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ANTHROPOGENICS: HUMAN INFLUENCE ON GLOBAL AND GENETIC HOMOGENIZATION OF PARASITE POPULATIONS

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ABSTRACT: The distribution, abundance, and diversity of life on Earth have been greatly shaped by human activities. This includes the geographic expansion of parasites; however, measuring the extent to which humans have influenced the dissemination and population structure of parasites has been challenging. In-depth comparisons among parasite populations extending to landscape-level processes affecting disease emergence have remained elusive. New research methods have enhanced our capacity to discern human impact, where the tools of population genetics and molecular epidemiology have begun to shed light on our historical and ongoing influence. Only since the 1990s have parasitologists coupled morphological diagnosis, long considered the basis of surveillance and biodiversity studies, with state-of-the-art tools enabling variation to be examined among, and within, parasite populations. Prior to this time, populations were characterized only by phenotypic attributes such as virulence, infectivity, host range, and geographical location. The advent of genetic/molecular methodologies (multilocus allozyme electrophoresis, polymerase chain reaction–DNA [PCR-DNA] fragments analysis, DNA sequencing, DNA microsatellites, single nucleotide polymorphisms, etc.) have transformed our abilities to reveal variation among, and within, populations at local, regional, landscape, and global scales, and thereby enhanced our understanding of the biosphere. Numerous factors can affect population structure among parasites, e.g., evolutionary and ecological history, mode of reproduction and transmission, host dispersal, and life-cycle complexity. Although such influences can vary considerably among parasite taxa, anthropogenic factors are demonstrably perturbing parasite fauna. Minimal genetic structure among many geographically distinct (isolated) populations is a hallmark of human activity, hastened by geographic introductions, environmental perturbation, and global warming. Accelerating environmental change now plays a primary role in defining where hosts, parasites, and other pathogens occur. This review examines how anthropogenic factors serve as drivers of globalization and genetic homogenization of parasite populations and demonstrates the impact that human intervention has had on the global dissemination of parasites and the accompanying diseases.

In 2000, a study surfaced examining the distribution of human genetic diversity. Researchers used a multitude of genes and different data sets from autosomal, mitochondrial DNA (mtDNA), and Y-chromosome loci with techniques such as restrictions-site polymorphisms, short-tandem-repeat polymorphisms, and single-nucleotide polymorphisms (SNPs), among others (Jorde et al., 2000). The investigation analyzed genetic diversity in 225 individuals from 3 continents and, unlike earlier studies, applied the same techniques to analyze all the DNA samples. In general, shared genetic traits ranged from 80 to 88%, depending on the methodologies used for analysis. It came as no surprise that individuals from Africa exhibited much greater genetic diversity than those from Europe and Asia. A second study by Yu et al. (2002) concluded that the genetic diversity observed among Eurasians was a subset of that present in Africans and, as previously determined, that genetic variation among Africans was greater than that between Africans and Eurasians. Not surprisingly, Jorde et al. (2000) concluded that heterozygosity in non-African populations generally declines with geographic distance from Africa. This finding supported the notion of an African origin for modern humans and that people show relatively little within- and between-population variation other than for those of African origin. It further demonstrated that the incursion of humans into other regions of the world was recent and probably the result of a single or concentrated event, given they appeared genetically homogeneous. As a result, recent bottlenecks have resulted in low within-population nucleotide diversity, especially in populations that became established outside Africa.

It would be quite convenient when studying parasites if we had such fossil records, sufficient sample sizes, and could easily evaluate individual members of a population. As an axiom, host species are involved, which confound the discovery and interpretation of parasite genetic diversity. Thus there is a spectrum, with variation partitioned between populations, but also potential variation within a single population or even within a single host (considering the relationships across infrapopulations and metapopulations). Over 30 yr ago, Price (1980) proposed that the population structure of parasites should exhibit low intrapopulation variation and high interpopulation variation. However, in the 1980s, when researchers began in earnest to look at parasite populations with the use of biochemical characters, and in particular isoenzymes, this hypothesis seemed not to hold. Studies on *Echinococcus granulosus* (Lymbery et al., 1990) and *Fascioloides magna* (Lydeard et al., 1989; Mulvey et al., 1991) collectively demonstrated that within-population variation was quite high and that distinguishing between parasite populations was difficult if not impossible with the techniques then available. Also, hypotheses had surfaced suggesting that the genetic variation in a population corresponded positively with the distance between populations, particularly in those involving predominantly sylvatic hosts, and in the environmental complexity of an organism including its life-cycle complexity and host range (Bullini et al., 1986) (to be discussed in more detail below). It was not until the early 1990s that biochemical techniques expanded to include DNA-based markers and began to shed better light on some of these questions.

Parkinson et al. (2004) examined gene discovery in nematodes by focusing on Expressed Sequence Tag (EST) data sets. They found a linear relationship between the numbers of new genes identified and the phylogenetic separation between organisms. Nearly 94,000 putative genes had been identified spanning the Clade V free-living nematode *Caenorhabditis elegans* (22,000

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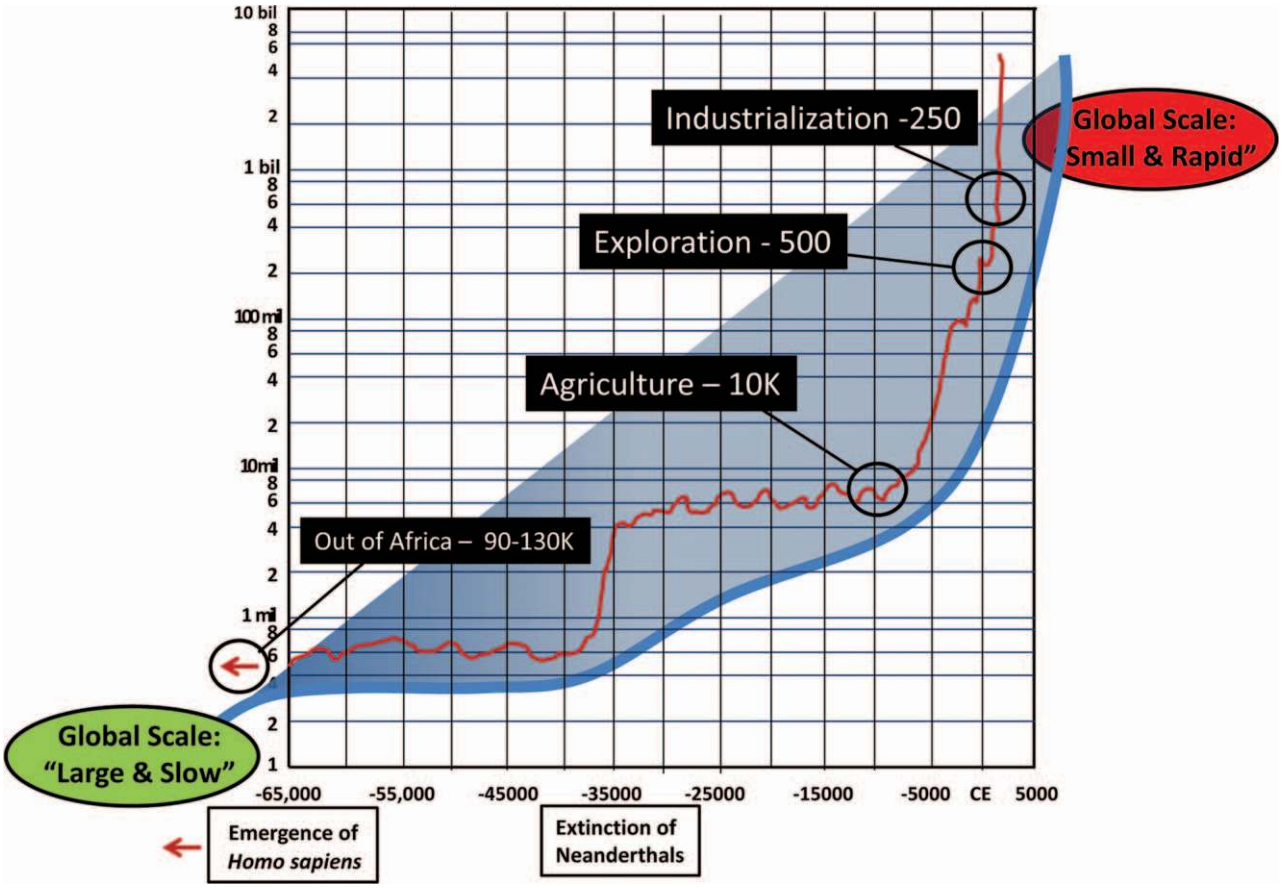

