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Genomics, the Origins of Agriculture, and Our Changing Microbe-Scape: Time to Revisit Some Old Tales and Tell Some New Ones

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ABSTRACT Though agriculture is often viewed as one of humanity's crowning achievements, skeletal evidence indicates that dependence on domesticated plants and animals was accompanied by an increase in infectious disease. Scientists have proposed that many important infections emerged in the period following the advent of agriculture, as a result of newly dense populations and novel proximity to domestic animals that served as reservoirs for novel pathogens. Here, we review genomic evidence regarding pathogen origins, analyzing these data using the epidemiological transition framework. Genetic information has forced us to reconsider how and when many important pathogens emerged; it appears that a number of infections thought to result from contact with domesticated animals arose much earlier than agriculture was adopted. We also consider the broader effect of agriculture upon the microbiome, exploring potential consequences for human health. We end by discussing the changes in the human microbe-scape we are likely to see in the future. Am J Phys Anthropol 57:135–152, 2013.

INTRODUCTION

Most of us view agriculture as one of the great achievements in human history, a development that eventually led to civilization as we know it (Childe, 1951a,b). Ideally, the ability to cultivate crops and raise farm animals results in better health by providing an abundant source of food. A food surplus means that not everyone in a society has to be directly involved in food production, which facilitates the rise of religion and specialist crafts (Brumfiel and Earle, 1987; Hopfenber and Pimpentel, 2001). This, in turn, allows the development of some of the finer things, like art, music, and great literature (Mithen, 1996). It also allows individuals to focus exclusively on activities that serve society, such as public safety, scientific research, road maintenance, and healthcare. In a sense, all of these things are a consequence of agricultural production. For this reason, the long period that predated agriculture has often been viewed as a dark chapter in human history. Hobbes (1651), in *Leviathan*, described life in early human history as "solitary, poor, nasty, brutish, and short." By contrast, the lyrics to "America the Beautiful" begin:

> O beautiful for spacious skies
> For amber waves of grain,
> For purple mountain majesties
> Above the fruited plain!

Here and elsewhere, a cultivated field is a symbol of beauty and plenty.

Not everyone is so enthusiastic about agriculture, however (Manning, 2004). In fact, dissenting views have been expressed for millennia. In the Bible (Genesis 3:17–19), agriculture figures largely in God's punishment of Adam and Eve:

> . . .I have placed a curse on the ground. All your life you will struggle to scratch a living from it. It will grow thorns and thistles for you, though you will eat of its grains. All your life you will sweat to produce food, until your dying day.

Similarly, in the *Ramayana* (Sen (Translator), 1976), one of India's great epics, agriculture is seen as a curse rather than a blessing (Mehta, 2001):

> In the Golden Age, agriculture was abomination. In the Silver Age, impiety appeared in the form of the agriculture. In the Golden Age, people lived on fruits and roots that were obtained without any labour. For the existence of sin in the form of cultivation, the lifespan of people became shortened.

Jared Diamond goes so far as to call agriculture "the worst mistake in the history of the human race" (Daimond, 1987). In the contrarian views described in this paragraph, agriculture may be a source of food, but it is also a source of backbreaking toil.

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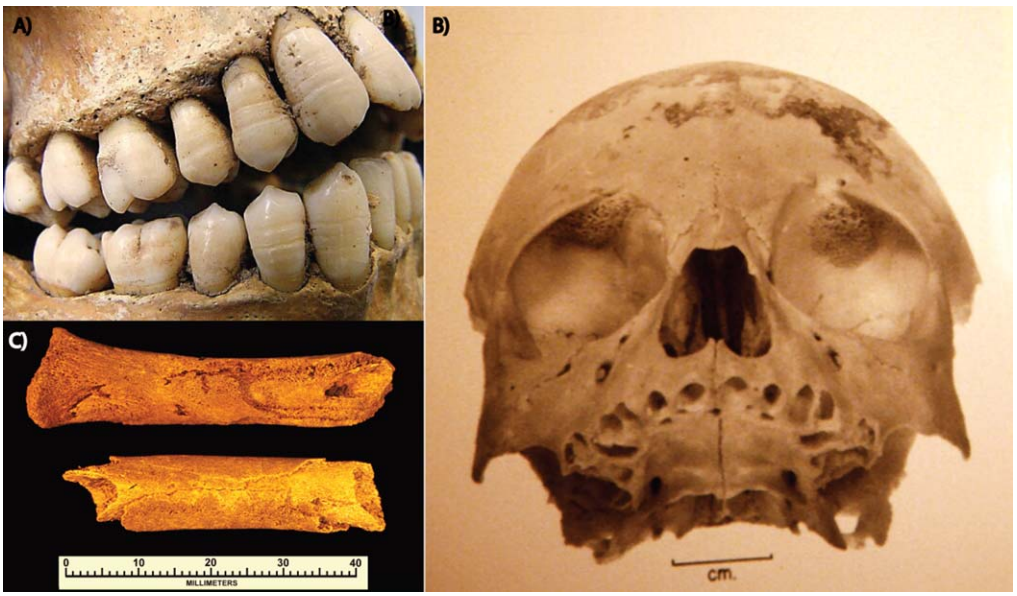

Fig. 1. Skeletal indicators characteristic of the pathological changes that became common after the advent of agriculture. **A**: Linear enamel hypoplasia: evidence of multiple episodes of interrupted growth. The age of onset of a stressor can be determined because the mineralization of the tooth follows a consistent pattern of timing. Barton-Upon-Humber Collection, English Heritage at St. Peter's Church. Printed with permission of Rebecca Watts, University of Reading. **B**: Cribra orbitalia: evidence of iron deficiency anemia. Sudanese Nubia. Printed with permission of Dennis P. Van Gerven. University of Colorado, Boulder. **C**: Chronic periostitis in a 6–12 month infant. Note the subperiosteal bone deposition over the normal cortex of this tibial fragment. Printed with the permission of Robert Mensforth, Cleveland State University. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

In the last few decades, it has also become clear that agriculture is an important source of human disease. Why? The first answer is the sheer number of humans it supports. Archeological evidence indicates that throughout the Paleolithic, which began 2.6 million years ago, hominid populations were small, widely dispersed, and stable. This changed when agriculture allowed people to aggregate in settlements. At first, these settlements were small. For example, the early agricultural villages spread over four acres at Jarmo (9,000 years before present, or YBP), in the Iraqi foothills of the Zagros Mountains, housed just over 150 people (Braidwood and Braidwood, 1950). The urban centers that followed were much larger. As long ago as 4,500 YBP, Ur in Mesopotamia had a population of 350,000 (Woolley, 1965), while a population of 100,000 people was estimated for the Valley of Mexico 2,800 YBP (Sjoberg, 1965). Following the Neolithic Revolution (8,000 YBP), there was a nearly sixteen-fold increase over Mesolithic population size (Deevey, 1960). Dense population centers facilitated the spread of novel human infections; many "crowd" diseases need a continuous supply of susceptible individuals to infect, or the chain of transmission breaks and they disappear. It has been estimated that the measles virus, for instance, requires a population of at least 300,000 individuals in order to maintain transmission (Grenfell and Bolker, 1998). With the rise of cities that followed the adoption of agriculture, these new "crowd" diseases could sustain themselves.

The second answer is that agriculture put humans and the animals they had domesticated in close contact. Over the years, researchers noticed that smallpox appears very similar to cowpox and measles appears very similar to rinderpest, a disease of cattle. In fact, some researchers believe that almost every major human infectious disease has an animal source (Diamond, 1997; Weiss, 2001). It has been estimated that domesticated and peri-domesticated animals are the source of at least 184 different zoonotic diseases (McNeill, 1976; Palmer et al., 1998; Weiss, 2001). As a result of new proximity, it is believed that many infections hopped from animals to humans, sometimes becoming permanent fixtures in their new hosts (Wolfe et al., 2007). In many cases, adaptation to large host populations may have begun before transmission to humans even occurred, because many of our domestic animals lived in herds prior to joining us on farms (McNeill, 1976).

