential for SFV to be transmitted from human to human via sex or blood, as is HIV (Switzer et al. 2008). Such human-to-human transmission events appear to occur relatively rarely in the case of SFV, however. At present, our ability to predict which souvenir pathogens will "take off," flourish, and become established within human populations is poor. Nonetheless, continued attention to the movement of pathogens across the NHP-human interface may contribute to our knowledge of this process.

It is worrisome that the trend of increased contact between NHPs and humans seems to be intensifying. Population pressure, expanded ecotourism and conservation programs, and ever more powerful technological advances are enabling humans to encroach further and further into NHP habitats (Auzel and Hardin 2001). For instance, the villages surrounding logging concessions in Equatorial Africa have grown rapidly, often having increased from a few hundred individuals to several thousand. Political instability and forced migration, from Liberia into Sierra Leone, for example, have also played a role in the dramatic redistribution of human populations into areas of increased contact with NHPs (Hodges and Heistermann 2003). This new proximity, paired with the desirability of NHPs as prey, has increased opportunities for cross-species transmission events. In addition, people in these areas can utilize new and improved roads to transport bushmeat from remote villages to major cities, greatly increasing the number of humans who come into

contact with NHP carcasses. In truth, contact with wild NHPs now spans continents, reaching consumers who have never set foot in wild NHP habitat (Ellicott 2011); examination of bushmeat samples confiscated at US airports has revealed NHP tissue infected with SFV and herpesviruses (Smith et al. 2012). It is expected that these trends will intensify in the future, in the absence of decisive community-level and governmental actions to regulate ecotourism and constrain environmental destruction and the bushmeat trade.

Examples of Major Diseases Transmitted from Humans to Nonhuman Primates

Naturally, the increasing proximity between humans and NHPs also leads to greater opportunity for human pathogens to infect both captive and wild NHPs. In general, as the level of interaction between humans and NHPs increases, so does the risk of transmission of diseases such as measles and tuberculosis (Wolfe et al. 1998). Not surprisingly, there are many well-documented examples of captive NHPs becoming infected with human pathogens, with "immunologically naïve" great apes proving especially susceptible. For instance, there are frequent reports of tuberculosis infections of human origin among captive NHPs (Montali et al. 2001). Poliovirus can also infect chimpanzees and gorillas, as well as more distantly related anthropoids, like Colobus monkeys (Brack 1987; Suleman et al. 1984). As such, accidental exposure to infected laboratory workers has led to poliovirus infections of chimpanzees and gorillas since the 1940s (Ruch 1959). In another example, *Arcobacter butzleri*, which is a member of the same bacterial family as *Campylobacter* (Campylobacteraceae) and is associated with chronic diarrhea in humans, was implicated in a spate of cases of chronic diarrhea among captive primate populations at a research center (Andersen et al. 1993).

There is accumulating evidence for similar episodes of disease transmission in the wild (Adams et al. 1999; Homsy 1999; Wallis 2000; Wolfe et al. 1998; Woodford et al. 2002). There are a number of "likely" instances of human-to-NHP transmission. In perhaps the most infamous instance, in 1966, six chimpanzees at Gombe Stream National Park in Tanzania died from a polio-like virus, and six others were paralyzed for life, shortly after a polio epidemic swept through neighboring human settlements (Wallis 2000). Unfortunately, as no biological samples were collected from the animals, it was impossible to verify if the epidemic was due to a poliovirus introduced by local human populations or researchers (Wolfe et al. 1998). Confirmed examples of human to wild NHP transmission are relatively rare, due to the difficulty inherent in collecting samples but include *Cryptosporidium* infections in mountain gorillas (Nizeyi et al. 2002) as well as the cases discussed below.