FIGURE 1. World population growth spanning the emergence of *Homo sapiens* to present day with key tipping points noted.

genes) up to, and including, the Clade I parasitic nematode *Trichinella spiralis* (Blaxter and Koutsovoulos, 2014). This was rather unexpected, given that many initially assumed nematodes should share a much higher level of genetic similarity than the evidence eventually exposed. Later studies showed that conserved genes in *Trichinella* spp. shared the same level of similarity (46%) with genes in *Drosophila melanogaster* as with those in *C. elegans*, suggesting that the common genes were only those required to sustain life among metazoans. Eventually, those studying the genetics of nematodes came to appreciate the tremendous genetic diversity that existed between species and certainly genera. However, what came as a greater and unexpected finding was the high genetic diversity that existed at the infrapopulation (within a single host) levels in many parasite groups, but the inability to distinguish between geographically distinct populations. It is this diversity at the infrapopulation level that we would like to focus on, and the role that humans, through their direct and indirect influence on diverse assemblages of other hosts, have historically played. Further, this influence continues to be manifested in shallow ecological time by shaping and counteracting forces that would otherwise be expected to increase differences among geographically disparate parasite populations. Against this backdrop is an extensive history of dispersal, contact, and genetic admixture among human populations. This serves as a proxy for exploring the impact of human intervention on the genetic structure of parasite populations and the processes involved in their isolation and/or dissemination (Hellenthal et al., 2014).

TIPPING POINTS, BIODIVERSITY, AND THE GEOGRAPHIC EXPANSION OF PARASITES

In examining human intervention as a contributing factor for the globalization of parasite populations, it is important to understand key tipping points or critical thresholds in human history (e.g., Hoberg, 2010; Hoberg and Brooks, 2013). A tipping point is apparent when key attributes of an ecosystem are altered by external forces, which, in turn, cause more rapid and sometimes irreversible changes (or cascades) within that system. These can occur across expansive geographic and spatial scales and leave identifiable signatures for structural changes in ecosystems and in the distribution of pathogens among humans, food animals, and free-ranging species. Important thresholds are evident extending into the early history of hominins in Africa (over 2–6 Million Years Before Present [MYBP]), the eventual emergence of archaic *Homo sapiens* (about 90–130 Thousand Years Before Present [KYBP]), and the geographic colonization that eventually drove final occupation of the northern continents by modern humans over the past 10,000–20,000 yr (Goebel et al., 2008; Gibbons, 2012; Harcourt, 2012; Raghavan et al., 2013).

To a great extent, tipping points reflect thresholds attained in a burgeoning human population and the attendant temporal

and spatial expansion of interfaces with the biosphere, initially at local, but increasingly at regional and global scales (Fig. 1). A pervasive human influence is recognized as a primary force in evolutionary trajectories across diverse ecosystems and among animals and plants, including those assemblages that are free-ranging, synanthropic in nature, or are now under selection pressure of domestication (Palumbi, 2001). In a like manner, the influential effects extend to the pathogens circulating in free-ranging and domesticated hosts and the potential for zoonotic transmission to humans. The magnification of human impact accompanied a critical transition from a slow and large world dominated by relative isolation and local effects, to a rapid and small world associated with extensive globalization, homogenization, and integrated, but often fragmented, ecological networks (Hoberg, 2010; Hoberg and Brooks, 2013).

Demonstrable human impact dates back as far as 10–12 KYBP with the advent of agriculture and the expansion of food resources that allowed local occupation resulting in increasing populations, and incipient urban infrastructure (Harcourt, 2012). Following the termination of the Pleistocene and the final glacial advances in the Northern Hemisphere, the climate rebounded rather quickly. The hunter–gatherers of the past found themselves in need of feeding larger numbers of peoples as sizeable communities and complex social organizations materialized. By 10 KYBP, the conversion of land to farming had established a foothold to accommodate expanding local populations. European exploration and colonization ensued about 500 yr ago, accompanied by continuing population expansions, globalization, invasions, and introductions of domesticated animals (and pathogens) to all continents except Antarctica. Industrialization over the past 250 yr and subsequent technological advances further increased travel (Fig. 1) and escalated food production in step with population growth; however, this occurred at the expense of natural resources such as soil, water, forests, and wildlife.

In our contemporary environments, human-induced changes have generated new tipping points such as those directly linked to accelerated global warming, ocean acidification, alterations in nitrogen and phosphorus cycles, and the loss of biodiversity across global ecosystems (IPCC, 2007a, 2007b; Lovejoy, 2008; IPCC, 2013; Meltofte et al., 2013; Hoberg and Brooks, 2014). Concurrent with ecological perturbation derived from climate change is the potential for development of new and unwelcome interfaces that lead to exchange of pathogens or host switching and concomitant emergence of disease (see Brooks et al., 2014). Our changing relationships to the environments in which we live, and our capacities for dispersal and interaction resulting from population growth and new technologies, are driving homogenization on global scales (Ricciardi, 2007; Hoberg, 2010) and, in particular, the distribution and dissemination of an array of foodborne parasites (Robertson et al., 2014). Further, they are directly influencing the emergence of diseases as a component of larger integrated crises for perturbation, pervasive extinction, and loss of diversity across the biosphere (Brooks and Hoberg, 2013; Mora and Zapata, 2013; Dirzo et al., 2014). These mechanisms lead to increasing homogenization and, we assume, gene flow within some assemblages. It is also historical genetic information, e.g., signatures of isolation and divergence of species and populations in source regions, that allows us to track the dissemination of parasites through anthropogenic invasion that introduces otherwise exotic faunal elements across regional and landscape levels (Hoberg, 2010).