Strong empirical evidence that human health worsened following the rise of agriculture has been uncovered by paleopathologists, and it points to yet another reason why infections soared after plant and animal domestication. At sites all over the globe, an increase in the telltale marks of both infection and nutritional deficiencies upon the skeleton are evident after the advent of agriculture (Fig. 1) (Cohen and Armelagos, 1984, 2013; Steckel and Rose, 2002). In addition, the age at death began to decline in populations that had adopted agriculture (Goodman and Armelagos, 1988; Steckel, 2005; Armelagos et al., 2009; Cohen and Armelagos, 2013). Not all investigators are convinced that agriculture resulted in increased mortality (Gage, 2005; Gage and DeWitte, 2009), and Pinhasi and Stock (2011) have even demonstrated that some transitions to agriculture were accompanied by improvements in health. Researchers have also questioned whether the "osteological paradox"—or the disconnect between indicators of pathology in skeletal samples and the frequency of these conditions

in the living populations from which they came—may make drawing conclusions about health in past populations problematic (Wood et al., 1992). However, studies of skeletal samples have shown that individuals who experience stress in early life die earlier, on average, contradicting a central tenet of the osteological paradox: that healthier people have "sicker" bones, because they do not succumb to illnesses before developing skeletal lesions (Goodman and Armelagos, 1988; Armelagos et al., 2009). Both theoretical and empirical evidence indicates that it is valid to compare relative pathology frequencies between two or more large skeletal samples, allowing us to infer that health really does appear to have suffered at many post-agriculture sites (Goodman, 1993; Cohen, 1994; Steckel and Rose, 2002). Why should this be the case? Throughout history, humans have used 5,000 plants as foods (Reid and Miller, 1989). Of these, only 150 have become major products of world commerce. As of the end of the 20th century, only 20 species provided most of the world's food, with wheat, rice, and corn contributing 69% of calories and 56% of protein (Reid and Miller, 1989). Agricultural communities that rely heavily on a few crops often experience compromised nutrition that predisposes their residents to infection (Mensforth et al., 1978; Scrimshaw, 2003, 2010; Cohen and Armelagos, 2013). This reduction in the dietary niche, in addition to growing population centers and proximity to domesticated animals, helps explain the decline in health associated with agriculture.

Agriculture and the first epidemiological transition

The growing evidence that agriculture resulted in an explosion of infections led to a paradigm shift in the way that people thought about the history of disease. Over thirty years ago, Omran (1971) introduced the concept of the epidemiological transition, describing three successive stages in human history: 1) The Age of Pestilence and Famine; 2) the Age of Receding Pandemics; and 3) the Age of Degenerative and Man-Made Diseases. New evidence that a relatively healthy, pre-agricultural time period existed before Omran's "Age of Pestilence and Famine" necessitated an important revision to this model. Barrett et al. (1998) realized that rather than representing the baseline, Omran's first stage, sparked by the transition to agriculture, instead represented the first epidemiological transition that humanity underwent.

Sprent (1969a,b) has suggested that human pathogens can generally be grouped into two broad categories: those caused by "heirloom" pathogens, which infected our anthropoid ancestors, and those caused by "souvenir" pathogens, which have been acquired more recently in human history. These latter diseases were generally zoonoses at first, infections transmitted from animals to humans (Kilks, 1990). Zoonoses can be contracted via insect or animal bites or through the hunting, preparation, and consumption of an infected animal. After a zoonotic pathogen enters a human host, several results are possible. If the pathogen finds humans to be unsuitable hosts, it may never spread beyond the initial infected individual or the transmission chain may be very short. If the human offers the invading microbe a similar environment to its natural host, a temporary host-switch without substantial levels of adaptation may be feasible (Kellogg, 1896; Bowden and Drake, 2013). While maintaining a specialized niche in its natural host, the microbe may simultaneously infect humans and any other suitable hosts that cross its path. One last possibility exists. A zoonotic pathogen may enter the human population permanently, adapting to *Homo sapiens*. It is this last scenario that many researchers believe has resulted in some of our most important infections.

Using genomics to test the hypothesis that agriculture is responsible for most major human infections

As described above, a number of independent lines of evidence support the idea that agriculture led to an increase in infectious-disease related morbidity and mortality. Pinning down the details regarding how this transition occurred has proved challenging, however. The wealth of recently available genomic evidence provides a valuable means of investigating this important period of history. Can most important human pathogens be traced to the domesticated animals of the Neolithic? If not, are other trends apparent? Does genomic evidence raise more questions than it answers? Here, we explore the history of a number of important micro- and macroparasites, grouping them together under the heading of "pathogens." We also explore the role of agriculture in the composition and evolution of the human microbiome. We end by considering the epidemiological transitions that humanity is currently undergoing, shifts that were set in motion 10,000 YBP, with the advent of agriculture.

GENOMICS CONFIRM AGRICULTURAL ORIGIN STORIES FOR SOME PATHOGENS

Studies performed using phylogenetics and the molecular clock have verified that many of our hypotheses regarding the origins of human infections are correct. This has been encouraging to the scientists who use first principles, such as population size and transmission mode, to reconstruct the conditions present when a pathogen first became established in humans. It has also been gratifying to molecular geneticists, who gain more confidence in their data when two independent lines of evidence coincide. In addition to confirming dates, genomics evidence has provided a surprising amount of novel information, adding new twists to old stories. We present two examples of this here (Fig. 2).

Lice: An ancient parasite that provides insight into early human history

Based on transmission mode, researchers have assigned a number of pathogens, including lice, to Sprent's "heirloom" category. No one would have guessed that the history of lice was as complicated as has been revealed recently, however. Mammalian lice are obligate parasites whose evolutionary history is typically closely intertwined with that of their host species. Whether or not head and body lice (*Pediculus humanus*) represent separate species has been a controversial subject for several hundred years, but the best supported view at present is that they are not genetically distinct (Light et al., 2008b). Genotyping studies suggest that humans with head louse infestations and poor hygiene provide an opportunity for lice to colonize clothing (Veracx et al., 2012); suited to life on clothes, possibly due to changes in gene expression patterns, these pioneers can then

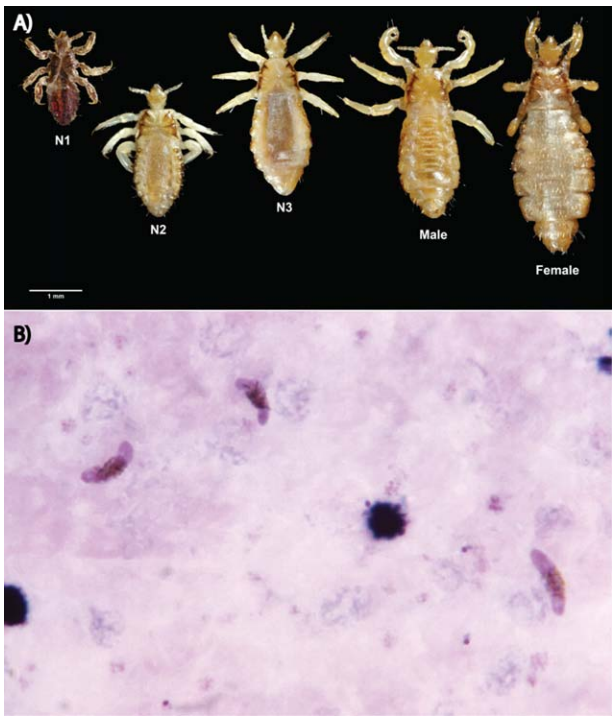

Fig. 2. Genomics has confirmed our origin stories for two pathogens: *P. humanus* (head and body lice), which emerged prior to the advent of agriculture, and *P. falciparum* (the parasite that causes malaria), which emerged post-agriculture. **A**: The lifestages of *P. humanus*. From left to right: the N1–N3 nymph stages followed by an adult male louse and an adult female louse. **B**: Three crescent-shaped gametocytes of *P. falciparum* present in the blood smear of an individual suffering from malaria. Credit for images: Public Health Image Library. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

spark body lice epidemics (Li et al., 2010; Olds et al., 2012). Thus, the generation of body lice may be continual, and the two types of lice may be indistinguishable.

Lice are divided into three genetic lineages; one, A, is found worldwide and includes both head and body lice (Light et al., 2008a). It appears to have undergone a population bottleneck with its human hosts roughly 100,000 YBP, as the latter were expanding out of Africa. The other two lineages, B and C, include only head lice. Molecular clock analyses suggest that lineage B, which is found in America, Australia, and Europe, diverged from lineage A roughly 1 million YBP (Reed et al., 2004; Leo and Barker, 2005). Lineage C is found only in Ethiopia and Nepal (Light et al., 2008a). Some researchers have proposed that the ancient divergence between lice lineages reflects a split between early species of *Homo*. According to this hypothesis, a recent host switch of the New World lineage (B) from an extinct host (perhaps *H. erectus*) to *H. sapiens* could account for its apparent localization to the New World, from whence it spread recently to Australia and Europe (Reed et al., 2004; Light et al., 2008a). Because lineage B lice have never been found in Asia, as the *H. erectus* hypothesis would suggest, it is unclear whether that is their real point of origin, however (Light et al., 2008a).

