

Genomics at the Origins of Agriculture, Part Two

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Agricultural expansion was such a momentous event that cultural or genetic evidence of its impact should be apparent. Abundant evidence indicates that agriculture was introduced into Europe at least 9,000 years ago. The primary issue remains whether agriculture spread by contact or by farmers moving into Europe. If agriculture was brought by farmers moving into foragers' territory, then genetic evidence should be apparent in the genes of modern Europeans. If foragers were displaced, then European genetic profiles should reflect the source population from the Near East. If there was interbreeding with the foragers who had a distinct genetic profile, then the genes of the Europeans descendants should reflect this admixture, with a clinal distribution of traits radiating from the Near East. These scenarios have been the focus of decades of debates between anthropologists and geneticists. In addition, genomic studies have been applied to pathogens in order to explore the link between agriculture and infectious disease.

Agricultural expansion into Europe has been described as a demic movement that spread into the continent as a wave.¹ It has been described as a "diffusional population wave of advance" (p. 8) or "wave of advance" that radiated from the Neolithic center in Anatolia. This process has been portrayed as "colonization without colonists"² in which there was not an *en masse* movement of people. Neolithic expansion occurred as population "bulged out" into what they perceived as underused arable land. The clinal distribution of genes^{3–7} is evidence of it.

ISSUE TWO: GENOMICS AND THE EXPANSION OF AGRICULTURE

After its initial rejection,¹ the wave of advance became the most widely accepted model for the European agricultural expansion. Fueled by agriculturalists' economic demand for labor, there was a small reproductive increase (as low as 1%⁵) that was enough to push these primary food producers beyond the land's carrying capacity. This forced the expansion into what they saw as underused land. The wave-of-advance concept, originally developed by Ammerman and Cavalli-Sforza^{3–5,8} and later expanded by Cavalli-Sforza and colleagues,^{7,9–13} remains at the very core of their model. In their original characterization of agricultural expansion,^{3,8} they used newly available radiocarbon dates¹⁴ to demonstrate the initial movement of the Neolithic package (cultigens, ceramics, and the technology of food production) into Europe. (Ammerman^{1,15,16} and Cavalli-Sforza^{17,18} offer an interesting 25th-anniversary retrospective).

The wave-of-advance⁴ model was derived from R. A. Fisher's¹⁹ analysis of the movement of an advantageous

mutation in an expanding population. J. G. Skellam²⁰ modified it to model the expansion of muskrats into Central Europe. The "wave of advance,"^{21,22} originally applied only to Europe, has also been used to model expansion into the New World.²³ Physicists²⁴ joined the debate by extending Einstein's use of Fickian diffusion to refine the model by including a delay element that better tracked European agricultural expansion. A 3% growth rate, which is much higher than evidence would support, was linked to 15- to 25-year delay between the origin and the eventual expansions of settlements. Other reformulations²⁵ of the model added complexity that considered interaction between farmers and foragers.

The Neolithic package included cereal grains (emmer wheat, einkorn wheat, and barley), domesticated animals (cattle, goats, pigs, and sheep), pottery, ground and polished stone tools, and patterns of settlement.² When the dates of the earliest evidence of the Neolithic package were plotted (any item from the package would define a site as Neolithic), they revealed a pattern of expansion radiating out from the Fertile Crescent.¹⁴ Superimposition of the pattern of genetic traits, including basic blood group data, human leukocyte antigens (HLA) and red cell enzymes on the isochrones generated from the radiocarbon dates suggested a wave that moved about 10 to 30 km a generation, or about 1 km a year. In 2,500 years, agriculture spread uniformly from Greece to the British Isles. The Neolithization of Europe was more rapid than the original expansion of agriculture in the Fertile Crescent.^{2,26}

The alternative model of agricultural expansion by cultural diffusion without the farmers was rejected by

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geneticists who believed the pattern of human genetic traits reflected expansion by people. Expanding the number of genetic traits and applying a more sophisticated methodology (spatial autocorrelation) than that used in the original study, Robert Sokal and colleagues^{27–30} supported a genetic transformation (also see Fix³¹). If the expansion resulted from the diffusion of the elements of the Neolithic package, there should be little evidence of genetic admixture in Europe.

Menozi, Piazza, and Cavalli-Sforza¹² applied principal component (PC) analysis to data from 29 alleles in modern Europeans, producing a synthetic map supporting the wave of advance. The first principal component (PC) explained nearly 27% of the genetic variation and was interpreted as reflecting the wave's southeast to northwest cline, as well as suggesting genetic interaction with the Mesolithic populations.⁵ The second and third PCs of this analysis revealed clines that moved from southwest to northeast (22% the variation explained) and from east to west (11% of variation explained). The third PC (the second was not interpreted) was attributed to Kurgan warriors armed with domesticated horses who swept through Europe, leaving their genes and language (Indo-European) in their wake.

Cavalli-Sforza, Menozzi, and Piazza⁷ suggested that these PCs could be viewed as a chronological sequence (the first PC being the oldest) of the spread of genes in Europe. The maps of PCs were claimed to represent a stratigraphic history of the Neolithic expansion. Even though Sokal, Oden, and Thomson^{32,33} (see Rendine and coworkers³⁴ for a response) had shown spatially random data can produce synthetic maps that can result in clines, the case for the demic expansion was solidly entrenched.