CESTODES

Taenia spp. tapeworms; historical and recent human associations

Large taeniid tapeworms as obligate parasites of human hosts exemplify the transformative nature of multilocus, molecular-based approaches and illustrate the role of anthropogenic influence on parasite distribution resulting from expansion, geographic colonization, and formation of faunal mosaics (Hoberg, 2010; Hoberg and Brooks, 2013). Three species, *Taenia solium*, *Taenia saginata*, and *Taenia asiatica*, are central to the "Out of Africa" hypothesis for initial origins and diversification, followed by regional and global dissemination (e.g., Hoberg et al., 2000, 2001; Hoberg, 2006). Phylogenetic inference among species of *Taenia* was critical in constraining hypotheses for their relationships and in defining ecological and geographic settings for initial diversification and association with humans as definitive hosts. Conventional concepts over the past century held that these species were associated with humans only within a short time frame, since the domestication for our primary ungulate food animals, i.e., cattle and swine. Thus, the temporal limits for tapeworm diversification were considered restricted to the period during which ungulate domestication took place over the past 12,000–15,000 yr (e.g., Baer, 1940; Cameron, 1956).

Phylogenetic exploration of *Taenia* spp., initially with the use of morphological data, revealed the potential for a different and considerably deeper history of association with early hominins and ancestors of modern humans extending into the late Pliocene and Pleistocene (3–2 MYBP) (Hoberg et al., 2001). Diversification of human *Taenia* spp. was linked to independent events of host switching from large African carnivorans (lions and hyenas) in association with foraging guilds and shared food resources (ungulates) during the transition by hominins from forest to savanna habitats. Initial relationships among these parasites could be attributed to historic ecological processes that played out on the plains of Africa prior to the origins of modern humans and considerably predating the history of domestication of our ungulate food animals (Hoberg et al., 2001; Hoberg, 2006). Later, dispersal from Africa into the western Palearctic and to southern Asia resulted in broadening ranges for these parasites, and may also have been the driver for geographic isolation in the later region and for divergence of *T. saginata* and *T. asiatica*, which are regarded as sister species. These species of *Taenia* did not arrive with humans in the Nearctic during expansion from Eurasia into Beringia and eventually to the Neotropics following the Last Glacial Maximum over 15,000 yr ago (Goebel et al., 2008; Hoberg et al., 2012; Raghavan et al., 2013). Rather, these species of *Taenia* emerged considerably later in the Americas, concurrent with colonization and trade from Western Europe and Africa only 500 yr ago.

Subsequently, it was found that this story is considerably more complex, a picture now being revealed by multilocus molecular phylogenies for *Taenia* (Lavikainen et al., 2008, 2010; Knapp et al., 2011; Nakao et al., 2013a; Terefe et al., 2014) in conjunction with population-level explorations of phylogeography and gene flow among species and populations (e.g., Nakao et al., 2002;

Martinez-Hernandez et al., 2009; Michelet et al., 2010; Yamane et al., 2012). Recognition of an intricate history among large carnivore hosts and geographic regions is further highlighted by the cryptic diversity found among cestodes of canids and ursids (Lavikainen et al., 2010, 2011; Haukisalmi et al., 2011), northern felids (Lavikainen et al., 2013), and hyaenids (Terefe et al., 2014).

A comprehensive phylogenetic test of the Out of Africa hypothesis based on molecular data has been hindered by limited taxon sampling for *Taenia* spp. especially in the Ethiopian region among large cats and hyenas (Terefe et al., 2014). Development and evaluation of new molecular and morphological data are providing a nuanced picture of *Taenia* spp. diversification, and the first direct re-consideration of evolutionary and biogeographic histories for lineages in humans. In contrast to the original hypothesis as outlined by Terefe et al. (2014), molecular phylogenies are consistent in proposing different sister-group relationships for *T. solium* and *T. saginata* + *T. asiatica*, although the latter 2 are considered sister species; alternative biogeographic histories also may be apparent. Specifically, *T. solium* is placed as the sister of *Taenia arctos* (in Holarctic bears, *Ursus* spp.) and is basal to an assemblage of species primarily in hyenas and canids, where *T. saginata* + *T. asiatica* are placed as the sister of *T. crocutae*. African origins may be consistent with these postulated relationships, and the original Out of Africa hypothesis cannot be immediately refuted. A major implication of this phylogeny, however, is the possibility that host-switching events leading to human lineages may have occurred in Eurasia (*T. saginata* + *T. asiatica*), where assemblages of hyaenids and bovids were well established during the Pliocene, following geographic expansion by early hominins from Africa near 2 MYA (Terefe et al., 2014). Additionally, the common ancestor for *T. solium* + *T. arctos* may still have had sub-Saharan origins, although divergence of these sister species may have occurred in the Palearctic, with distributions related to sequential events of host colonization among hyaenids, ursids, and later hominins subsequent to emergence from Africa.

A fascinating series of questions arise from these most recent analyses among human taeniids, (Terefe et al., 2014), that are essential in focusing future discussion, and in exploring the global distribution and socioeconomic impacts of these cestodes. For example, relative to origins and speciation of human taenias, what were the regional arenas (African/Eurasian/Palearctic) and ecological context? What roles did hominins or early *Homo sapiens* play in determining geographic distributions for the *Taenia* spp. assemblages in Africa and Eurasia over the past 2 MY? What factors define the timing and geographic context for divergence of *T. saginata* and *T. asiatica*? And, what is the basis for the genetic substructuring (genotypes) that has been identified in *T. solium*, and how have patterns of dispersal for modern humans from Africa, and continental occupation over the past 120,000 yr influenced genetic diversity and distribution (e.g., Harcourt, 2012)?

Host switching can play a major role in the diversification and dissemination of parasites. A current understanding of the history of diversification among *Taenia* spp. in humans establishes temporally deep origins (Pliocene to Pleistocene) and a strong historical ecological context for 2 independent events of host switching (Hoberg et al., 2001; Terefe et al., 2014). Given the life-history patterns of taeniids, one would predict that the directionality of host colonization would have been from carnivorans to hominins; however, in recent molecular phylogenies, optimization of hosts and identification of basal associations appears equivocal. Further, the concept for independent origins of lineages associated with humans, decoupled from domestication events for swine or cattle, is consistent with the original hypothesis. Complete resolution of the evolutionary and biogeographic history for this assemblage will require expanded taxon sampling in Africa and from the *Taenia* spp. encompassing the nearly 50 species currently recognized (Terefe et al., 2014).

Following initial diversification, human taenias were restricted to Africa, Eurasia, and the western Palearctic for a considerable period of time, extending into the Holocene, whereas *T. asiatica* was regionally endemic to SE Asia. The pattern and temporal limits on human occupation and population dispersal on regional to continental scales were presumably major determinants of geographic distributions strongly influenced by agriculture, the domestication of primary food animals, and husbandry after 10,000–12,000 yr ago (Loftus et al., 1994; Nakao et al., 2002; Larson et al., 2005). *Taenia* spp. parasite assemblages in modern humans did not reach the Western Hemisphere until European colonization after the 1500s. This involved multiple events of introduction and establishment (*T. saginata* and *T. solium* only) on local scales, followed by broader dissemination that has been observed (Martinez-Hernandez et al., 2009; Hoberg, 2010).