Genetic diversity is greatest among African lice, suggesting that this macroparasite originated there, and mtDNA sequences indicate that a demographic expansion of body lice occurred around the same time that modern humans dispersed out of Africa (Kittler et al., 2003). Moreover, the origin of the clade that contains all body lice has been estimated at roughly $72{,}000 \pm 42{,}000$ YBP; because many researchers have hypothesized that body lice could not have evolved until clothing was worn regularly, providing a novel niche for the parasite researchers have concluded that clothing was likely invented around 100,000 YBP, prior to when modern humans' movement to cooler climes would have required a new way to keep warm (Kittler et al., 2003; Toups et al., 2011). *P. humanus* and other pathogens that originated prior to the advent of agriculture are listed in Table 1.

Malaria: An infection that followed agriculture

Over fifty years ago, Allison (1954) suggested a link between malaria and sickle cell trait. Shortly after, Livingstone (1958) hypothesized that malignant malaria, caused by the parasite *Plasmodium falciparum*, became hyperendemic to West Africa when farmers with newly introduced iron axes began chopping down the tropical rain forest to plant crops. Livingstone argued that hunter–gatherer population sizes were not sufficient to maintain malaria. In addition, small-scale swidden agriculture would have increased the number of breeding spots for the mosquito *Anopheles gambiae*, which transmits *P. falciparum*, the cause of the most severe type of malaria. As Allison and Livingstone predicted, in East and West Africa, the more intense a community's reliance on swidden agriculture, the higher the prevalence of the sickle cell trait, which protects against malaria (Wisenfeld, 1967; Piel et al., 2010). Livingstone believed that the infection was likely to have arisen as a zoonotic disease transmitted from chimpanzees, eventually becoming a human specialist (Livingstone, 1971). His hypotheses regarding agriculture and malaria have been borne out by a number of lines of genomic evidence.

For example, research on polymorphisms in the glucose-6-phosphatase dehydrogenase, or *G6PD*, gene, which can provide resistance against malaria, is consistent with the hypothesis that this disease became an important problem for humans practicing agriculture in tropical climes. A signature of positive selection present in the *G6PD* gene of humans, but not in non-human primates (NHPs), suggests that malaria represents a much stronger selective pressure for us than for our close relatives (Verrelli et al., 2006). The A-polymorphism, which confers protection against infection, is estimated to have arisen between 3,800 and 12,000 YBP (Tishkoff et al., 2001). This is consistent with Livingstone's estimate of when swidden agriculture was adopted in West Africa.

Pinpointing the ultimate origin of the malaria parasite itself proved more difficult. As Livingstone predicted, for years the closest genetic relative of *P. falciparum* that geneticists could identify was *P. reichenowi* (Escalante and Ayala, 1994), a parasite found in chimpanzees. For decades, all we knew about this parasite came from a single strain isolated from a chimpanzee in the Democratic Republic of Congo (Collins et al., 1986). On this basis, it seemed reasonable to believe that humans and chimpanzees both harbored their own distinct "heirloom" malaria strains. This would mean that malaria was an ancient infection in humans, predating agriculture by millions of years.

TABLE 1. Pathogens That Infected Humans Prior to Agriculture, According to Genetic Evidence

Pathogens	History
Viruses	
Epstein Barr virus (causes infectious mononucleosis, associated with some types of cancer)	Appears to have originally resulted from transfer from an Old World monkey, sometime in the ancient hominid past (Ehlers et al., 2010)
Hepatitis G	Genetic evidence consistent with ancient origin, disseminated with human migrations out of Africa (Pavesi, 2001)
Herpes simplex viruses 1 and 2 (HSV-1 and 2)	Sequence analysis suggests HSV subtypes diverged millions of years ago, giving these viruses an ancient origin (Gentry et al., 1988)
Human papillomavirus (causes genital warts, cervical cancer)	Phylogenetic evidence suggests HPV has been evolving in humans for hundreds of thousands of years, originating in Africa (Ong et al., 1993)
JC virus (causes progressive multifocal leukoencephalopathy in immunosuppressed individuals)	Genetic evidence consistent with ancient origin, disseminated with human migrations out of Africa (Pavesi, 2005)
Bacteria	
Bordetella pertussis/*B. bronchiseptica* (cause whooping cough)	Human-adapted *B. bronchiseptica* strains appear to have existed for millions of years, and *B. pertussis* most likely evolved from these (Diavatopoulos et al., 2005)
Borrelia burgdorferi (causes Lyme disease)	Genetic evidence indicates that this pathogen has long been present in both Europe and North America, consistent with a pre-agricultural origin (Margos et al., 2008)
Helicobacter pylori (causes gastric ulcers)	Phylogenetic evidence suggests *H. pylori* has been evolving in humans for hundreds of thousands of years, originating in Africa (Falush et al., 2003; Linz et al., 2007)
Mycobacterium tuberculosis	Genetic evidence consistent with ancient origin, disseminated with human migrations out of Africa (Hershberg et al., 2008)
Salmonella enterica serovar *typhi* (causes typhoid fever)	Genetic evidence indicates that pathogen originated 15,000–150,000 YBP, predating agriculture (Margos et al., 2008)
Parasites	
Pediculus humanus (lice)	Genetic evidence consistent with ancient origins, disseminated with human migrations out of Africa (Kittler et al., 2003; Toups et al., 2011)
Schistosoma mansoni (causes schistosomiasis)	Genetic evidence suggests an East Asian origin 0.30–0.40 million YBP (Morgan et al., 2005)
Taenia saginata, Taenia solium (tapeworms)	Originated in the Pleistocene; probably picked up via tainted meat from animals preyed on by hyenas and big cats, then transmitted from us to domesticated animals in the Neolithic (Hoberg, 2006)
Toxoplasma gondii (causes toxoplasmosis)	Appears to have originated in pre-Columbian South America, where it would have infected wild cats and occasionally humans (Lehmann et al., 2006).

Around 2009, our understanding of *P. falciparum*'s history in humans began to change, as the results of intensive studies of malaria infections in NHPs were reported. The ability to obtain *Plasmodium* DNA from NHP feces revolutionized the ability of scientists to collect samples for sequencing. And as these new sequences poured in, it began to appear that malignant malaria was not an heirloom pathogen of humans after all. Sequence analysis showed that the global genetic diversity of human *P. falciparum* strains was very low relative to the diversity present in chimpanzee *P. reichenowi* strains, indicating that the human species had diverged more recently than the chimpanzee species (Rich et al., 2009). This finding was inconsistent with *P. falciparum* being an heirloom pathogen in humans. Moreover, a genetic study of nearly 3,000 wild great apes, including chimpanzees, gorillas, and bonobos from throughout central Africa, found that the strains most closely related to human *P. falciparum* were found in gorillas rather than chimpanzees (Liu et al., 2010). Transmission of *Plasmodium* from great apes to nearby humans appears to be infrequent. A survey of 1,402 blood samples collected from people living in remote areas of southern Cameroon found *Plasmodium* DNA in 1,000 of them (Sundararaman et al., 2013); none were infected with the *Laverania* parasites from which *P. falciparum* originated, though. It appears possible that all circulating human *P. falciparum* strains may be the result of a single, very successful cross-species transmission event from a gorilla to a human.