Respiratory diseases, in particular, have been recognized as a major source of morbidity and mortality among free-living NHPs. This class of diseases is widely regarded as the most important cause of morbidity and mortality among wild great

apes habituated to the presence of humans, whether due to research, tourism, or human communities living in close proximity (Goodall 1986; Hanamura et al. 2007; Homsy 1999; Nishida 1990; Woodford et al. 2002). For example, a serological survey demonstrated that 100 % of macaques at a temple in Katmandu were seropositive for antibodies to the measles virus (Jones-Engel et al. 2006). Of more potential significance for NHP conservation efforts, about half of long-term chimpanzee research populations have shown major population declines that are likely a consequence of respiratory disease (Hill et al. 2001). For instance, Köndgen et al. (2008) have documented transmission of two common strains of human paramyxoviruses—human respiratory syncytial virus (hRSV) and human metapneumovirus (hMPV)—from humans to chimpanzees at a research station in the Taï Forest in Côte d'Ivoire. These two viruses are common causes of respiratory disease in humans. They are the leading causes of lower respiratory disease in children and, in developing countries, are a major source of infant mortality (Boivin et al. 2003; Weber et al. 1998). Transmission of the viruses from humans to the chimps of the Taï Forest resulted in five discrete epidemics during the study period, each accompanied by high morbidity, with an average of 92.2 % of individuals showing clinical symptoms. In three of the epidemics, 18–34 % of chimpanzees in the study population succumbed to the infection. Viral strains sampled from the deceased chimpanzees were found to be closely related to strains circulating in contemporaneous, worldwide human epidemics, indicating a link between the epidemic and the continuous flow of outside ecotourists and researchers at the station (Köndgen et al. 2008).

Unfortunately, such epidemics are not unique to the Taï Forest. hMPV was also identified in association with acute and fatal respiratory illness outbreaks in the chimpanzees of Mahale Mountains National Park, in Tanzania (Kaur et al. 2008). Additionally, hMPV was documented in association with two mountain gorilla deaths in Rwanda (Palacios et al. 2010). Thus, molecular epidemiology has confirmed that human pathogens are responsible for many of the "mysterious" ailments currently driving population declines in NHPs. Not surprisingly, fatal outbreaks of respiratory disease at Mahale Mountains National Park have coincided with peak tourist season (Kaur et al. 2008). Similarly, wild chimpanzees in Kibale National Park, Uganda, have been found to harbor *E. coli* strains genetically similar to those carried by the humans they come into proximity with via research or tourism. This underscores the fluid transmission of microbes from humans to NHPs made possible by high rates of ecotourism and conservation-oriented research (Goldberg et al. 2007).

As noted, while it is clear that human-derived pathogens have been responsible for swift epidemics and dramatic declines in NHP populations, often the identity of the agent responsible for a given epidemic remains merely suspected or wholly unknown. For example, outbreaks of gastrointestinal illness (Goodall 1983) and respiratory disease (Ferber 2000) suspected to originate in human populations have been recorded among chimpanzees in Tanzania from the 1960s onwards. Similarly, suspected cases of measles among gorillas were documented in Rwanda in 1988. Finally, suspected but unconfirmed cases of scabies among gorillas have been

reported in multiple regions (Kalema-Zikusoka et al. 2002). Our inability to determine the etiological agent responsible for most NHP diseases is due in large part to the difficulty of acquiring samples for diagnostic testing from wild NHPs. Systematic screening for the pathogens involved in NHP fatalities is performed infrequently, even though such investigations can reveal both the causal agents and, given the right molecular data, their transmission dynamics (Leendertz et al. 2006).

There is no evidence—yet—of sustained transmission of human pathogens among NHPs. It is probable that many human pathogens that have adapted to large populations with constantly replenished pools of susceptible hosts (i.e., crowd diseases) "burn out" after rapidly infecting small groups of NHPs. The possibility of sustained transmission of human pathogens in NHPs is certainly possible, however, especially for infections with long latent periods. Kaur et al. (2008) note that persistent infection with hMPV in the absence of respiratory symptoms has been demonstrated in humans; if the same is true in NHPs, then the potential of individual animals to carry the disease from one group to another via emigration could have devastating consequences. Implementing rigorous, systematic monitoring of infectious disease outbreaks as part of modern conservation practice is being strongly encouraged (e.g., Leendertz et al. 2006) and gradually implemented (e.g., the Great Ape Health Monitoring Unit (http://www.eva.mpg.de/primat/GAHMU/ index.htm) and the Mountain Gorilla Veterinary Project (http://www.gorilla doctors.org/)). It seems reasonable that given increased surveillance of NHP infections, examples of human microbes capable of sustained transmission among NHPs will be identified.