The wave-of-advance model has received a number of criticisms. The term implies an agricultural advance that literally and figuratively plowed under populations in its path. The online Bioinformatic Glossary (<http://big.mcw.edu/display.php/1550.html>) defines the "wave of advance" as "The hypothesis that the spread of agriculture into Europe was accompanied by

a large-scale movement of human populations." The idea of rapid and uniform movement is further implied by description of the expansion of the languages of agriculturalists as a "steamroller"³⁵ expanding from centers of domestication.^{13,36–41} The linking of the wave of advance with the language dispersal theory⁴² proposed by Renfrew^{43,44} was beneficial to both theoretical positions, even though neither has ever received universal acceptance.

The wave-of-advance model has been criticized by both archeologists and geneticists. Archeologists claim that this model fails to consider the evidence of indigenous developments in Europe^{45–49} and has been viewed by some as a Ludditic response to the intrusion of geneticists onto their ac-

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ademic turf. However, the complexity of the archeological evidence did not seem to fit the model. For example, archeologists argued that Mesolithic populations in Europe had sophisticated cultural systems⁵⁰ and were able to maintain their integrity in the face of the Neolithic advances.⁴⁹ An analysis of demic diffusion into Greece⁵¹ demonstrated discontinuities in human settlements, with "jump dispersal" as the agricultural package leapfrogged across geographic barriers. Recently, Colledge, Conolly, and Shennan,⁵² using archeobotanical evidence (preserved crops and associated weeds) as a signature for a pattern of contact, found support for the wave-of-advance model.

Geneticists were also critical of the meaning of the clinal maps generated by Ammerman, Cavalli-Sforza, and their colleagues.^{33,53} Alan Fix's³¹ initial acceptance was later tempered by concerns that the model failed to consider adaptation as a factor in explaining the clinal distribution of genes.⁵⁴ Richards² and Sykes,⁵⁵ who have used mtDNA analysis to examine the theoretical underpinnings and empirical basis for the Neolithic invasion of Europe, question the extent of its genetic impact. Their mtDNA analysis produced clines similar to those seen with classic genetic traits. When looking at the distribution of mtDNA haplogroups (maternal lineages) in Europeans, they noted a cline with one pole at the Near East and another at the Basque country, with geography accounting for 51% of genetic variation in this pattern.⁵⁶

Richards² and Richards and colleagues,^{57–60} as well as Sykes^{55,61,62} claim that the mtDNA evidence showed that this genetic contribution was small, and that there was evidence for rapid earlier Paleolithic population movements into Europe dating to the late glacial or postglacial periods.^{63,64} This expansion could account for Cavalli-Sforza and Ammerman's second PC, oriented from the southwest to the northeast, which had previously been unexplained. Mitochondrial data, according to Richards and Sykes, indicates that agricultural demic diffusion from Eurasia contributed minimally to the gene pool of modern Europeans. Richards and colleagues⁶⁵ conclude that the immigrant Neolithic component contributed less than one-quarter of the mtDNA pool of modern Europeans. The majority of present day mtDNA lineages entered Europe in several waves during the Upper Paleolithic period. They further claim that back-migration to the Near East and a bottleneck associated with the Last Glacial Maximum complicates the interpretation of a single rapid wave of advance into Europe.

These conclusions were vigorously challenged by Barbujani and colleagues^{66–70} and others.^{71–74} These criticisms centered on the fact that mtDNA is maternally inherited and represents only a limited genetic pro-

file of human population movements. Others criticized the mtDNA analysis for producing incorrect phylogenies because their mutation rate estimates were wrong and haplogroups dates were incorrect.⁶² Martin, Sykes and others were criticized for equating the age of the molecular common ancestor with the age of the founding population. For their part, Richards, Macaulay, and Bandelt⁷⁵ have replied that they

rely on the population concept, in its technical, population-genetic sense, as little as possible. We do not subscribe to the belief (common amongst geneticists), that there are such entities as “human populations,” which are the units of study and whose “population history” it is our mission to discover (p. 461).

Rather, they claim that they are using a regional approach for interpreting the genetic data. Richards and Macaulay⁵⁸ considered these criticisms and defended the use of mitochondrial data.

Y-chromosome data have also been used to assess the Neolithic male contribution to the European gene pool. Semino and coworkers⁷⁶ determined from analysis of nonrecombining Y-chromosome data that the genetic contribution of Neolithic farmers may have been as low as 22%. This percentage was determined from the proportion in Europe of four haplotypes that show a distinct gradient from the Levant, the epicenter of the agricultural revolution. Semino and colleagues' nonrecombining Y-chromosome data set was reanalyzed by Chikhi and coworkers,⁷⁴ who criticized it for lacking explicit models of population admixture. Basing their analysis on estimates of ancestral allele frequencies, Chikhi and coworkers⁷⁴ chose the modern Basques and modern Sardinians as representatives of pre-Neolithic Europeans. Their analysis suggested that the Neolithic contribution was substantially higher than that noted by Semino and colleagues,⁷⁶ and perhaps as much as 70% higher. In fact, they found that the proportion of Neolithic genes decreased from modal values of around 85% to 100% in areas such as Albania,

Macedonia, and Greece to around 15% to 30% in areas more distant from the Levant, such as France, Germany, and Catalonia.

In considering these results, Chikhi and coworkers cautioned that the 70% contribution could actually be an underestimate, since the Basque and Sardinian gene pools are likely to contain a proportion of Neolithic genes not considered in their analysis. They also found that drift was highest in areas where the archeological record suggested that agriculture came last. This observation supports the idea that demographic growth was associated with agriculture.