In summary, genetic evidence supports Livingstone's hypothesis that malignant malaria 1) accompanied the adoption of swidden agriculture in Africa and 2) originated in a cross-species transfer from a great ape, although it looks as though that ape may have been a gorilla rather than a chimpanzee. *P. falciparum* and other pathogens that became persistent infections in humans post-agriculture are listed in Table 2. In general, it seems the post-agriculture pathogens tend to cause greater levels of morbidity and mortality than the pre-agriculture pathogens, as might be expected for microbes that are assured a large pool of susceptible hosts to infect. Most of the infections we associate with epidemics can be found in this list: measles, smallpox, the bubonic plague, etc. Many are associated with the WHO's list of the top ten causes of death in low income nations, though tuberculosis, a pre-agriculture infection, can also be found there (WHO, 2011). Not surprisingly,

TABLE 2. Pathogens That Did Not Regularly Infect Humans Until After the Advent of Agriculture, According to Genetic Evidence

Pathogens	History
Viruses	
Hepatitis C virus	Sequence analysis suggests hepatitis C diverged from other viruses 500–2,000 YBP (Smith et al., 1997)
Human immunodeficiency virus 1 (HIV-1, cause of AIDS)	Arose from a cross-species transfer with chimpanzees during the last century (Sharp and Hahn, 2010; Zhu et al., 1998)
Measles virus	Appears to have arisen from the rinderpest virus, which affects cattle, around the 11th–12th centuries (Furuse et al., 2010)
Rotavirus A	Some groups appear to have originated in domesticated animals (pigs, cattle, etc.). Recombination between human and animal strains is frequent (Ghosh and Kobayashi, 2011; Martella et al., 2010)
SARS coronavirus	Emerged recently, probably from farmed civets sold at Asian markets, though bats may be the ultimate reservoir (Kan et al., 2005; Wang et al., 2006)
Smallpox virus	Appears to have diverged from a rodent virus 3,000–4,000 YBP, possibly in the horn of Africa (Babkin and Babkina, 2012; Shchelkunov, 2009)
Bacteria	
Shigella sonnei (causes shigellosis or bacillary dysentery)	Genetic evidence suggests that this pathogen emerged in Europe, less than 500 YBP, then expanded across the world (Holt et al., 2012)
Yersinia pestis (causes bubonic plague/Black Death)	Pandemic strains originated in China after the advent of agriculture; originally contracted from infected rodents (Morelli et al., 2010)
Parasites	
Plasmodium falciparum (causes malignant malaria)	Resistance originated roughly 3,800–12,000 YBP, consistent with the adoption of swidden agriculture (Tishkoff et al., 2001); pathogen most likely originated from a cross-species transfer from a gorilla (Liu et al., 2010)
Trichinella spiralis (causes trichinosis)	European lineages appear to have evolved several thousand years ago, with the domestication of pigs (Rosenthal et al., 2008)

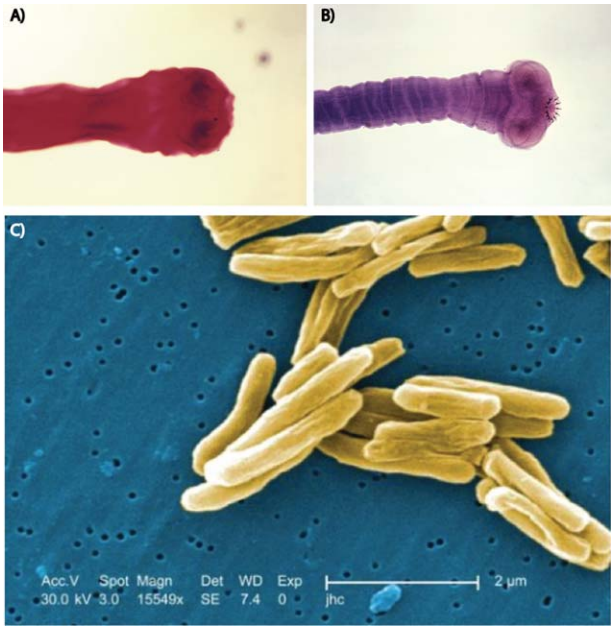

Fig. 3. Two pathogens for which genomics overturned our origin stories: *T. saginata* and *T. solium* (tapeworms) and *M. tuberculosis*, both of which emerged prior to the advent of agriculture. **A**: Photograph of the scolex, or head region, of *T. saginata*, which infects humans and cattle. **B**: Photograph of the scolex of *T. solium*, which infects humans and pigs. **C**: Image of *M. tuberculosis* bacilli. Credit for images: Public Health Image Library. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

many of the post-agriculture pathogens, including measles, *Trichinella spiralis*, and Rotavirus A, appear to have originated from contact with domesticated animals (Rosenthal et al., 2008; Furuse et al., 2010; Martella et al., 2010; Ghosh and Kobayashi, 2011), while others, such as malaria, resulted from cross-species transfers that were likely facilitated by new ecological patterns associated with agriculture.

GENOMIC STUDIES HAVE MADE US RETHINK THE LINK BETWEEN AGRICULTURE AND OTHER PATHOGENS

In the following two examples, we describe the history of two pathogens that most people believed to have originated in pigs and cattle. As it turns out, genetic evidence indicates that they originated in humans before spreading to domesticated animals (Fig. 3). In these cases, rather than confirming hypotheses about which we were confident, sequence data have turned prevailing theories on their heads.

We gave tapeworms to the livestock

In modern times, we are infected with tapeworms by eating cyst-tainted pork or beef, so it has long been believed that these parasites emerged in humans following the domestication of pigs and cattle. Molecular studies have demonstrated that all three human species of tapeworms, *Taenia solium*, *Taenia asiatica*, and *Taenia saginata* (the intermediate host for the first two is pigs, the third is cattle), actually originated in the Pleistocene (Hoberg et al., 2001; Michelet and Dauga, 2012). Although these tapeworms may be "souvenir" species,

we did not pick them up during the course of agricultural activity. Since our tapeworms are most closely related to those harbored by big cats (in the case of *T. saginata* and *T. asiatica*) and hyenas (in the case of *T. solium*), it is likely that *Homo* species originally became infected with the tapeworms of meat eaters that were competing with us for food (Hoberg, 2006). Interestingly, seventy years ago, long before the first phylogenetic study on this subject emerged, Baer (1940) argued that cave-lions could have harbored tapeworms, infecting humans via their prey. That is, prey animals could have become infected by ingesting vegetation contaminated with tapeworm eggs or gravid proglottids by cave lion feces; humans that then ate these animals could become infected, eventually becoming a primary host themselves. It seems that Baer's hypothesis was not so far off.

After becoming infected via tainted prey, it appears we then passed along our tapeworms to pigs and cattle, which eventually became intermediate hosts for the macroparasites. Although all three species of tapeworm afflicted humans long before the development of agriculture, animal husbandry did help disperse tapeworms across the globe. Post-agriculture, paleoparasitological evidence for Taeniids has been found around the world (Gonçalves et al., 2003). Reed et al (2004) propose that, in terms of human history, tapeworms may tell a similar story to lice; of the two pig-infecting species of tapeworms that diverged around 1 million YBP, one is predominantly found in Asia. Did this species evolve in *H. erectus*, later infecting *H. sapiens* via a host switch? Or does this second lineage merely coincide with the arrival of humans in Asia (Michelet and Dauga, 2012)?

We can't blame cows for tuberculosis

Tuberculosis seems like an obvious candidate for a human pathogen that originated in a domesticated animal. Before we began pasteurizing milk, becoming infected with tuberculosis from contaminated dairy products was a common occurrence. The tuberculosis pathogen that infects cows, *Mycobacterium bovis*, is sufficiently related to our own species, *Mycobacterium tuberculosis*, to form the basis of the Bacille de Calmette et Guérin, or BCG, vaccine. This putative example of a cattle-derived pathogen has been oft-repeated (as discussed in Smith et al., 2009). However, it turns out not to be true.

In fact, some of the earliest genetic studies of the bacterium responsible for tuberculosis were able to dispel this myth (Brosch et al., 2002; Garnier et al., 2003). *M. tuberculosis* and *M. bovis* are members of what is called the *M. tuberculosis* complex (MTBC), a group that also includes *M. africanum*, a source of tuberculosis in Africa, and some animal-adapted *Mycobacterium* species. Research on the MTBC quickly demonstrated that the direct evolution of *M. tuberculosis* from *M. bovis* was virtually impossible, as the latter had a smaller genome (Garnier et al., 2003)—and the very clonal *M. tuberculosis* bacterium would have had no way, such as interstrain recombination, to replace missing genes. Furthermore, a phylogeny of the MTBC shows that all animal-adapted strains form a single clade stemming from a group of West African human-adapted lineages (Hershberg et al., 2008). Thus, it appears that animal MTBC strains originated from human infections. Are we to believe that humans transmitted tuberculosis to cattle then? The answer appears to be no, at least not directly. Based on the order in which taxa diverged, it seems that a human-adapted strain of the MTBC became established in some other mammal, which served as a source of infection for yet another mammal, and so on, until cattle became infected as well (Smith et al., 2009). At present, a number of mammalian species harbor host-adapted MTBC strains, including goats, badgers, deer, boar, and possums.