The structure of these mosaics, primarily within *T. solium*, which exhibits discrete Asian and African/American genotypes, are particularly revealing about the history and timing of human dispersal and global occupation on varying spatial and temporal scales (Nakao et al., 2002; Michelet et al., 2010; Yanagida et al., 2014). During the 15th and 16th centuries, trade routes linking Africa, the Americas (Peru and Mexico), the Philippines, and southern Asia were especially prominent in the dispersal, introductions, and gene flow among populations of *T. solium* (Martinez-Hernandez et al., 2009). A specific genotype that is most commonly observed in the Americas is actually derived from Africa, whereas a second major genotype appears restricted to Asia (Nakao et al., 2002; Martinez-Hernandez et al., 2009). A similar route seems to have influenced the dispersal of *Onchocerca volvulus* in association with the slave trade. In contrast, across Madagascar, both Asian and African genotypes have been identified in sympatry, and suggest an elaborate history of introductions coincident with discrete periods of human colonization from different source populations in Africa and the Indian subcontinent resulting in a complex spatial and temporal mosaic (Hoberg, 2010; Michelet et al., 2010; Yanagida et al., 2014). Interestingly, although parasite genetic diversity reveals a history of human dispersal, these patterns reflect temporally shallow introductions for specific genotypes, which had prior origins substantially deeper in time (Pleistocene) relative to human migrations into the Americas and other regional settings (Nakao et al., 2002; Yanagida et al., 2014). Thus, the specific distribution of genetic diversity has served as a proxy for the source regions and parasite populations that were distributed and introduced sequentially through early human movements, more coordinated expansion, and later organized global trade.

Implications for the distribution of the major genotypes of *T. solium* are considerable given apparent differences in infectivity and pathogenicity with a varying propensity to cause neurocys-

ticercosis (Nakao et al., 2002; Campbell et al., 2006; Martinez-Hernandez et al., 2009). Understanding historical processes that have determined geographic distributions are of further importance given the emergence and re-emergence of this cestode and human cysticercosis globally (Schantz et al., 1998).

Complexity among species of *Echinococcus*

The interface for humans and species of *Echinococcus* differs substantially from *Taenia* spp. As with *Taenia* spp., species of *Echinococcus* circulate through predator–prey associations where strobilate adults are found in canid, felid, or other carnivoran hosts. Species of *Echinococcus*, however, are the agents of hydatid disease caused by metacestode infections of organs and tissues among herbivorous mammalian intermediate hosts (Eckert et al., 2000). Among 9 currently recognized species, most human infections are associated with *Echinococcus multilocularis* and *Echinococcus granulosus* sensu stricto and, to a lesser extent, other species of the *E. granulosus* complex (*Echinococcus canadensis*, *Echinococcus equinus*, *Echinococcus ortleppi*), *Echinococcus vogeli* and *Echinococcus oligarthra* (Nakao et al., 2013b). Knowledge about diversity of *Echinococcus* species has resulted from incremental advances over the past 200 yr. Taxonomic stability through the 1970s was based on comparative morphology and life history, recognizing 4 species (Rausch and Bernstein, 1972; Eckert et al., 2001). Diversity was linked to host-based strains, e.g., cervid, sheep, camel, cattle, buffalo, and swine, of varying pathogenicity for humans (Thompson, 1995). Subsequently, extensive data from mtDNA demonstrated the independence of specific genotypes (G-1 to G-10) and suggested putative species status to account for the considerable cryptic diversity within *E. granulosus* (McManus and Thompson, 2003; Nakao et al., 2013b). Recognition of cryptic species has transformed our concept for host and parasite associations among this assemblage of pathogens. Robust phylogenies based on mitochondrial and, to a lesser extent, nuclear DNA data, support 9 species and resolution of the status of recognized genotypes (Nakao et al., 2007, 2013b; Knapp et al., 2011).

Taeniids and their associations with carnivorans have a relatively deep history, extending minimally to the mid-Tertiary (Hoberg et al., 1999). Diversification has been linked to episodic processes for host (among carnivorans) and geographic colonization over time, which have driven distributions across the northern continents, Africa, and the Neotropics (Hoberg and Brooks, 2008; Hoberg et al., 2012; Nakao et al., 2013b). Humans as hosts for *Taenia* spp. were intimately involved in life cycles, transmission, and circulation to near the Pliocene–Pleistocene boundary, although our associations with *Echinococcus* spp. are more recently circumscribed by events in the late Quaternary. For example, infection of *Echinococcus* and unilocular hydatid disease attributable to the *E. granulosus* complex among people may have emerged in natural settings prior to the origins of agriculture and domestication of ungulates and companion animals (Rausch, 1967; Yanagida et al., 2012).

Domestication of dogs, cattle, sheep, and horses and inception of fully synanthropic patterns of life history were substantial drivers of increasing prevalence at local and landscape scales as precursors to regional and global expansion associated with colonization and trade (Rausch, 1967; Nakao et al., 2010, 2013b; Yanagida et al., 2012). Established trade routes across Eurasia as deep as 10,000 yr ago, and later European expansion after the 1500s, including occupation of Iceland, South America, North America, Australia, New Zealand, and Africa, led to broad global distributions for *E. granulosus*, *E. equinus*, *E. ortleppi*, and the G6/G7 genotypes of *E. canadensis* in an ungulate/dog pattern of transmission. Consequently, anthropogenic forces are implicated in the introduction and establishment of this species complex and in the varying degrees of sympatry within this assemblage. The global range of these species of *Echinococcus* is a primary example of temporal and spatial mosaics resulting from recurrent geographic invasion over shallow ecological time frames (Hoberg, 2010; Hoberg et al., 2012). Past history, founder events, and the time and origin of human introductions of *E. granulosus* with livestock and dogs can be directly inferred from haplotype diversity at specific geographic localities (Yanagida et al., 2012; Nakao et al., 2013b).

Contrasting with *E. granulosus* sensu stricto, patterns of transmission and human exposure resulting in alveolar hydatid disease for *E. multilocularis* historically were not as strongly defined by domestication of intermediate hosts and emergence through synanthropic cycles (Rausch, 1967). In areas of hyperendemism such as St. Lawrence Island in the Bering Sea, human infection is driven by the density of arvicoline rodents as intermediate hosts, widespread infection of dogs (and Arctic foxes), and only secondarily with the contamination of food and water resources (Rausch and Fay, 2002; Jenkins et al., 2013). In urban areas of Europe, the parasite is maintained principally in red foxes, with human exposures mediated through companion animals (Eckert et al., 2000).

Studies of genetic diversity and phylogeography in *E. multilocularis* have revealed an intricate history with distributions tied primarily to high-latitude systems of the Northern Hemisphere and a linkage between Eurasia and the Nearctic established through Beringia (Nakao et al., 2009, 2013b; Hoberg et al., 2012). Episodes of intercontinental expansion and isolation spanning multiple glacial–interglacial cycles during the late Pleistocene appear to account for the distribution of discrete genotypes in western Europe and in eastern Eurasia and North America (Nakao et al., 2009, 2013b). Perhaps significantly, most cases of alveolar echinococcosis (excluding those in Alaska) appear associated with European haplotypes of *E. multilocularis*, highlighting the need for focused survey and inventory to establish the history and limits on distribution for these cestodes (Gesy et al., 2013; Nakao et al., 2013b). Recently, an autochthonous distribution for a European haplotype of *E. multilocularis* was demonstrated in central British Columbia, suggesting that taiga forest may be an incomplete barrier for transmission. The origins of these parasites, however, remain unresolved, and may be indicative of anthropogenic translocation, introduction, and establishment coinciding with exotic European red fox (Gesy et al., 2013), or a deeper historical pattern related to postglacial expansion from Beringia following the last glacial maximum (Hoberg et al., 2012).