Richards² rebutted Chikhi and coworker's findings and questioned their assumptions that Paleolithic Europeans were a unitary group that could be represented by the Basques and Sardinians and that modern Near Eastern populations represented the original agriculturalists. Richards also claims that Chikhi and coworkers failed to consider back-migration and did not provide a time scale for these processes.² Furthermore, Sardinia is known to be highly genetically heterogeneous because of multiple movements of human groups into the island over the past 10 to 20 millennia.⁷⁷

Chikhi and colleagues^{71,73} also examined seven autosomal sequences in European populations and detected clines in allelic distributions. Richards criticized them for arguing, without any directional data, that these clines represented Neolithic expansions, especially given that most population splits were estimated to be less than 1,000 years old. Moreover, the older splits did not involve the Basques, a group believed to be representative of Paleolithic Europeans.²

Barbujani and Bertorelle⁶⁶ and Barbujani and Dupanloup⁶⁹ have vehemently argued against continuity of the European gene pool from the Paleolithic to modern times. Barbujani and Dupanloup⁶⁹ state forcefully that there is confusion “between molecular evolution and demographic history” that leads to an unwarranted belief that mtDNA and Y-chromosome data suggest strong continuity (p. 422). They argue that we should accept Ammerman and Cavalli-Sforza's

work from the 1980s and reject the later Cavalli-Sforza group's analysis.

Even with the above commentary, there appears to be some suggestion that the issue can be resolved. Brown and Pluciennik⁷⁸ have suggested that mutual distrust was fostered by archeologists who felt that geneticists were oblivious to cultural processes and geneticists who saw archeologists as anti-scientific humanists. Brown and Pluciennik⁷⁸ have claimed that there is much to be gained by cooperation between archeologists and geneticists. Archeologists have revised⁷⁹ and updated radiocarbon dates available since the original study¹⁴ and their reanalysis supports the original model of Neolithic expansion. However, significant variability remains in the speed and acceptance of agriculture regionally in Europe.⁷⁹ Unfortunately, the genetic data can also be used to support both a model of cultural diffusion or demic expansion.

Using a different approach, Bentley, Chikhi, and Price⁸⁰ evaluated the broad-scale genetic evidence of the wave of advance in terms of local-level processes. They used stable isotopes of strontium to establish evidence of migration at a southwest Germany Neolithic site between 5,400 and 5,000 BCE. Using ⁸⁷Sr/⁸⁶Sr comparisons,⁸¹ they could distinguish nonlocal females who were buried in early Neolithic cemeteries from those who came from autochthonous groups. They suggested that there was significant social interaction between the sedentary early Neolithic farmers and local mobile foragers. In a more general sense, this analysis suggests that local adaptations must be considered in interpreting global trends.

Lell and Wallace⁸² also believe that interpretations of the mtDNA and Y-chromosome are moving toward a consensus. While citing the limitations of Y-chromosome analysis (much smaller effective population size, fewer markers, and an undetermined mutation rate), they also note a general agreement with respect to the geographic pattern of the autosomal, mtDNA, and Y-chromosome variation. Richards² agrees that a consensus is emerging with respect to the archeological evidence and the mtDNA and NRY data that is consis-

tent with some Neolithic ancestry for modern Europeans. While claiming that the Neolithic transition left a “deep imprint”¹⁸ (p. 304) on modern Europeans, only about a fifth of genes can be traced to our Neolithic ancestors.¹⁸

It may be time to reassess the theoretical underpinnings of the wave-of-advance model. Renfrew,⁴⁴ a strong supporter of the wave-of-advance hypothesis, has suggested that we are ready for a second stage of research on the topic.⁸³ He proposes a new model, the stage population interaction wave of advance, which would move beyond the notion of uniformity and consider stages in the Neolithization of Europe. This approach considers the interaction of Mesolithic and Neolithic populations in a regional context, attempting to model the variability in geographic distribution and density that existed before the expansion of agriculture. In this regard, Renfrew⁸³ has suggested that the gradient found by Semino and coworkers, which is highest in the southeast and lowest in the northwest, is consistent with a modified wave-of-advance model. Thus, the Neolithization of Europe is now being viewed as having occurred in a series of stages in which incoming farmers interacted culturally and genetically with Mesolithic inhabitants. The major difference between the stage population interaction model and the original wave-of-advance model is that gene flow, and thus the clinal reduction of allelic distributions, falls off exponentially rather than linearly.

The exact biological makeup of the preagricultural European population remains a mystery. This hinders determination of the extent of demic diffusion through comparisons of newly agricultural societies with preagricultural and established agricultural societies. Without a Paleolithic population as a baseline, researchers are forced to use Sardinian and Basques as proxies for pre-Neolithic Europe.

In a review of human migration and population structure, Goldstein and Chikhi⁸⁴ describe the issue as one of “storytelling” to develop a narrative to explain interesting patterns of human variation. However,

ambiguities and inaccuracies in data analyses make these studies problematic.⁸⁵ Present-day allelic frequencies are difficult to interpret, in part because a single pattern is often consistent with multiple explanatory models.⁸⁴ The information gleaned from genetic studies of present-day populations is necessarily inferential in nature, and must be evaluated in light of information from other areas such as archeology, paleontology, and linguistics.

Goldstein and Chikhi⁸⁴ also take issue with the practice of estimating haplogroup ages in order to date the arrival of population groups in Europe. Richards² explains that when a founder event occurs, after an individ-

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ual migrates from a source to a sink population, the founder’s descendants will form a new lineage whose arrival on the scene can be dated. Goldstein and Chikhi counter that it would be highly unlikely to find such an extreme situation, an extreme bottleneck followed by a rapid expansion, in Europe’s history.