So where and when did *M. tuberculosis* originate? The best genomic evidence supports an "Out of Africa and Back" model. The only continent on which all six major human MTBC lineages occur is Africa, and all of the "ancient" lineages—those that diverged earliest—are found only in West Africa (Hershberg et al., 2008). During hunter-gatherer times, the bacterium could have sustained itself in small populations via its long latency period. "Ancient" strains that diverged early in MTBC evolution can be found along the routes of human migration out of Africa (Hershberg et al., 2008). Overland migration is believed to have seeded MTBC infection in Western Europe, Northern India, and East Asia, and as human populations in these areas grew with the advent of agriculture, strains present in these regions formed the basis for the three major *M. tuberculosis* lineages present today. Afterwards, a second wave of migration moved the MTBC lineages around once more, as European settlers brought their strains to the American Continent, Indians brought their strains to East Africa, and East Asians brought their strains to South Africa.

From humans to animals: A common theme

Tapeworms and tuberculosis are just two examples of pathogens that traveled from people to animals. *Staphylococcus aureus* appears to have jumped from humans to chickens (Lowder et al., 2009) and small ruminants (Guinane et al., 2010). More exotic transfers have occurred as well. For example, *Helicobacter pylori* moved from humans to big cats (Eppinger et al., 2006). These host switches require us to view ourselves as not only the victim of cross-species transfers but also an important source of infection in our own right.

DESPITE GENETIC STUDIES, THE JURY REMAINS OUT ON THE ANTIQUITY OF SOME PATHOGENS

Although genomic data have proved very useful in reconstructing the history of a number of pathogens (see Tables 1 and 2), no especially helpful genetic information has been obtained yet for many significant pathogens. For example, humanity's shared past with cytomegalovirus, the mumps virus, and the Hepatitis B virus remains shrouded in mystery. As the price of whole genome sequencing drops and new technologies facilitate the retrieval of DNA from even non-ideal biological samples, it is likely that we will learn more and more about the evolutionary history of even minor pathogens. However, despite technological advances, the past of some microbes may remain elusive.

One example of the difficulty in leveraging genomic data to answer historical questions comes from our own research: Did the existence of treponemal disease in the Old World predate agriculture? The treponematoses are a family of diseases caused by different subspecies of the bacterium *Treponema pallidum*. They include syphilis and the non-sexually transmitted infections yaws and

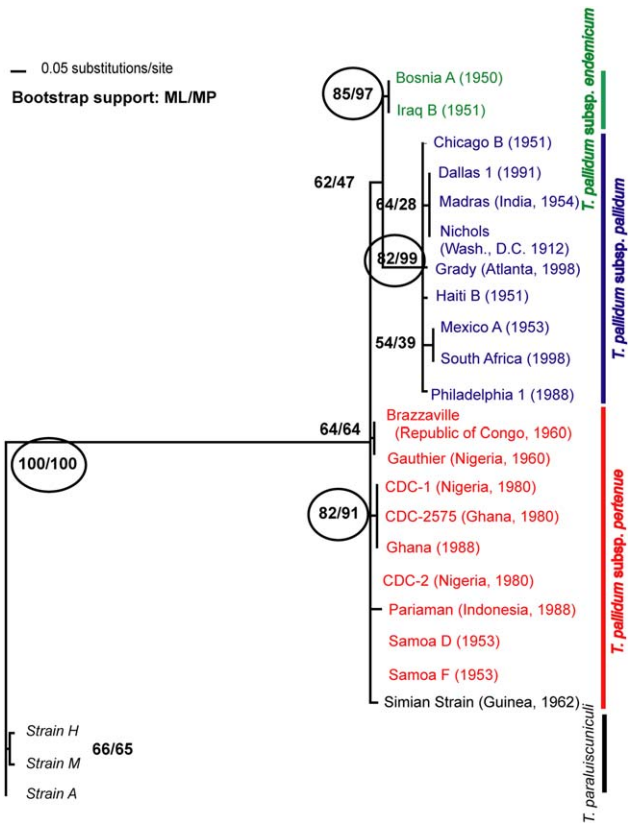

Fig. 4. A phylogenetic tree for the *T. pallidum* species illustrates the early divergence of subsp. *pertenue*, the cause of yaws (Harper et al., 2008). However, without a molecular clock, it is not possible to determine when yaws emerged in humans. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

bejel, which are typically contracted during childhood in tropical and arid regions of the world, respectively. The treponematoses leave telltale marks upon the skeleton, and, as a result, they have been studied intensively by paleopathologists. In the New World, there is clear skeletal evidence that treponemal disease was present both prior to and after agriculture came to dominate the food economy (Powell and Cook, 2005). However, whether or not treponemal disease in the Old World predated the advent of agriculture is unclear. Many historians and physical anthropologists have argued, on the basis of written records and skeletal patterns of disease, that syphilis was introduced into Europe by Columbus and his men (Baker and Armelagos, 1988; de Isla, 1539; andez de Oviedo y Valdes, 1526; er et al., 2011). Although some investigators have argued that there is evidence of Old World treponemal disease dating from the Pleistocene (Rothschild et al., 1995), the skeletal lesions described could also be due to other nontreponemal causes (Harper et al., 2011).

It seems genomic evidence should be able to swoop in and put an end to this controversy. Unfortunately, progress has been slow. We performed a phylogenetic study on *T. pallidum* and found that the subspecies that causes yaws diverged prior to the other subspecies (Fig. 4) (Harper et al., 2008). However, due to a number of factors, including a lack of knowledge regarding substitution rates among these bacteria, we could not use these genetic data to determine whether the early divergence of yaws-causing strains occurred pre- or post-agriculture. Genetic studies have also demonstrated that strains of *T. pallidum* collected from wild African NHPs closely resemble human yaws-causing strains, so much so that it appears they should all be considered members of a single species (Harper et al., 2012; Harper and Knauf, 2013; Zobanikova et al., 2013). However, current genetic data are compatible with several scenarios, including: 1) that African primate species, including humans, have each evolved with their own *T. pallidum* strains, which would mean that yaws predates agriculture in the Old World or 2) that human yaws infection was originally acquired from NHPs, which could have occurred pre- or post-agriculture. The presence of treponemal disease in the pre-Columbian New World suggests that humans were infected by *T. pallidum* prior to crossing the Bering Strait. However, no compelling evidence of Pre-Columbian treponemal disease has been found in Northern Asia (Harper et al., 2011). In some cases, sequencing ancient pathogen DNA has shed light on the history of microbes [e.g. confirming *Yersinia pestis* as the cause of the Black Death (Bos et al., 2011; Schuenemann et al., 2011)]. For a variety of reasons, including poor preservation over time and the absence of bacterial DNA in bone during late-stage disease, it appears unlikely that we will be able to obtain *T. pallidum* DNA from affected skeletons (Bouwman and Brown, 2005; von Hunnius et al., 2007). Thus, the history of treponemal disease in the Old World remains ambiguous, despite a substantial effort to apply genetics to this problem. Genetics may never provide all the answers we would like concerning past human infections, though new technologies will certainly uncover important new information.

AGRICULTURE AND THE MICROBIOME

Thus far, we have focused on human pathogens, but the harmful microbes we encounter are far outnumbered by the harmless or beneficial microbes that share our bodies. The human body is home to between 10 and 100 trillion microbes, which weigh three pounds and include thousands of species that nestle on our skin (Grice and Segre, 2011) and in our guts (Guarner et al., 2006), mouths (Arbes et al., 2006), sinuses (Feazel et al., 2011), nostrils (Lemon et al., 2010), vaginas (Ravel et al., 2011), and navels (Hulcr et al., 2012). These microbes "... congregate in our digestive systems and our mouths, fill the space between our teeth, cover our skin, and line our throats" (Specter, 2012, p 33). The human environment is ideal for both commensal microorganisms (i.e., harmless freeloaders) and mutualist microbes (i.e., those that trade favors with us), and together the number of bacteria inhabiting our bodies comprises more than ten times the number of our own cells. Justin Sonneburg has aptly described the human body "... as an elaborate vessel optimized for the growth and spread of our microbial inhabitants" (Pollan, 2013).