Zoonotic infections of *E. multilocularis* are emergent in central Europe, possibly coinciding with geographic expansion from multiple focal populations and invasion of urban settings by red fox, and an association with invasive raccoon dogs (*Nyctereutes procyonoides*) (Davidson et al., 2012). Anthropogenic drivers include limited controls on the movements of dogs and cats, variable treatment regimes, and, in some instances, translocation

and establishment linked to reintroduction programs for wild definitive hosts and a changing periurban interface for people and free-ranging carnivores (Eckert et al., 2001; Davidson et al., 2012). Determinants for the distribution of *E. mutilocularis* vary spatially and temporally. These reflect the influence of local ecological assemblages as indicated by the preponderance of infections in coyote from western Canada (Gesy et al., 2013), or by the apparent limitations in distribution in western Europe that may reflect associations with specific vole intermediate hosts (*Microtus arvalis*) (Guerra et al., 2014). Interestingly, a focus of *E. multilocularis* was established on Svalbard following the inadvertent introduction of a suitable intermediate host, the sibling vole (*Microtus rossiaemeridionalis*), which enabled the completion of the life cycle (Henttonen et al., 2001). Prior to this point, the parasite had not been detected within the Norwegian archipelago. Tracking isolated and sequential patterns of expansion, or introductions and subsequent establishment and dissemination, depends on continued development and applications of molecular-based markers appropriate for phylogeographic approaches to characterize the origins and distribution of diversity (Nakao et al., 2013b). Given its sylvatic origins and host species, clear genetic subdivision of *E. multilocularis* has been observed in the isolates obtained from North America, Europe, Mongolia, and Asia (Nakao et al., 2009; Ito et al., 2010).

A human association with taeniids demonstrates dual and diverse origins that are either temporally deep (linked to hominin evolution and expansion for *Taenia* spp.) or considerably shallow (linked to host domestication, translocation, introduction, and establishment among the *E. granulosus* complex) in ecological time measured in thousands of years. In both instances, anthropogenic drivers and an extensive history of recurrent invasion and introduction have had prominent outcomes demonstrated by widespread (often global) geographic distributions for host–parasite assemblages. Considerable human impact through host domestication, alteration of environments, and involvement in synanthropic cycles has strongly influenced the potential for disease and related socioeconomic cascades. Increasingly sophisticated means for detection and identification now support a refined capacity to track pathogens and to apply molecular-based approaches to a fine-scale understanding of diversity. Examples of pathogen tracking and support for anthropogenic movement can be seen in studies by Yanagida et al. (2012) who found high haplotype diversity, but low nucleotide diversity, in *E. granulosus* s.s. examined from Iran and Jordan. As in China and Peru (Nakao et al., 2010), the EG01 subgroup was present at all locations and harbored sequences identical to those found in the European EG1 subgroup. They concluded that this mtDNA haplotype had worldwide distribution. Also, using microsatellite markers, Bartholomei-Santos et al. (2003) found that the South American ovine isolates of *E. granulosus* differed little from those in Australia. Future resolution of the population genetics among cestodes will rely heavily on state-of-the-art, molecular-based technologies.

NEMATODES

Terrestrial parasitic nematodes

Regional biogeographic histories and the process of faunal assembly, such as the development of mammalian parasite faunas including those in ungulates, are intricate and complex (Hoberg et al., 2004, 2012; Hoberg and Brooks, 2008, 2013). Recurrent processes of faunal expansion and isolation linking Eurasia, the Nearctic, and ultimately the Neotropics had a demonstrable effect on the structure of parasite assemblages over the past 10–20 million years. Processes of geographic invasion set the foundations for the contemporary structure of the Holarctic fauna. Thus, coincident with European exploration, discovery, and colonization, another element of these faunas was introduced that is associated with domesticated hosts and synanthropic cycles, contributing yet another facet of the puzzle of these interacting mosaics (Hoberg et al., 2008; Hoberg, 2010). Deeper historical processes of invasion, in addition to those under anthropogenic forcing, involve the breakdown of ecological mechanisms for isolation and the cascading effects of faunal mixing (Hoberg and Brooks, 2013).

Human influence on faunal structure is evident relative to the introduction of otherwise exotic parasite assemblages, the introduction of hosts and host groups, which facilitate establishment, and to landscape perturbations that enhance parasite invasion and colonization (Hoberg et al., 2008; Mas Coma et al., 2008, 2009; Hoberg, 2010; Brooks and Hoberg, 2013; Hulme, 2014). This human-based signature is manifested in the expansion of ecological impacts related to accelerating climate change and technologies that drive massive and rapid interconnectivity around the world (IPCC, 2007a, 2007b, 2013; Lovejoy, 2008; Hoberg et al., 2008; Brooks and Hoberg, 2013; Brooks et al., 2014).

Work performed by Blouin et al. (1992) was among the earlier studies demonstrating the human-based signature on the complexity and dispersal of populations of nematodes infecting food animals. Investigations using simple restriction-site polymorphisms and mtDNA probes (Tarrant et al., 1992) demonstrated that virtually all genetic diversity in the cattle nematode, *Ostertagia ostertagi*, was distributed within any single population and that multiple samples from the same population did not preferentially cluster together. Geographical distance seemed not to be a contributing factor to the variation, unlike what was observed in *Fascioloides magna* in white-tailed deer. Numerous explanations have arisen to explain this lack of genetic partitioning, all of which could be contributing factors such as (1) the absence of clonality or sterile protection, (2) the existence of a free-living stage accompanied by quick regeneration times, (3) an exceedingly large population size, (4) high genetic mutation rates among certain parasite groups and certain genes, and (5) the intentional or unintentional movement of infected host species. Biological differences between northern and southern populations of *Ostertagia* and inheritance (or lack thereof) of the temperature-related developmental arrestment raised questions as to panmixia among these parasites (Lymbery, 1993). It has yet to be determined if this phenotypic trait is invoked by environmental queues, and therefore exists in the genetic makeup of both northern and southern populations, or if the difference in summer and winter arrestment characteristics is normally maintained by large population sizes and selection (Dame et al., 1993). Nonetheless, these early studies drew significant attention to the complicated nature of performing population research on parasites and to the putative involvement of human intervention in the movement of hosts and, consequently, the parasite, thereby resulting in lost global diversity. A later study (Blouin et al., 1995) looking at variation within other domestic (*Haemonchus placei*,

Haemonchus placei contortus, and *Teladorsagia circumcincta*) and sylvatic (*Mazamastrongylus odocoilei*) parasites, revealed similar levels of within-population variation that seemed to occur even among sylvatic hosts, e.g., white-tailed deer. However, it is believed that this issue was confounded by misidentification of a second species of *Mazamstrongylus*, i.e., *Mazamstrongylus pursglovei*, where large population sizes and extensive gene flow were not expected to dominate (E. P. Hoberg, unpubl. obs.). This finding seemed to conflict somewhat with the distance hypothesis supported by the work on *F. magna* in white-tailed deer, which also encompassed animals from southeastern United States.