Stumpf and Goldstein⁸⁵ are especially critical of the use of Y-chromosomes to infer genealogies and migration. However, Goldstein and Chikhi⁸⁴ do say that the quantitative interpretations of the clinal maps of Europe are “intriguing and suggestive,” but obviously do not provide a definitive

answer. It may be that the “wave of advance” is such a compelling metaphor⁶² that researchers were driven to provide support for it, just as the systematic analysis of the relationship of agricultural expansion, genetic expansion, and language dispersal provides “more smoke than fire.” In a review of the hypothesis of language dispersal with farming,⁴² in which archeogenetics is a major part of the methodology, Mithen⁸⁶ is cautious about what he sees:

When we look at the wide geographical distribution of languages, there is something to be explained, and some general processes should be at work. But as soon as we examine one language family or one region, we are immersed in historical particulars. When considering the explanation for these, we find not only the absence of an interdisciplinary consensus but the lack of agreement among practitioners within a single field.

Smith⁸⁷ agrees that attempts at “triangulating” language, genes, and the archeological evidence have been disappointing.

An alternative source of evidence that uses cranial morphology has been reported to support the wave of advance. Pinhasi and Pluciennik⁸⁸ claim that a regional cranial comparison showed extensive variability among the earliest Pre-Pottery Neolithic Levant farmers when compared with the earliest southeastern European agriculturalists. They used published data from a pooled sample of 231 crania from both sexes that were recovered from three regions that spanned a 6,000-year period. A third to a half of the sample had missing data that was reconstructed using NormV.2.03 software. While admitting that their results were equivocal, Pinhasi and Pluciennik claim that the more homogeneous early mainland European agriculturalists were the result of a “bottleneck” experienced by the earliest farmers migrating into Europe. They do not consider the possibility that changes in cranial morphology may have been the result of a shift in subsistence and diet. Given the small samples (southern Europe

from Greece to Spain is represented by only 38 crania), the significance of these results must await larger and more complete samples.

In retrospect, the demic-diffusion hypothesis provided a focus for an understanding of the Neolithization of Europe. However, the wave-of-advance model may have been oversold, and Ammerman and Cavalli-Sforza did little to correct the misunderstandings that developed. For example, the issue of gene flow between the expanding Neolithic population and the Mesolithic foragers was minimized by many supporters of this model. Ammerman and Cavalli-Sforza point out that they did, in fact, include a variable to consider this genetic interchange but, in actuality, it was overlooked by those who saw the wave of advance as the key to the introduction of agriculture and people into Europe. Nonetheless, this issue represents one of the most intensively studied problems in human population migration.

ISSUE THREE: GENOMICS OF HUMAN PATHOGEN INTERACTION

Agriculture and Infectious Disease: Exploring the First Epidemiological Transition

The increase in infectious disease that accompanied the adoption of agriculture has been well documented. Agriculture resulted in the first epidemiological transition, beginning a pattern of emerging disease that continues to this day.⁸⁹ An increasing disease burden, the potential for malnutrition, and an increase in the demands of labor constitute major costs associated with agriculture.

The First Epidemiological Transition

The exponential population growth after the Neolithic has implications for the demographic transition theory,⁹⁰ one of the basic theoretical models in population studies.⁹¹ The model was first proposed by Warren Thompson,⁹² enhanced by C. P. Blacker,⁹³ and given its modern formulation by Frank

Notestein,⁹⁴ who argued that preindustrial populations could be characterized as being demographically stationary, their high birth rate balanced by their high mortality rate. In contrast, in the industrial era, a decline in mortality resulted from revolutionary changes in agricultural development, the industrialization of economy, and improvements in nutrition, public health, and medicine. Notestein⁹⁴ posited that a dramatic shift in declining mortality would lead to rapid expansion in a population experiencing maximum fertility. Fertility would gradually decline as the economic and social underpinnings of population expansion disappeared and families began

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to limit their reproductive potential. Eventually, with this decline in fertility, population size should become stationary again.

Archeological evidence supports the theory that hominid population size remained stable throughout the Paleolithic. Fertility and mortality rates must be balanced in order for a population to remain at a low and constant size. Conventional wisdom, supported by the demographic transition theory, argues that Paleolithic populations, which were characteristic of all preindustrial societies, must have experienced maximum fertility and high mortality. A lower rate of mortality

associated with agriculture would have resulted in a Neolithic population expansion.

Armelagos, Goodman, and Jacobs⁹⁵ offer an alternative model. Given the empirical evidence of a substantial increase in infectious and nutritional diseases following the shift to agriculture,^{96,97} the assumption of improved health because of Neolithic changes is difficult to support. Rather than occurring as a result of a decrease in mortality rate, population expansion would have occurred through an increase in a population's fertility rate above the increase in mortality rate caused by the new disease burden. The implication is clear. Paleolithic populations were controlling fertility. The pattern of increasing disease exposure associated with agriculture, which has great implications for how we understand modern human demography, has been deemed the first epidemiological transition.

What are the factors that would have contributed to the increasing level of infectious disease? Explanations come from a variety of sources, both theoretical and empirical. First, many infectious diseases require that populations must reach a certain size to maintain themselves. Measles, for example, requires a population size of 300,000 individuals to be maintained as an endemic disease.⁹⁸ Human communities did not reach such a size until urban development. Second, many diseases are believed to result from interspecies transmission from domestic animals. Domesticated and peri-domesticated animals harbor 184 different zoonotic diseases,^{99–101} and some believe that almost every major human disease has an animal source (see Diamond¹⁰²). Third, agriculture often leads humans not only to modify their environments, but also to expand into new types of environments due to the large land requirements that agricultural production requires. These changes expose them to novel pathogens. Finally, a reduction in their diet niche brought about by the reliance on a few domesticated crops would have resulted in compromised health that predisposed many to infection.



Figure 1. The *Anopheles gambiae* mosquito, which is responsible for transmitting the malaria parasite. Photo credit: Center for Disease Control.