The term microbiome (i.e., the collective genes of the microbiota) was coined by Lederberg and McCray (2001) to describe the ecological community of commensal, symbiotic, and pathogenic microorganisms that share our body space. The microbiome is like a second genome, including more than 3.3 million unique genes found in the organisms inhabiting our gut and other body parts (Zhu et al., 2010). The study of the microbiome has

become such an important subject that the NIH has initiated a Human Microbiome Project (Turnbaugh et al., 2007; Peterson et al., 2009), aiming to characterize the microbiota of 250 individuals with the goal of improving human health via the monitoring and/or manipulation of the human microbiome. Microbiomes are self-sustaining ecosystems that have important implications for health and disease. When in balance, our microbiota can ward off illness, but when this balance is impaired, we become susceptible to disease. For example, kwashiorkor is a form of severe, acute malnutrition that affects children. It appears that diet alone is not to blame, though; studies of twins discordant for this disease, as well as animal studies, indicate that the disease results from the combination of a low-protein, highcarbohydrate diet, and a poorly developing microbiome (Smith et al., 2013). As we shall discuss below, more and more examples of how the microbiome is linked to health are being discovered.

Direct effects of agriculture upon the microbiome

By changing our diet and providing close contact with domesticated animals colonized with their own set of microbes, agriculture was bound to have a revolutionary effect on the human microbiome. What kind of changes might we expect agriculture to have wrought? Research shows that one of the most important influences upon the microbiomes of the mouth and gut is diet. The composition of the microbiome appears to be exquisitely sensitive to what we eat; for example, strains of *Bacteroides plebius* obtained from Japanese subjects frequently harbor a gene capable of degrading the porphyran in edible seaweed, while this gene is absent in North American strains (Hehemann et al., 2010). Both across species and within humans, the proportion of proteins, carbohydrates, and insoluble fiber in the diet is associated with the composition of the gut microflora (Muegge et al., 2011). Wu et al. (2005) have found that higher levels of protein and animal fats favor the dominance of certain bacterial groups, such as *Bacteroides*, while carbohydrates are associated with other bacterial groups, such as *Prevotella*. Thus, one might hypothesize that the increased carbohydrate levels associated with the advent of agriculture would have increased the proportion of *Prevotella* species in the microbiome while decreasing *Bacteroides* levels. In addition, a decrease in the variety of foods consumed may have resulted in a loss of microbiome diversity. And as humans and animals spent more time in close proximity, one might predict that their microbiomes would begin to resemble one another. Finally, as the high-protein, high-fat western diet has become more and more common worldwide, we might expect another set of dramatic changes in the microbiome, with *Bacteroides* again becoming more common.

Unfortunately, directly testing these hypotheses is difficult. Agriculture has become so ensconced that there are few hunter–gatherer groups left to study, making it difficult to establish the characteristics of a non-agriculturalist microbiome. Moreover, the groups that do remain, such as the Spinifex of Australia and the Sentinelese of the Andaman Islands, have been able to maintain their lifestyle only because of their isolation, limiting opportunities for scientists to study their microflora. Finally, it is important to remember that modern hunter–gatherers are not living fossils; it is possible that their microbiomes, even if sequenced, would differ from ancient hunter–gatherer microbiomes in important ways. One study of a population that recently left their hunter–gatherer past behind, the Batwa Pygmies of Uganda, found that they harbored a saliva microbiome significantly more diverse than those found in agriculturalists from Sierra Leone and the Democratic Republic of Congo (Nasidze et al., 2011). Aside from this observation, though, the effect of the dietary transition responsible for the first epidemiological transition upon the microbiome remains largely mysterious.

It has been much easier to compare western and non-western microbiomes. As predicted, studies have shown that non-western diets are associated with increased levels of *Prevotella* and decreased levels of *Bacteroides*. For example, a comparison of upper middle class US children and children residing in a Dhaka slum found that the latter had gut flora enriched for *Prevotella*, *Butyrivibrio*, and *Oscillospira* and depleted in *Bacteroides* (Lin et al., 2013). Although less studied, the yeast composition of the gut may also change in response to diet. A study of a Wayampi community in the Amazon found that *Candida albicans* carriage, normal in western countries, was unusual, and that Wayampi individuals were colonized by yeast species only rarely observed in the West (Angebault et al., 2013). These observations may be due to differences in the yeast strains acquired via diet. In addition, numerous studies have shown that the western gut microbiome is significantly less diverse than the microbiome of non-western populations in regions such as Dhaka (Lin et al., 2013), rural Malawi, and the Venezuelan Amazon (Yatsunenko et al., 2012). Finally, the overall volume of the microbes carried appears to vary depending on diet. In high-income nations, humans typically carry a gut microbiota that weighs less than 1.3 kg. However, in low-income, rural nations, the gut microbiota typically weighs approximately 2 kg (Bengmark, 2000). Thus, the shift in diet associated with the second epidemiological transition appears to have shifted the composition of the gut flora in favor of *Bacteroides*, reduced gut flora diversity, and reduced the total mass of the gut microflora.

Researchers have also extracted ancient DNA from coprolites to learn about the gut microbiomes of early agriculturalists. Not surprisingly, this is a difficult process. In one study, which examined coprolites from the US, Chile, and Mexico (8,000–1,400 YBP), the first two samples did not bear a close resemblance to modern human gut microbiomes, possibly due to poor preservation (Tito et al., 2012). The Mexican sample was more informative; it was *Prevotella*-rich and quite similar to modern samples obtained from rural Malawi and the Venezuela Amazon. Interestingly, *Treponema* species were found to be a significant component of this ancient Mexican sample as well as of microbiomes independently characterized in three modern, rural communities gathered from various continents (Tito et al., 2012). This suggests that *Treponema* may play an important role in the digestion of high-fiber diets. The microbiome of Ötzi, the Tyrolean Iceman, has also been analyzed via an intestinal coprolite, and its composition resembles that of modern African children (Tito et al., 2012). Curiously, it has been reported that the microbiome of an Austrian soldier, killed in 1918 and mummified on ice, resembles that of African children more than that of modern US adults as well (Tito et al., 2012). These findings emphasize the continuity between the microbial composition of ancient and modern non-western farmers.

Studies of changes in the mouth microbiome over time have also been performed. One analysis of European dental plaque dating from the Mesolithic, the Neolithic, the Middle Ages, and modern times showed that the microbe composition in all post-agriculture groups clustered, being quite different from that found in Mesolithic samples (Adler et al., 2013). In addition, phylogenetic diversity among modern plaque samples was significantly lower than that in Mesolithic or Neolithic samples, and the prevalence of cariogenic bacterial species, such as *Streptococcus mutans*, was elevated (Adler et al., 2013). Using a different approach, researchers have performed a genetic analysis of modern *S. mutans* strains and demonstrated that the demographics of this pathogen changed significantly around 10,000 YBP (Cornejo et al., 2013). It appears that the dietary shift toward carbohydrate consumption and the resultant change in the oral environment resulted in selection for this tooth-decay causing pathogen.

The post-agricultural proximity between humans and domesticated animals has also had an effect on our microflora. Research shows that dog ownership influences the skin microbiome of adults, contributing novel, rare taxa (Song et al., 2013). The net result is that dog owners have significantly more diverse skin microflora than non-owners. Interestingly, other pets, such as cats, do not seem to have the same influence on their owners' microflora (Morelli et al., 2010). Studies of Wayera communities in the Amazon suggest that cross-transmission of *C. albicans* between humans and domesticated animals occurs (Angebault et al., 2013). Similarly, research on humans and cattle living near Lake Victoria in Uganda suggests considerable microbial exchange between the two species (Ellis et al., 2013). Although relatively little research has been performed on the exchange of non-pathogens between humans and domesticated animals, the scant evidence available indicates substantial amounts of cross-species transfer.

Indirect effects of agriculture on the microbiome

Thus far, we have focused on agriculture's direct effects on the genome. Agriculture has also had important indirect effects upon our microflora, ramifications that are still playing out in the continually rearranging makeup of the human microbiome. Agriculture facilitated a number of important changes. First, population size climbed and the nature of social interactions changed. Novel social groups, such as classmates and roller derby teams, developed and now serve as efficient social networks along which microbes travel (Meadow et al., 2013). Second, medical knowledge improved. Antibiotics were developed, for example. Studies have shown that although the microbiome quickly begins to recover after antibiotic use, the original microflora of the mouth and gut not restored weeks and even months after treatment ends (Dethlefsen and Relman, 2011; Lazarevic et al., 2013).