Conclusion

The surveillance of humans living in close proximity to NHPs has revealed tantalizing clues about the process of disease transmission from NHPs to humans. Perhaps intensive study of circulating strains of HIV/SIV, HTLV/STLV, and SFV will increase our knowledge of the features which characterize cross-species transmission events that result in subsequent sustained transmission between humans. In addition, the explosion of knowledge surrounding pathogens of NHP origin, such as *P. falciparum* and HIV, in the last few years underscores the need to delve into the disease-scape of closely related NHPs to better understand our own infections. For instance, it was not until 2010 that researchers demonstrated that wild chimps in the Taï Forest appeared to be naturally infected with five different *Plasmodium* species (Kaiser et al. 2010). Casting a wider net for pathogens may lead to similar advances in our understanding of the other pathogens that make up the NHP disease-scape.

It is likely that the rapid development of sophisticated, noninvasive means of NHP sampling will provide insight into the existence and/or prevalence of various pathogens. These noninvasive methods include approaches similar to those developed in primatology to study endocrinology (e.g., Deschner et al. 2003; Hodges and Heistermann 2003), characterize NHP genetics (e.g., Boesch et al. 2006; Bradley

et al. 2004; Vigilant et al. 2001), and perform urine assessment (e.g., Knott 1996; Krief et al. 2005). For instance, fecal samples have already been used to assay SIV and malaria in NHPs. In addition, a recent retrospective study of the epidemics in the Taï Forest suggests that it is possible to monitor infections caused by paramyxoviruses, such as hMPV and respiratory syncytial virus, using fecal samples (Köndgen et al. 2010). A pioneering study using aDNA techniques to study curated early-twentieth-century NHP skeletal material even suggests that we can explore the history of viruses such as STLV using museum specimens (Calvignac et al. 2008).

Such noninvasive approaches may also help address the role of human pathogens in NHP demographic declines. There are many unresolved questions. Do human pathogens associated with epidemics in NHPs tend to rapidly infect small groups before burning out? Or are some human-derived pathogens circulating continuously and even adapting to their new hosts? In some cases, whether or not the pathogens sweeping through NHP populations derive from humans is not clear. For example, *S. pneumoniae* was recently found to be responsible for clusters of sudden death in the chimpanzees of the Taï Forest (Chi et al. 2007). However, comparison to sequences obtained from people living nearby suggested that the pathogen might not be of human origin. Chimpanzees in different areas, but in frequent contact with one another, were also found to harbor distinct *S. pneumoniae* clones. If not from humans, from what reservoir did this pathogen arise? Similarly, adenoviruses were isolated from two chimpanzees with signs of acute respiratory disease in Mahale Mountains National Park (Tong et al. 2010). Sequence analysis identified two distinct viruses, but their origin was unclear; they could have been acquired from humans, acquired from another species, or circulating among chimpanzees for some time. Further investigation may shed light on the processes underlying such outbreaks.