Pregenomic Views on Neolithic and Paleolithic Diseases

Even before any genomic data on pathogens were available, many felt that our understanding of the diseases affecting Paleolithic and Neolithic populations was relatively complete. Based on diverse data obtained from archeological finds, observations of modern hunter-gatherers, and epidemiological principles, a detailed portrait of the disease-scape of the past was formulated.

Paleolithic diseases

Sprent^{103,104} distinguished two classes of pathogens, “heirloom species” and “souvenir species,” that would have afflicted hunter-gatherers. “Heirloom species” are classes of parasites that have had a long-standing relationship with our anthropoid ancestors and that continued to infect them as they evolved into hominids. Head and body lice (*Pediculus humanus*), pinworms (*Enterobius vermicularis*), yaws (*Treponema pertenue*), and malaria (*P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*) are among the pathogens that are purported to be heirloom species, although the occurrence of malaria and yaws remains controversial (Fig. 1). Certain parasites have great antiquity. Based on paleontological evidence, it has been determined that certain species of lice have been ectoparasites since the Oligocene.¹⁰⁵ Most of the internal protozoa found in modern humans, as well

as bacteria such as salmonella typhi and staphylococci^{106,107} have also been associated with anthropoids and hominids for quite some time.

In contrast, “souvenir” species are “picked up” along the course of human daily activity. The primary hosts of these zoonoses are nonhuman animals; they only incidentally infect humans. Zoonoses are passed on to humans through insect and animal bites and through the preparation and consumption of contaminated flesh. Wild animal species harbor at least 114 infections that they share with humans.^{99,101} Sleeping sickness, tetanus, scrub typhus, relapsing fever, trichinosis, tularemia, avian or ichthyic tuberculosis, leptospirosis, and schistosomiasis are among the zoonotic diseases that likely afflicted earlier gatherer-hunters.¹⁰⁸ Synanthropic relationships with the vectors that serve to maintain such human host-specific diseases, such as yellow fever and louse-borne relapsing fever,¹⁰⁵ may have been a problem for earlier foragers.

Neolithic diseases

The novel diseases that emerged during the Neolithic would include influenza, measles, mumps, and smallpox. Burnet¹⁰⁹ argued that there would have been few viruses infecting early hominids until the Neolithic. Cockburn^{106,107} disagreed, claiming that nonhuman primates could have been a source of viral infections in early hominids.

Livingstone¹¹⁰ dismissed the threat of

malaria in early hominids because of their small population sizes and their home on the savanna, an environment that would not have included mosquitoes carrying the malarial plasmodium. Coluzzi¹¹¹ points out that malaria would require especially adapted mosquitoes (*Anopheles funestus* and *Anopheles gambiae*) to parasitize humans. Anthropophilic mosquitoes adapt to permanent settlements such as rural villages, that have a relatively high host density. *A. gambiae* in tropical rainforests require human settlements with clearings for larval pools to breed successfully. The level of virulence of *P. falciparum*, long considered a recent human pathogen because of its high pathogenicity,¹¹⁰ is now thought to have little to do with the length of its relationship with the host species. It appears that malaria may occasionally have been contracted by preagricultural humans, but such infections would have been isolated incidents.

Pathogen Genomes Shed Light on Their Role in Hominids’ Past

In the past, we have relied on the disease ecology of contemporary gatherer-hunters as a model for the types of disease that could have affected Paleolithic foragers. Now the forensic application of genomic analysis has stimulated the development of statistical procedures for defining the degree of relatedness between and among disease isolates.¹¹² These procedures have been used in the forensic identification of anthrax,¹¹³ and can be used to study disease outbreaks and to analyze the evolutionary relationships among pathogens. Recent genomic analyses challenge the theory that many, if not most, of the diseases that plague us today did not affect humans until the Neolithic.

Genomics has helped to clarify when macroparasites began preying on early hominids. The genetic analysis of lice¹¹⁴ suggests that body lice (*Pediculus humanus humanus*) became differentiated from head lice (*Pediculus humanus capitis*) about 70,000 years ago, when clothing may have become part of the human wardrobe. Although weaving is thought to be a more recent cultural innova-

tion,¹¹⁵ with evidence of its existence dated at about 28,000 years ago, lice may have lived in the seams of skins that were worn earlier.

Genomic and biogeographic evidence also suggests that tapeworms originated as human parasites in the Paleolithic.^{116,117} Three species of taenids that infect humans and require domesticated cattle or swine as intermediate hosts show extensive diversity, indicating that a species separation occurred between 780,000 and 1.71 million years ago, long before domestication. Hoberg and colleagues¹¹⁷ claim that these data provide evidence that a regular pattern of scavenging and hunting¹¹⁸ originated on three separate occasions and resulted in the transfer of taenids to humans from game animals. These processes may have been enhanced by the practice of cannibalism and the consumption of dogs.

Many enteric bacterial infections also appear to date back to the Paleolithic. *Shigella*, a pathogenic form of *E. coli* that causes dysentery, is one of the human pathogens that was thought to postdate agriculture, since the pathogen has no carrier state or alternative host and since earlier human groups would have been too small and too widely dispersed to support populations of this bacterium. However, a recent study indicates that *Shigella* strains evolved 35,000 to 270,000 years ago. Thus, dysentery could have been one of the early, pre-agricultural diseases of humans. Moreover, the *Shigella* strains do not have a single evolutionary origin, indicating that convergent evolution has taken place.¹¹⁹ It was surmised that *Shigella* must either have a greater capacity to survive in small human bands than was previously thought or that human social organization was more complex in the Paleolithic. Similarly, the genetic analysis of *Salmonella typhi*, another pathogen that lives only in humans and that causes typhoid fever, indicates that the bacterium existed 15,000 to 150,000 years ago, well before the development of agriculture.