In addition, the conditions in which infants and children are born and reared have changed dramatically in high-income nations. Some of the most important determinants of the composition of an infant's gut microbiome include mode of delivery and type of feeding (Penders et al., 2006). Newborn infants are more or less germ-free, but as soon as babies leave their mothers' bodies, this begins to change. While vaginally delivered babies develop microbiota that mirror their mother's vaginal microbiota, babies delivered via C-section harbor microbiomes that resemble those found on the skin's surface (Dominguez-Bello et al., 2010). Differences in the microflora linked to delivery mode persist even in seven-year-old children (Penders et al., 2006). In addition, babies who are delivered via C-section or formula-fed are more likely to harbor potentially pathogenic bacteria, such as *Clostridium difficile* (Harmsen et al., 2000; Penders et al., 2006). And while *Bifidobacterium* strains dominate the guts of breastfed infants, *Bacteroides* are equally common in formula-fed infants (Harmsen et al., 2000). Breastmilk even contains its own microbiome, which is itself influenced by whether a mother gives birth vaginally or via C-section (Cabrera-Rubio et al., 2012). Finally, a focus on hygiene means children are exposed to fewer microbes. Experiments in piglets indicate that limiting the microbial exposure of developing animals disrupts the normal maturation of the gut microbiota (Schmidt et al., 2011), and new variants of the "hygiene hypothesis" posit that similar processes may help explain the rise in prevalence of certain human diseases, such as allergies and diabetes (Huffnagle, 2010; Musso et al., 2010; Rook, 2012). Given both the direct and indirect effects of agriculture upon our microflora, it seems its impact on the human microbiome has been considerable.

Health effects of the changing microbiome

As described above, studies suggest that modern life has the potential to significantly reduce the diversity of the human microbiome (Blaser and Falkow, 2009). Some of the microbial species lost may be "Old friends": microbial symbionts that co-evolved with us and play a role in up-regulating the immune system (Rook et al., 2004; Rook and Brunet, 2005), digesting food, producing hormones and vitamins, participating in human metabolism, keeping weight in check, and affecting brain chemistry (Specter, 2012).

The role of *H. pylori* in health and disease provides a cautionary example of the effects of a changing microbiome. *H. pylori*, a bacterium that typically colonizes the stomachs of children, is an ancient member of the human microbiota. Phylogenetic studies demonstrate that it accompanied humans as they moved out of Africa, migrating around the world, and followed Neolithic farmers as they expanded across Europe (Falush et al., 2003; Linz et al., 2007). Although the majority of people infected with *H. pylori* have no symptoms, this bacterium is the primary cause of gastric and duodenal ulcers worldwide and can eventually lead to gastric cancer (Graham et al., 1992; Fuccio et al., 2009). For this reason, treatment for ulcers often involves eliminating *H. pylori* infections with antibiotics.

In recent decades, the prevalence of *H. pylori* infection has begun to fall dramatically in high-income nations, due to antibiotics and improved hygiene (Roosendaal et al., 1997; Fujisawa et al., 1999; Apostolopoulos et al., 2002). As *H. pylori* infection has become less common, the incidence of allergies and autoimmune disorders has risen. A number of studies have shown that individuals infected with *H. pylori* have lower levels of allergies, asthma, and autoimmune disorders (Feeney et al., 2002; Chen and Blaser, 2007; Janson et al., 2007; Chen and Blaser, 2008; Reibman et al., 2008; Luther et al., 2010; Amberbir et al., 2011; Zevit et al., 2012). Moreover, although still controversial, it appears that *H. pylori*

may protect against acid reflux (Nam et al., 2010) and, thus, Barrett's esophagus (Corley et al., 2008; Thrift et al., 2012) and esophageal cancer (Whiteman et al., 2010). As the incidence of *H. pylori* infection has fallen, esophageal adenocarcinoma incidence has been increasing markedly in Western nations (Thrift and Whiteman, 2012). These examples emphasize that the complicated role of this bacterium in health and disease requires further study; some researchers believe that the current evidence draws into question the wisdom of eradicating *H. pylori* from the microflora (Blaser and Falkow, 2009). Neither completely friend nor foe, *H. pylori's* "frenemy" status may characterize other microbes that have evolved with *H. sapiens* over millennia as well. This example of the complexity of our relationship with microbes highlights the varied changes that can result from the removal of even a single microbial species from our bodies as well as the difficulty inherent in health interventions that seek to change the composition of our microflora.

LIMITATIONS OF USING GENOMIC EVIDENCE TO ELUCIDATE A MICROBE'S PAST

Over the years, genetic evidence has not always proven helpful in reconstructing a microbe's past. Often, genetic articles contradict one another, describing opposing evolutionary scenarios for the same species. Although trying to interpret the literature in such situations can be frustrating, these cases have provided insight into the major limitations of using genetic data to learn more about a microbe's past. Knowledge of these problem areas can help researchers determine the level of confidence they should place in a given article's conclusions.

The first lesson we have learned concerns the molecular clock. In order to estimate when an infection originated, investigators must typically use the molecular clock, but this valuable tool requires that a number of assumptions be met. The most important feature of the molecular clock is its calibration. We must have an accurate estimate for the rate at which nucleotide substitutions occur within the genomes we are studying; that is, we must know the rate at which the clock "ticks." As was discussed in the section on treponemal disease, calibration can be tricky. Estimates should come from a relevant species, and as we have learned in recent years, it is also important that they are obtained over a time period similar to the one of interest. Substitution rates that are estimated over shorter evolutionary time periods are significantly higher than those that accumulate between species over greater time periods, making the molecular clock time-dependent (Ho et al., 2005). An example of the importance of calibration comes from research on *Shigella*, the bacterium responsible for dysentery. One early study used methods standard at the time to estimate divergence times for the various *Shigella* lineages and determined that they had emerged well before agriculture, which would make dysentery one of the early infectious diseases of humans (Pupo et al., 2000). However, a recent study, which used a combination of old and new isolates and paid special attention to molecular clock calibration, suggests that *Shigella sonnei* infection is a relatively recent phenomenon, having emerged within the last 500 years in Europe, from whence it expanded across the world (Holt et al., 2012).

Sampling has also proven a crucial determinant of a study's worth. Obtaining an extensive sample collection, especially for rare pathogens or those that cannot be cultured in the lab, can be substantially more difficult than generating and interpreting sequence data. The greater the number of samples sequenced, and the greater the variety, the more likely we are to get an accurate picture of a species' past. As more samples become available, our understanding of a pathogen's history may change rapidly. During the period 2009–2010, this occurred in the study of *P. falciparum*. As discussed, the ability to obtain DNA sequences from non-invasive samples collected from NHPs revolutionized the field. A flurry of studies came out, as each sample expansion yielded new data. Researchers found closer genetic relatives to *P. falciparum* in NHPs than had ever been identified before. We rapidly learned that *P. falciparum* infection could be found in apes (Duval et al., 2010; Krief et al., 2010) and that human *P. falciparum* was the result of a zoonotic transfer rather than an heirloom pathogen (Rich et al., 2009). As the studies came out, we sequentially believed that this transfer occurred from a chimpanzee (Rich et al., 2009), then from a bonobo (Krief et al., 2010), and finally from a gorilla (Liu et al., 2010). These rapid changes in the best available evidence illustrate both the importance of sampling and the flux that can characterize our conclusions about a microbe's past.

It is also important to consider that most phylogenetic studies allow us to draw conclusions only about the ancestors of pathogen strains circulating today. The history of a species may be substantially different from the history of current strains, if, for example, ancient strains have been replaced by modern strains. aDNA studies indicate there has been substantial strain turnover for certain pathogens; in some cases, historically important strains have gone extinct (Bouwman et al., 2012; Yoshida et al., 2013). Obviously, this may prove problematic in reconstructing a microbe's past, so understanding pathogen transmission dynamics is important. For pathogens like the influenza virus, in which the complete turnover of strains is typical, attempting to apply phylogenetics or the coalescent to modern samples to learn more about ancient events is likely to prove fruitless. Even for species with lower levels of turnover, it is not always possible to identify when the association between humans and a given microbe began. While genetic studies allow us to detect significant changes in a microbe's demographics over time, our ability to reconstruct an organism's history does not always extend to the initial period of contact with humans.