Continued study of the relationship between humans, pathogens, and NHPs confers several substantial benefits. First, knowledge in this area is fundamental when assessing the impact of pathogen exchange between species (Wolfe et al. 2007), including research on the footprint of natural selection imposed by various infectious diseases upon the human genome (e.g., Hamblin et al. 2002; Sabeti et al. 2002; Tishkoff et al. 2001). Second, understanding more about how NHP pathogens are introduced into human populations and then spread has practical implications. According to Wolfe et al. (2007), benefits include a better understanding of disease emergence and the potential for novel laboratory models helpful in studying public health threats. Applications might include the development of indicators useful in monitoring pathogen transmission between NHPs and high-risk individuals, such as hunters and wildlife veterinarians; predicting which NHP pathogens might represent a future threat; and detecting and even controlling local human outbreaks before they become epidemics (Wolfe et al. 2007). Third, some scholars have argued that wild NHPs can serve as "sentinel species" for predicting disease outbreaks among humans (Leendertz et al. 2006; Rouquet et al. 2005).

Finally, studying the relationship between pathogens, NHPs, and humans has important conservation implications. Köndgen et al. (2008) and others have argued that the close proximity between NHPs and humans, which is critical to both

research and ecotourism programs, represents a serious threat to the existence of wild primate populations. Obviously, this represents a dilemma, as both of these activities have clear benefits for conservation efforts, whether via suppressing poaching, generating income for local communities, or creating additional knowledge about primate biology and behavior. Do the benefits associated with conservation efforts outweigh the health costs for apes and other NHPs wrought by increased contact between NHPs and humans? Research efforts should be directed towards reducing deleterious health outcomes, and an improved understanding of the evolutionary trajectory and dynamics of pathogen exchange between humans and NHPs stands to make a substantial contribution to this effort. For instance, research on disease transmission from humans to NHPs can be used to perfect targeted strategies for preventing infection, including close monitoring of the health and behaviors of human observers and workers in conservation, scientific, and veterinary contexts (Homsy 1999; Nizeyi et al. 2002; Woodford et al. 2002).

Findings from the studies discussed above have already been used to generate specific recommendations for reducing the negative effects of tourists, local communities, and researchers upon NHPs, especially endangered great ape communities (see Ryan and Walsh 2011). These guidelines include a variety of strategies for limiting disease spillover into NHPs via the use of facemasks, minimum approach distances, limited-duration visits, and strict hygiene protocols. They also encompass the education of and collaboration with local stakeholders to determine optimal rates of tourism for preventing disease transmission while maximizing tourism revenues (maximum sustainable yield concept); vaccinating NHPs and treating infections when they arise; prohibiting human access to restricted areas in order to minimize both direct and indirect contact, such as through human feces, between local humans and NHPs; and establishing health programs for local communities and staff involved in habituating NHPs for tourism and research (Ryan and Walsh 2011). An active area of research focuses on how these disease-mitigating measures can be carried out with the full participation of local communities throughout Africa and other regions home to endangered NHP populations, in order to make these endeavors sustainable, practical, and desirable for the people involved (Ryan and Walsh 2011).

In terms of more research-intensive interventions, observations stemming from invasive and noninvasive tests on chimpanzees involved in the Taï Forest epidemics have been used to generate demographic, clinical, and diagnostic monitoring systems which could potentially enable humans to intervene quickly in future NHP epidemics there. Researchers involved in this ongoing project have strongly encouraged other investigators to implement similar systems at NHP research centers and parks (see Ryan and Walsh 2011). Such efforts would not only protect NHP populations but also objectively document the negative effects of research or ecotourism on NHPs (Köndgen et al. 2008).

In summary, the rapid and extensive destruction of forest ecosystems and changing patterns of contact between humans and NHPs, both stemming from the increase in size and changing distribution of human populations, have changed the disease-scape of all species involved. Someday, as detection and surveillance

improves, we may be able to perform comprehensive analyses of the different disease-scapes of humans and NHP species. When this happens, we will be able to explicitly test hypotheses such as whether host genetic similarity correlates neatly with the proportion of pathogens shared between two given species. Moreover, in the future we may learn more about how different primate species react to identical pathogens, which will yield important information on how immune responses and transmission dynamics differ within and between populations. The relationships between NHPs, humans, and pathogens are fluid. Targeted research may help us prevent the worst possible consequences of these constantly shifting associations by allowing us to learn some general lessons about the processes underlying pathogen host switches.

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