Transmissible spongiform encephalopathies,¹²⁰ which include a bovine form that causes “mad cow disease,” have been thought to have arisen after the Neolithic. A common polymorphism in the human prion protein

gene (PRNP) suggests that codon 129 is in balanced selection. Individuals who are homozygous for codon 129 (genotype 129M/129M) are more susceptible to iatrogenic and sporadic Creutzfeldt-Jacob disease (CJD),¹²¹ while heterozygotes (129M/129V) possess some protection against prion diseases such as Kuru¹²² and CJD. Extensive study of the prion gene in chimpanzees indicates that they have only the 129M/129M genotype.¹²³ These findings suggested that the PRNP gene has only four noncoding and two coding changes between humans and chimpanzees, and has evolved very slowly.

Interestingly, Mead and coworkers¹²² suggest that codon 129V originated about 500,000 years ago, and that cannibalism was a factor in the balanced selection for PRNP gene heterozygosity. This interpretation has

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been challenged. Sekercioglu¹²⁴ suggests that human transmissible spongiform encephalopathies as Mead and coworkers¹²² also note, can be transmitted by many other practices besides cannibalism. The second highest polymorphic frequency (0.48) of 129V occurs in Turkish populations that consume sheep brains and other neural tissue.¹²⁴

Perhaps the most surprising evolutionary genetic findings concern tuberculosis (TB). It was believed that TB was acquired by humans after the domestication of cattle. *Mycobacterium tuberculosis* is one strain in the “tuberculosis complex” consisting of *M. tuberculosis*, *M. africanum*, *M. bovis*, and *M. microti*. It has been assumed that TB was acquired from domestic animals,¹²⁵ when ancient

Europeans began to share their homes with their animals during the cold winters. This indoor proximity would have exposed humans to airborne pathogens such as *M. bovis*, the *M. tuberculosis*-like strain carried by cattle. Mutants that were more pathogenic to humans could have been created in this environment.

Recent examination of the *M. tuberculosis* genome supports parts of this scenario and refutes others. Analysis of single nucleotide polymorphisms (SNPs) at silent (synonymous) sites found in 26 different genes in bacteria sampled from all over the world indicates that *M. tuberculosis* did indeed emerge relatively recently in human history.¹²⁶ However, the range of dates for its emergence, from 15,000 to 20,000 years ago, predates the advent of agriculture. While these dates are roughly consistent with cattle domestication, genetic evidence argues against a bovine source for human TB. A phylogeny based on deletions in the *M. tuberculosis* genome suggests that the human form of TB preceded the form found in voles, seals, goats, and cows.¹²⁷ This phylogeny is supported by other analyses of deletions, which rule out linear evolution of *M. bovis* into *M. tuberculosis*¹²⁸ and suggest that *M. africanum*, *M. microti*, and *M. bovis* evolved from the ancestor of today's *M. tuberculosis* strains. (Whether or not this ancestor was a human pathogen is open to interpretation.¹²⁹)

M. tuberculosis complex DNA has reportedly been obtained from a 17,000-year-old bison that was found in a North American cave.¹³⁰ Its DNA pattern is nearer to that of *M. tuberculosis* and *M. africanum* than to that of *M. bovid* or *M. microti*. Citing tubercular lesions in various Pleistocene ruminants, Rothschild and colleagues¹³⁰ posited that TB carried by bovids was widespread during this period. It can be concluded that the human pathogen *M. tuberculosis* emerged relatively recently, but before the onset of agriculture, and that the disease was not acquired from domesticated cattle carrying *M. bovis*.

Neolithic Pathogens

Despite the findings that certain pathogens infected hominids much

earlier than had been previously thought, genomics has confirmed a Neolithic origin for many other diseases, supporting the theory that agriculture led to an increase in disease burden. The *P. falciparum* genome has yielded conflicting results concerning the antiquity of the malaria pathogen. One study using intronic SNPs to obtain an emergence time using the molecular clock,¹³¹ indicated that the plasmodium evolved less than 6,000 years ago, a date that would be coincident with the establishment of slash-and-burn agriculture in the rainforests of Africa. These results complement those obtained in other studies that used mtDNA sequences to date the emergence of the pathogen, but conflict with earlier studies of ribosomal RNA gene sequences. The latter studies indicate that *P. falciparum* diverged from *P. reichenowi*, a plasmodium that infects chimpanzees and gorillas, when the human and chimpanzee lineages split 6 to 8 million years ago.¹³²

Recent studies may reconcile these findings. Analysis of variation in 100 plasmodium mtDNA sequences indicates that the parasite is quite ancient but did not expand until relatively recently.¹³³ The antiquity of pathogen populations worldwide suggests that the plasmodium spread across the world fairly early, perhaps during the Pleistocene migration of hominids, but remained at low densities until it precipitously expanded around 6,000 years ago. Thus, the parasite seems not to have played a major role in the human disease-scape until the Neolithic. This interpretation is also supported by the analysis of malaria resistance genes in the human genome, which seem to have originated with the advent of swidden agriculture.¹³⁴

Toxoplasmosis gondii is another parasitic protozoa that is a major cause of foodborne illness and severe infection in immunocompromised individuals. This protozoan is remarkable for the extremely wide range of animals that can serve as its intermediate hosts, although sexual propagation must take place within the cat family. Its ribosomal DNA polymorphism¹³⁵ dates the origin of the major lineages within the last 10,000 years, around the time of agricultural expan-

sion and the domestication of the cat. One salient infectivity characteristic of *T. gondii* is its ability to circumvent the sexual reproduction step and infect intermediate hosts successively through oral ingestion. This ability would make *T. gondii* especially suited to infect humans and the animals in a farming community. The adoption of agriculture and domestic animals by humans possibly provided the selective pressure that molded the genetic traits of modern strains of *T. gondii*.