As a result of these limitations, researchers would be wise to examine genetic data critically. While genomic information is capable of providing novel insights, it also has the potential to mislead. When a new study comes out, it is helpful to ask several questions. Do the genetic data make sense in light of what we know about the microbe from other sources? Do the assumptions investigators made when using the molecular clock seem reasonable? Have similar studies tended to reach a consensus, or are conclusions still in a state of flux? The answers to these questions are important when weighing the findings of genetic research on a particular species. In the text and tables of this article, we have taken care to describe the best available evidence. We have omitted studies of pathogens that rapidly turn over, such as the influenza virus, or those for which conflicting evidence precludes a clear picture of the microbe's past. Even so, there is no guarantee that our understanding of a given microbe's history with humans will not change. The field

is still young, and researchers are still learning how best to gather and interpret genetic data.

CONCLUSION

Genomics have changed our understanding of agriculture and infections. We have been able to confirm that many infections, such as malaria, became established in humans after the advent of agriculture (Table 2). There have also been some surprises: that we didn't get tuberculosis from cattle or tapeworms from livestock, for example (Table 1). Instead of simply viewing domestic animals as a source of infection, we have been forced to recognize that we represent an important source of infection for animals as well. We have also come to realize that many pathogens have infected us for much longer than was previously thought, most likely originating during the Paleolithic (Trueba and Dunthorn, 2012). For example, *Bordetella pertussis*, the bacterium responsible for whooping cough, has long been thought to be a recent acquisition in humans, a souvenir pathogen acquired from livestock. Molecular genetic analyses suggest that it has been evolving in humans much longer (Diavatopoulos et al., 2005). It appears that *B. pertussis* originated from a human-adapted clade of *B. bronchiseptica*, a pathogen that causes respiratory infections in a wide variety of mammals. As new genetic data are gathered, it is likely that similar stories will emerge. We have had to reconsider the list of events assigned to each epidemiological transition.

In addition, as genomic analyses of the microbes inhabiting our bodies have accumulated, it has become clear that the effect of agriculture upon our microbial ecosystems is more complex than once imagined. Traditionally, physical anthropologists have focused on changes in human pathogens over time. Now we are learning about the importance of all of the members of our microbiota, many of which cannot be easily classified as beneficial or pathogenic. Animal experiments indicate that gut bacteria can influence bodily functions that have nothing to do with digestion, playing roles in neurodevelopment, stress reactivity, and behavior (Foster and Neufeld, 2013). Diet, interactions with other species, population size, hygiene, and medical interventions have all changed as a result of our dependence on agriculture, and each of these factors has affected the microbiome. In other words, genetic studies of the microbiome have shown us that we have been missing the "big picture." We are beginning to flesh out the details, gaining a better understanding of the way these ecosystems function and change in response to the environment. Although this work is just beginning, it is possible that it will revolutionize the way that we practice medicine, and given the microbiome's influence on health, our model of epidemiological transitions should be broadened to include commensals and microbes that can both help and harm, as well as pathogens.

It may appear that the insights that genetics has provided into the effect of agriculture upon the human microbe-scape are primarily of intellectual interest. However, these lessons translate into a better understanding of the epidemiological transition that we are currently undergoing, and better understanding may lead, in time, to more effective health interventions. Currently, we are experiencing the third epidemiological transition, which succeeds Omran's "Age of Degenerative and Man-Made Diseases." Although chronic diseases are still a major source of morbidity and mortality, we are now battling the failure of antimicrobials and the rapid spread of novel infections, such as West Nile virus, along global networks (Harper and Armelagos, 2010). In addition, pathogens are being pinpointed as the causes of diseases, such as peptic ulcers and cervical cancer that remained, until recently, poorly understood, further increasing the amount of damage that can be attributed to microbes (Lipkin, 2013). Understanding pathogen transmission and evolution as well as the microbial ecology of our bodies is as important as ever.

Genomic data supporting the role of host switches in the microbe-scape of both humans and the species with which we interact have underscored the importance of such transfers in the third epidemiological transition. In the last century, rare transfer events have resulted in human infections that have swept the globe, including HIV, SARS, and the 1918 flu. Even after controlling for reporting bias, the number of emerging infectious diseases appears to be increasing, and zoonoses dominate recent lists (Jones et al., 2008). As a result, methods of pathogen discovery and surveillance are continually being developed and improved (Lipkin, 2013), although much of this effort may be aimed at the regions least likely to host important emerging disease events (Jones et al., 2008). By learning more about the places, species, and interactions that characterize such events, hopefully we will be able to better target resources to the regions where they are most likely to occur. The history of agriculture and pathogens is rich with information about scenarios in which host switches to humans have occurred (Table 2). Alternately, we can mine this history for scenarios in which pathogens jumped from humans to nearby species, which may have important implications for conservation and livestock management. Finally, we may be able to apply the methods developed studying pathogen cross-species transfer events to better understand the exchange of non-pathogenic microbes between species. Future research should focus on areas where activities such as agriculture are changing patterns of contact between humans and animals. Increased sampling, sophisticated methods of microbial identification, and thorough genetic characterization will help us better understand when, where, and how microbes shift hosts.

Although we have begun to appreciate the complexity of agriculture's effects upon the microbiome, we are still a long way from understanding how to use this knowledge to influence health. That antibiotics are problematic has become clear. Antibiotic resistance is continually growing, and extremely drug resistant strains of tuberculosis (often paired with HIV), *Acinetobacter baumannii* (found in intensive care units), *Salmonella enterica*, *Klebsiella pneumonia*, and other bacteria are increasingly common and very difficult to treat (Gandhi et al., 2006; Park et al., 2009; Jacobsen et al., 2010; Frasson et al., 2012; Hendricksen et al., 2013). Even when they work, the effect of antibiotics upon the entire microbiome is undesirable. As a result, alternatives to antibiotics, such as probiotics and phage therapy, are looking more and more appealing. There is still a long way to go before these therapies represent viable options for most infections, and our current regulatory system is not currently equipped to deal efficiently with approvals for these treatments. Nevertheless, preliminary studies of options such as fecal transplants to cure *C. difficile* (van Nood et al., 2013) and bacteriophage to treat drug-resistant ear infections (Wright et al., 2009) are

encouraging, and it is likely that antibiotic alternatives will be used more and more in the future. Will our understanding of the effects of the Western diet upon our microflora prove useful? Can pre-agricultural microbial communities serve as guides, providing a model composition to which we should aim to return? Which changes to the microbiome are essential adaptations to modern life, and which represent deleterious outcomes that must be fixed? These are important questions that remain to be answered.

The price of genetic sequencing has fallen dramatically. Meanwhile, our ability to sequence DNA from non-optimal samples has improved by leaps and bounds: we have sequenced the *Y. pestis* genome from Medieval teeth (Bos et al., 2011), the *P. falciparum* genome from NHP feces (Liu et al., 2010), and the Neandertal (Green et al., 2010) and Denisova (Meyer et al., 2012) genomes from ancient bone fragments. The scope of our interest has grown ever broader, as we explore the microbiota inhabiting permafrost, deep-sea vents, and our armpits. There are now large-scale services that will genotype an individual for $99 (23andme) and characterize his or her microbiome for even less (uBiome). Soon such projects are likely to yield whole genome sequence data. As we sequence more and more samples from more and more places, we are likely to gain a better understanding of the history of the microbes within and around us—and the role that agriculture has played in shaping these communities. A robust framework for understanding this influx of data will be needed. Well-developed concepts such as the epidemiological transition model and Sprent's heirloom and souvenir classification system, are likely to prove useful in this capacity. These models should be broadened to include important non-pathogens; recent research makes it clear that the distinction between pathogens and commensals is not a clear one and that non-pathogenic microbes have a large effect on health in their own right. A dialectical process in which our models are refined in the light of newly available sequence data and novel genetic information is processed through the lens of these conceptual frameworks may eventually help us 1) craft better interventions, ridding ourselves of problematic microbes without devastating entire ecosystems and 2) aid in preventing disastrous interspecies pathogen transfers. It is important to recognize that the effect of agriculture upon the human microbiome is still unfolding, with tainted meat, farm animals, and produce spreading *E. coli* 0157, mad cow disease, influenza, antibiotic-resistant infections, and Rift Valley fever (Lipkin, 2013) and individuals converting to the Western microbiome as highfat, highsugar, agriculture-based diets spread. This is an exhilarating time for scientists, as each passing year brings fascinating, and sometimes startling, insights into the history of our microbe-scape. It will be exciting to see how knowledge of our shared past with microbes shapes future interactions between us and them, especially as we have come to realize that the distinction between "our" cells and "theirs" is often blurry.

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