More recent studies seem to bear out the absence of significant variation among populations of gastrointestinal nematodes. Grillo et al. (2007) utilized microsatellite markers to target nuclear diversity rather than mtDNA variation in populations of *T. circumcincta,* an economically important nematode parasite of sheep and goats. This study examined samples from France, Scotland, Wales, and New Zealand. Once again, a lack of population substructuring was observed and was ascribed both to a large effective population size and a high degree of gene flow because of host movement. Surprisingly, this genetic diversity and lack of observed subpopulation divergence was seen in lab or clonal lines of the parasite passed in experimental animals as well as in field isolates. In that study, the New Zealand population was somewhat genetically differentiated and this was initially attributed to quarantines and restrictions on imports in the past 90 yr, which, in turn, reduced gene flow (Pierce, 1975). However, the nematodes parasitizing Soay sheep on the St. Kilda archipelago, which have been effectively isolated for 80 yr, do not seem to show genetic differentiation from those examined in other U.K. populations. The long-term history of animal movement in this region is somewhat unclear, but evidence suggests both successes and failures dating back to the early 1500s in order to establish other breeds in this region. This, coupled with the high level of parasitemia, may result in population structures being shaped by both naturally dense populations capable of maintaining abundant genetic variation along with human activities that have only partially restricted host movements (Cheyne et al., 1974).

Species of *Trichinella* provide both unique and compelling arguments for human involvement in their global dissemination. In general, animals infected with *Trichinella spiralis* become refractory to additional infections because of the strong and persistent gut immunity that develops. In effect, this creates a clonal infrapopulation. Multiple infections have been observed among species, but these mostly involve sylvatic genotypes or very lightly infected animals where the immune response is poorly established. Unlike most nematode parasites, *Trichinella* spp. do not have a free-living stage and complete their entire life cycles within a single host. It is difficult to ascertain population numbers, although one might surmise that historically, the infrapopulations were at one time quite large. However, this has been substantially pared down in recent years because of control measures imposed by the commercial food industry.

Rosenthal et al. (2008b) used microsatellite markers and mtDNA sequencing to study isolates of *Trichinella* spp. derived from 28 countries and 4 continents. Among *T. spiralis* isolates, 2 closely related, but discernable, genotypes emerged, predicated upon geographic locality. Those from Europe, North Africa, and the Americas defined essentially 1 genotype that could be differentiated from the small number of samples obtained from Asia. Further, the isolates from Asia, where pig domestication is believed to have originated, exhibited substantially higher within-population variation, as did all sylvatic genotypes. Given that extant organisms of the *Trichinella* spp. date back approximately 20 million years (Zarlenga et al., 2006), along with the clonal nature of the infection, one might have anticipated much greater diversity among populations of *T. spiralis* and, therefore, substantial regional differentiation. This has simply not been observed. A more recent study (La Rosa et al., 2012) showed that outside of China, animals were infected with highly inbred larval cohorts from parents, which themselves were highly inbred. However, in China, infected pigs seem to harbor more diversity among *T. spiralis* larvae than that observed among all the European and American isolates. This further supports human movement as a factor in creating a Western population because this has likely taken place in only the last 400–500 yr with the increase in trade and human travel. The specific role of agriculture in dispersing parasites has been discussed elsewhere (Rosenthal, 2009).

Although the role of humans in disseminating *T. spiralis* appears well established, translocation of other swine nematodes is less clear. Unlike *T. spiralis*, early studies on *Ascaris suum* with the use of RAPD markers revealed subdivision in mid-western populations (Nadler, 1996). However, in recent years, our understanding of the biology of *Ascaris* spp. has become more complicated. Evidence for polyandry (Zhou et al., 2011), the ability of *A. suum* and *Ascaris lumbricoides* to hybridize (Criscione et al., 2007), the identification of *A. suum* as a zoonosis (Anderson, 1995; Nejsum et al., 2005, 2006), and the spontaneous cure of fourth-stage larvae resulting in displacement of >90% of the worms from a given host (Roepstorff et al., 1997), all weigh heavily on deciphering the population structure of *A. suum*. It is not clear if spontaneous cure is totally random or if it involves some level of genetic selection. However, the natural ability of the host and/or parasite to control infection levels within the animal can demonstrably affect the population biology of this organism. Moreover, work performed with microsatellite loci has shown that host-associated populations have emerged following geographical isolation (Criscione et al., 2007). Another more recent study also demonstrated that concurrent infections of 2 different nematodes in pigs may affect infection levels (Petersen et al., 2014). Studies in pigs concurrently infected with *Trichuris suis* and *Oesophagostomum dentatum* clearly showed an antagonistic interaction between the 2 organisms at the expense of *O. dentatum* worm burdens. As such, translocation of 1 species can affect the population structure of a co-infecting species.

Human associations with the distribution of parasites need not be linked to agriculture. Onchocerciasis, or river blindness, is a debilitating tropical disease found in sub-Saharan Africa, the Arabian Peninsula, and Central and South America. Humans are the only definitive host for the causative agent, *Onchocerca volvulus,* which is transmitted by the intermediate black fly host (*Simulium* spp.). It is estimated that over 37 million people suffer from this disease. Early studies examining *O. volvulus* populations in Mali (savanna), the Ivory Coast (forest), and Zaire (forest/savanna) using isoenzymes were among the first to show sufficient heterogeneity to allow biochemical identification among parasites originating from different geographic regions and habitats (Cianchi et al., 1985). In essence, there seemed to have emerged "African savanna" and "African forest" isolates of this parasite.

However, PCR studies of repeat sequences showed that worms introduced into the New World were indistinguishable from those in the African savanna (Zimmerman et al., 1994). This was attributed to a recent introduction during peak periods of the slave trade, wherein the primary source of slaves in the 18th and 19th centuries was the African savanna.

Much later, Morales-Hojas et al. (2007), through the use of nuclear ITS2 rDNA data, indicated that little, if any, population structure separated the Brazilian and African strains. They also observed strong similarities among *O. volvulus* and the cattle parasites *Onchocerca ochengi* and *Onchocerca* sp. 'Siisa' (Krueger et al., 2007) and suggested that *O. volvulus* evolved from an ancestral bovine parasite in Africa because of host switching during the process of domestication by humans (Morales-Hojas et al., 2006). The gene flow among the African populations was consistent with the migration patterns of the host, i.e., West African black flies (Boakye et al., 1998).

Free-living nematodes

The loss of genetic distinction among disparate populations is not limited to parasitic nematodes. *Caenorhabditis elegans* comprises free-living, hermaphroditic nematodes, the preponderance of which are females. Generally, they occupy nutrient- and bacteria-rich environments derived from decaying organic matter. Inasmuch as normal soil is lacking sufficient organic matter to support self-sustaining populations, these nematodes tend to exist commensurate with humans in compost heaps and rotting fruit, though local movement can be at the expense of small invertebrates. To this end, most maintained isolates have been derived from synanthropic sources.

Earlier genetic studies of population variation among isolates of *C. elegans* showed that the global genetic diversity was at least 20× less than that observed in *Drosophila* spp. and more akin to the diversity seen in humans (Barriere and Felix, 2005a). Global and local diversity have been examined with the use of a multitude of technical parameters. The general conclusions from studying subsets of loci in many isolates of *C. elegans* is that globally, the genus has a small population size, low genetic diversity, and high gene flow, whereas locally, the population size is quite large (Sivasundar and Hey, 2003, 2005; Barriere and Felix, 2005b; Haber et al., 2005; Andersen et al., 2012). To this day, this phenomenon remains an enigma. It has been argued that this is due to neither recent colonization and expansion events nor to natural selection and global selective sweeps (Sivasundar and Hey, 2003). However, more recent studies have shed new light on these possibilities. Most agree that anthropogenics plays a large, though not exclusive, role in the migration patterns of *C. elegans* and the appearance of global homogenization of the populations.