Citing tubercular lesions in various Pleistocene ruminants, Rothschild and colleagues posited that TB carried by bovids was widespread during this period. It can be concluded that the human pathogen *M. tuberculosis* emerged relatively recently, but before the onset of agriculture, and that the disease was not acquired from domesticated cattle carrying *M. bovis*.

Primary Food Production and Selection for Human Polymorphisms

There are a few signs of the difficult-to-detect direct selection in human populations.¹³⁶ Sick cell gene, lactase persistence, glucose-6-phosphate deficiency, and alcohol dehydrogenase (ADH) are among the few examples that have been uncovered. Among these traits are genes that were influenced by Neolithic-driven dietary changes and continue to affect the nutrition of contemporary popula-

tions. The domestication of milk-producing cattle and the use of milk resulted in selection for unique polymorphisms in certain human populations. Thirty minutes after consuming more than a glass of milk (9 to 14 grams of lactose), 70% of human populations will experience extreme bloating and diarrhea. Gas in the large intestine is produced by *E. coli* digesting the milk lactose.¹³⁷ Lactose intolerance (the inability to digest milk) is due to deficiencies in lactase, the enzyme that is essential for hydrolyzing lactose into galactose and glucose. In mammals in which milk is not normally available for adults, the lactase enzyme is turned off at weaning. Given the uniqueness of lactase persistence in humans, lactose intolerance demands an explanation beyond our "species-centric" perspective that it is a disease.

Geographers¹³⁸ and anthropologists¹³⁹ have speculated on the co-evolution of milk-producing cattle and lactase persistence that results in maintaining the ability to digest lactose. The definitive evidence for this linkage has recently emerged with the finding of a geographic concordance in Europe between milk proteins found in 70 native cattle breeds and lactose tolerance (lactase persistence) in Europeans.¹⁴⁰ Neolithic archeological sites (ca 5,000 ya) with domesticated cattle¹⁴¹ correspond with the area of the highest level of lactase persistence.

The persistence of lactase occurs in the northern latitudes, where milk provides a source of calcium and where the level of ultraviolet light limits the body's natural production of vitamin D. Lactose intolerance represents an ancient and global condition.^{137,142} Lactose tolerance results from a recent mutation in the lactase gene that underwent rapid selection. Swallow¹⁴² notes that Mongol cattle herders, who are lactose intolerant, process milk by fermentation to reduce its lactose levels. This observation counters the argument that lactose intolerance inhibited the domestication of milk-producing cattle during the Neolithic. As Marvin Harris¹⁴³ pointed out, if human groups had possessed domesticated milk-producing bovines, they could

have processed the milk products to reduce lactose levels or have undergone selection for lactase persistence.

Just as lactose intolerance has an impact on their diets, many human populations have taste sensitivity to the bitter thiourea compounds found in some foods. The ability to taste phenylthiocarbamide was accidentally discovered in 1931.¹⁴⁴ While it was initially considered a curiosity, Fisher, Ford, and Huxley¹⁴⁵ suggested that there was selection for the heterozygote condition. Recent genomic analysis provides evidence of selection that predates the modern hominid's diaspora out of Africa. The ability to taste phenylthiocarbamide and structurally similar compounds such as 6-n-propylthiouracil is related to antithyroidal compounds¹⁴⁶ that protect humans against ingesting harmful substances that could inhibit growth and against naturally occurring toxins. Tasters do have a lower incidence of thyroid deficiencies and a greater number of food aversions.¹⁴⁷

Similar analyses have related the aversion to alcohol to variation in the alcohol dehydrogenase (ADH) gene.¹⁴⁸ ADH enzymatically converts alcohol to acetaldehyde, a toxin. The accumulation of acetaldehyde in individuals from some populations results in a flushing response. Acetaldehyde is converted to acetate by acetaldehyde dehydrogenase (ALDH). ADH has several isoforms (ADH2*1, ADH2*2, and ADH2*3), which vary in their efficiency in breaking down alcohol to acetaldehyde. The various isoforms of ALDH also vary in their rate of converting acetaldehyde to acetate. ADH2*1 transforms alcohol more slowly than do ADH2*2 and ADH2*3; ALDH2*1 converts it faster than do the other isoforms. In East Asian populations with ADH2*2 or ADH2*3 genotypes, the ALDH2*2 genotypes results in flushing after the consumption of alcohol.

Primary Food Production, Disease and Selection for Human Polymorphisms

One of best known adaptive genetic systems is the hemoglobin variant (sickle cell trait), which, in heterozygous form, protects humans against

malaria. While the initial explanation of sickle cell gene was that it was a racial trait, J. B. S. Haldane^{149,150} suggested that hemoglobin variants were selected for their resistance to malaria. Allison¹⁵¹ demonstrated hemoglobin S (Hb^s) protection against malaria infection and Livingstone¹⁵² provided a biocultural interpretation of selection for the sickle cell variant. Swidden agriculture increased the breeding area for the Anopheles mosquitoes that were the vectors for malaria. As malaria became endemic, selection for the Hb^s gene increased. Selection for Hb^s is a recent adaptation; its relationships to Hb^c and Hb^e have been studied extensively.¹⁵³ These variants are among 693 hemoglobins that have been reported to date,¹⁵⁴ the data for which are available⁹ online (<http://globin.cse.psu.edu>).¹⁵⁵ In addition, the thalassemias¹⁵⁶ and their response to malaria are well known. There is also evidence that the major histocompatibility complex (MHC) system (HLA-B*5301) provides some measure of resistance to malaria,¹⁵⁷ as does Duffy,^{158,159} a red blood cell antigen.