Until recently, most analyses examined variations in small numbers of loci. Andersen et al. (2012) examined over 41,000 SNPs in 200 wild strains of *C. elegans*. As robust an analysis as this was, they were unable to detect any meaningful subdivision within the global population corroborating what had been observed from smaller-scale analyses. They further noted that all isolates, except for 2 strains from Hawaii and California, exhibited large haplotype homozygosity and concluded that 1, or more, global sweeps driven by positive selection were at the root of the current population structure and that this probably occurred within the past 100–200 yr. Among the many possibilities, they attribute this finding to human activity. Most recently, Vergara et al. (2014) examined genetic variation via whole genome sequencing between the common N2 strain of *C. elegans* and the Hawaiian strain CB4856, which is regarded as the most genetically distinct from the more common N2 isolate. Both large and small indels were identified. Most importantly, many of the genetic variations could be associated with behavioral and biological traits that distinguish the 2 strains.

Unlike its close relative *C. elegans*, *Caenorhabditis briggsae* seems to exhibit a bit more structure (Cutter et al., 2006). Even though the habitats of *C. elegans* and *C. briggsae* are basically the same, there appears to be differences between those of temperate (northern hemisphere) and tropical (Tropic of Cancer) origins, though little variation is observed among those from temperate localities. However, additional works concluded that although genetic differentiation is strong in relative terms among the different groups, it remains quite modest in absolute magnitude, further supporting low species-wide polymorphism (Félix et al., 2013). High gene flow and recombinations were also observed in *Caenorhabditis remanei* (Dey et al., 2012) except in 1 population of worms obtained from Germany, which can be genetically differentiated from the North American populations, suggesting some degree of isolation by distance. In 1 case, substantial genetic differentiation was observed between a strain collected from China (*Caenorhabditis* sp. 23) and those of North American, European, and Japanese origins. However, the *Caenorhabditis* sp. 23 isolate has since been characterized as a new species (Félix et al., 2013) rather than as an isolate of *C. remanei*.

Moving a bit away from species of *Caenorhabditis,* we examined the population structure within *Pristionchus pacificus,* also a free-living nematode with close associations to scarab beetles and the Colorado potato beetle (Herrmann et al., 2006). Whole-genome sequencing performed on 104 isolates showed a level of genetic diversity that was 10 times greater than that observed in *C. elegans,* along with a more discernable population structure (Rödelsperger et al., 2014). Within this analysis, genetic diversity was low in gene-rich regions, and nonsynonymous variations were eliminated over short timescales. When McGaughran et al. (2014) considered the contribution of environmental factors to genetic variation among populations of *P. pacificus*, they found strong associations between environment and genetic variation at local scales and also found that variation was more attributable to environmental heterogeneity than to geographic distances. The impact of environment on population diversity was also observed in numerous marine parasites that exhibit more complex host systems, as discussed below.

Marine nematodes and the effects of habitat disturbance

Man-made, environmental stress impacts the genetic diversity not only of terrestrial parasites, but also those of aquatic ecosystems. The integrity of the water supply is a driving force for change. However, because many factors can alter water quality, it is difficult to ascribe changes in the interactions between aquatic ecosystems and parasitism to any single type of disturbance. In some cases, habitat degradation and pollutants from human activity can facilitate disease outbreaks (Lafferty and Kuris, 1999; Lafferty, 2008) where parasite communities of fish are influenced by pollutants toxic to fish and invertebrate hosts, as

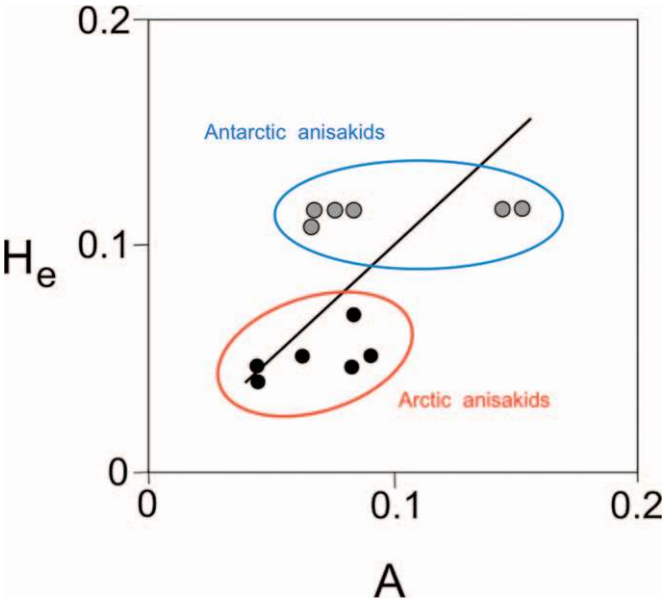

FIGURE 2. Comparing the genetic diversity and abundance of infection between Antarctic and Arctic species of the *Contracaecum osculatum* s.l. complex. Kendall's rank correlation, i.e., Kendall tau test, was performed to compare the abundance of infection (A) and the heterozygosity (*He*) in *Contracaecum* species sampled from Antarctic seals and fish hosts (gray circles), and from seals of the Arctic Boreal region (black circles) (data from Mattiucci and Nascetti, 2007). Parasite abundance was log-transformed, $\log(x+1)$. Both A and *He*, were standardized to their sums to obtain dimensionless (and comparable) estimates. The significance of the correlation between the 2 parameters is given by the Kendall's τ statistic ($\tau = 0.45$, $P < 0.05$). Results demonstrate a statistically significant correlation between the abundance of the infection (A) and the value of genetic diversity (mean *He*), which is consistent with less habitat disturbance in the Antarctica ecosystem than that observed in the Arctic.

well as directly to the parasites in their free-living stages (Pietrock and Marcogliese, 2003; Marcogliese, 2005; Lafferty, 2008). Numerous aquatic ecosystems have become contaminated with man-made chemical pollutants (organic compounds, polyclic aromatic hydrocarbons, polychlorinated biphenyl, metals), which act directly on the physiology and survival of aquatic organisms and endohelminths (trematodes, acanthocephalans, cestodes, and nematodes). Such contaminants may also reduce the immunological capacity of hosts, rendering them more susceptible to parasitic infections (Harvell et al., 1999). Lafferty (1997) demonstrated that infection levels by some monoxenous parasites of fish having direct life cycles could actually increase with oil pollution from industrial effluent; they attributed this to adverse effects of the pollutants on the host's immune system. Still, other pollutants can alter abiotic and biotic factors such as water pH, oxygen content, temperature, and salinity, among others, which can reduce helminth survival (Pietrock and Marcogliese, 2003). In-depth discussion on the effects of pollutants on host–parasite relationships have been discussed elsewhere (Marcogliese, 2005; Thompson et al., 2005; Hudson et al., 2006; Brooks and Hoberg, 2007).