Glucose-6-phosphate dehydrogenase (G6PD), a sex-linked enzyme, is involved in mediating oxidative stress in red blood cells (RBCs).¹⁶⁰ A deficiency of the G6PD enzyme (there are 140 variants)¹⁶¹ interferes with the plasmodium parasite's ability to reproduce in RBCs because the oxidative stress produced by parasitic infection causes the RBCs to lyse. As a result, the plasmodium is unable to mature. Males who carry the mutation for the deficiency are hemizygous; only females who are G6PD deficient are heterozygous for the condition.

Variants of G6PD confirm that malaria has only recently had a major impact on human populations.¹⁶² The independent "A" and "Med" mutations, two of the G6PD variants, suggest that this polymorphism originated no earlier than 10,000 years ago. The analysis of Hb^s and G6PD deficiency supports the contention that malaria had little impact on Paleolithic foragers and arose only after the development of agriculture.¹⁶²

We have discussed the response of G6PD deficiency as a response to ma-

laria, but there is an additional consequence of this adaptation. For those who possess G6PD mutants, the consumption of sulfonamides, either as antimalarial drugs (for example, primaquine) or in fava beans, can cause hemolytic anemia. When individuals with G6PD deficiency consume these substances, their RBCs hemolyze.

The study of human leukocyte antigens of the MHC and disease has been both promising and disappointing. Numerous studies have detailed the association of human leukocyte antigen variants with disease resistance and susceptibility. However, there have been questions about the methods used to determine the significance of these associations. Certain human leukocyte antigen genotypes provide resistance to diseases (tuberculosis Class I, B53; AIDS, Class I B57; typhoid fever, Class II, DRB1*04) while some increase susceptibility to them (pulmonary tuberculosis, Class I, B8 and Class II DR2; hepatitis B, Class II, DR7).^{157,163,164} The different immunological responses to these diseases may be related to the heterozygosity of the HLA system, which has been studied extensively.¹⁶⁵

More controversial has been selection in the ABO blood groups related to infectious disease.¹⁶⁶ Vogel¹⁶⁷ was one of the first to suggest the possibility that the distribution of the blood groups reflected adaptation to disease. While many studies have examined this relationship, they have obtained ambiguous results.¹⁶⁸⁻¹⁷⁰

CONCLUSIONS

Genome studies of pathogens leave many questions to be answered and, in some cases, genetic data may provide little help in reconstructing a pathogen's history. Often, the unique pattern of evolution in viruses precludes analyses using the conventional molecular clock. For example, the rapid genetic change noted in the hepatitis G and B viruses in modern times cannot be reconciled with the paucity of genetic differences found in their genomes despite the pathogens' great age, as indicated by their presence across disparate human populations.¹⁷¹ In other cases, conditions simply do not allow the easy identification of a pathogen's origin. Small-

pox has close relatives in a variety of animals so that it is impossible to determine its source.⁹⁹ Similarly, the measles virus is most closely related to the "peste des petits ruminants," which infect sheep and goats,¹⁷² indicating that these domesticates may be its source. Some feel that the measles and peste viruses are sufficiently different that the latter cannot have given rise to the former. Thus, the source of measles and the date of its emergence as a human pathogen remain unclear.

As shown by some of the cases discussed, the same genome may be analyzed multiple ways, with each analysis yielding a different origin scenario. Studies of *Helicobacter pylori* are a case in point. This Gram-negative bacterium is associated with duodenal and gastric ulcers and stomach cancer, and is found in the guts of half the world's population.¹⁷³ Analyses of its genome have alternatively dated human infection by the pathogen to before the New World-Old World separation of human populations many years before the onset of agriculture¹⁷⁴ and to sometime much later, after migration to the New World had ceased.¹⁷⁵

Even when reliable dates can be obtained, their interpretation is not simple. The case of *P. falciparum* illustrates that the date of a pathogen's origin does not necessarily coincide with the date when the pathogen became a significant disease agent for humans. Similarly, dating the origin of a pathogen to some time coinciding with the advent of agriculture does not necessarily imply a cause-and-effect relationship. For instance, genomic analysis indicates that the Ebola and Marburg viruses diverged 7,000 to 10,000 years ago,¹⁷⁶ dates that are coincident with the rise of agriculture, but no connection between the birth of this pathogen and the rise of agriculture and civilization is immediately evident. Thus, coalescence dates estimated using molecular-clock approaches must be considered in the context of historical, archeological, and epidemiological information. These same disciplines will continue to provide much of the basis for our construction of the disease ecology of the past.

Even with the greater availability of genomic data, many questions remain regarding the time and circumstances surrounding the emergence of various human pathogens. Certainly, information gleaned from genetic sequences has contributed greatly to our understanding of the first epidemiological transition. The theory of the first epidemiological transition, which implies a significant disease cost associated with agriculture, has been strengthened by the numerous major human pathogens shown to

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have emerged around the time of agriculture. At the same time, a significant number of pathogens believed to be quite recent in human history have turned out to be ancient, causing us to reassess our understanding of human life in the Paleolithic. Genomics have not necessarily resolved the controversy of the causes and consequences of neolithic revolution. It provides the tools to better understand this perplexing problem.

ACKNOWLEDGMENTS

We thank Kenneth Maes, Kenneth Weiss, T. Douglas Price, T. G. Schurr, Carol Worthman, and Albert Ammerman for thoughtful comments on earlier drafts of this manuscript.

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