Although much information has been presented on the degradation of aquatic ecosystems from direct and indirect human activity, less work has been done correlating habitat degradation with genetic diversity among parasites populations. Clearly, large-scale anthropogenic stressors such as overfishing, pollution, toxicants, global warming, and by-catch of animals can impact species diversity by reducing the population sizes of the host. This in turn can lead to the concomitant reduction in parasite populations and the genetic diversity within. The negative impact of human activities on parasites appears greater in those heteroxenous parasites, whose life-history stages are associated with the food web of a water ecosystem (Marcogliese, 2005).

One only need look at genetic diversity within anisakid nematodes of the genera *Anisakis*, *Pseudoterranova*, and *Contracaecum*, which are integral parts of marine and freshwater ecosystems all over the world, to see examples of human intervention on parasite diversity. These organisms are heteroxenous parasites, whose life cycles require stable trophic webs. Indeed, the transmission routes of anisakid nematodes closely follow the trophic relationships of their successive hosts. Because of this, any type of habitat disturbance or anthropogenic stressor that affects the habitats and therefore population size of the intermediate and/or definitive hosts can also reduce the population size and associated genetic diversity of their anisakid nematodes. Negative actions such as these can increase the probability for genetic drift within the gene pool of a population. Two complementary strategies have been used thus far to examine the effects of habitat disturbance (anthropogenic impact) on the genetic diversity of anisakid nematode populations, i.e., the comparison of genetic variability among different populations inhabiting disrupted ecosystems (spatial dimension), and a comparison of the genetic variability among populations from the same geographical area at different points in time (temporal dimension) pre- and postdisturbance.

Research involving spatial comparisons, i.e., disturbed versus undisturbed populations, has shown differences in the distribution of genetic variability of populations of anisakid nematodes in geographical areas undergoing different levels of environmental stress. This was most apparent when examining distinct geographic areas such as in the Boreal and Austral hemispheres that are subject to diverse levels of habitat disturbance (Mattiucci and Nascetti, 2007). In this work, the genetic variability in anisakid populations from fish and marine mammals was examined with the use of 19 allozymes. Results showed significantly higher levels of genetic diversity in Antarctic and sub-Antarctic parasite populations from fish and pinnipeds than those observed in the Arctic and sub-Arctic nematode populations. This was accompanied by higher worm burdens and population sizes in the undisturbed "pristine" ecosystems (Battaglia et al., 1997). The genetic variability expressed as mean Heterozygosity (*He*) in the *Contracaecum osculatum* complex, i.e., the sibling species, *C. osculatum* sp. D and *C. osculatum* sp. E, was substantially higher in parasites from the Antarctic ecosystem ($He = 0.20$) relative to those obtained from Arctic members of the same *C. osculatum* species complex ($He = 0.07$). Also, thousands of worms were periodically collected even from a single infected fish host in the Antarctic region (Mattiucci and Nascetti, 2008, unpubl. obs.; Santoro et al., 2014), whereas only low worm burdens were commonly found in Arctic boreal pinnipeds and fish (Mattiucci and Nascetti, 2007). A statistically significant correlation was observed between the abundance of the infection (A) as a measure of effective population size of parasite (N) and the value of genetic diversity (mean *He*) (Fig. 2). These results were recently confirmed when sequence data from the mitochondrial gene *cox2* (mtDNA *cox2*) from these same parasite populations showed high

nucleotide diversity (π) in *C. osculatum* sp. D ($\pi = 0.020$) and *C. osculatum* sp. E ($\pi = 0.013$) from Antarctic hosts, relative to the low diversity ($\pi = 0.009$ observed in the Arctic members of the *C. osculatum* s.l. complex (for instance, *C. osculatum* sp. B) (Mattiucci and Nascetti, unpubl. obs.). These studies demonstrate that the density and genetic variability of anisakid populations can be used as valuable indicators of environmental stress on the overall health, i.e., productivity, biodiversity, and resilience, of a marine ecosystem.

The allozymes and mtDNA data sets exhibiting high levels of genetic diversity are also consistent with high-density levels of definitive and intermediate hosts for the anisakid nematodes in the Antarctic (Wickens, 1995), relative to those from the Arctic-Boreal regions (Read et al., 2006). In Antarctic waters, the Weddell seal (main definitive host of *C. osculatum* D and *C. osculatum* E) has not suffered a reduction in its population numbers in recent years (Kendall et al., 2003). This is contrary to the phocids of the Arctic–Boreal region, whose population size has decreased dramatically from human activity, i.e., hunting, by-catch, viral diseases, etc. (Hauksson, 2002; Barron et al., 2003; Pastor et al., 2004; Di Guardo et al., 2005; Andersen et al., 2006; Harding et al., 2007). Similarly, Antarctic fish species belonging to the Channictiydae, Bathydraconidae, and Nototheniidae, and that function as intermediate hosts for these nematodes, have not been subject to the population reduction from overfishing that has occurred in host fish species, i.e., *Gadus morhua*, in the Boreal region found infected by the Arctic members of the *C. osculatum* complex (Cook et al., 1997; Masood, 1997). Thus, the high level of nematode genetic variability can be explained by the lower habitat disturbance of the Antarctic region, which permits the maintenance of more stable trophic webs. These results offer support to the hypothesis that parasite diversity can be used as an indicator of the health and diversity of the hosts they infect and, therefore, of the integrity and stability of the food webs within a given marine ecosystem (Hudson et al., 2006; Poulin, 2006).

We noted that global homogenization can also reduce genetic variability within a species or among populations at temporal scales (pre- and postdisturbance at a given geographical location) where bottlenecks in local parasite populations along with lower effective population sizes can occur from habitat disturbance. Indeed, it has recently been shown in several organisms that natural and anthropogenic-derived environmental changes affect the genetic structure of animal populations resulting in "genetic erosion" (loss of number of alleles per locus, and decrease in heterozygosity and polymorphism rates) in their gene pools. This can result from population fragmentation and size reduction, interruption of gene flow, and genetic drift (Schwartz et al., 2006). Thus, assuming that habitat disturbance and fragmentation reduce the local effective population size (N), migration rate (m), or both in a parasite population, increased genetic drift should redistribute genetic diversity such that variation within populations should decrease, and variation between populations should increase. In small and isolated populations, the average heterozygosity should decrease at a constant rate per generation, so that small populations have a higher probability of losing genetic diversity than larger and continuously distributed populations. The extent to which a species could be affected by habitat disturbance is determined, therefore, by its degree of specialization and potential for dispersal. Two of the main factors influencing the genetic variability of a population are the amount of gene flow between populations and the population size (N). High gene flow has the ability to homogenize genetically divergent populations by counteracting the effects of genetic drift. If the determination of gene flow is based on the standardized variance of allele frequencies, *Fst* (Crow and Aoki, 1984; Slatkin and Barton, 1989), where m is the fraction of immigrant individuals in a population of effective size N, then among conspecific populations of anisakid nematodes, gene flow is generally found to be high. This is largely determined by the dispersal of host animals (Mattiucci et al., 1997) and parasite abundance (as a proxy for parasite population size); 2 parameters that are strongly correlated with host density (Arneberg et al., 1998). It follows, therefore, that variation in host dispersal and density would lead into differences in the patterns of genetic diversity distributed among anisakid parasite populations.

Allozyme data have indicated low levels of genetic differentiation among conspecific populations of anisakid nematodes even if located thousands of kilometers apart (see *Anisakis pegreffii*). This has been attributed to the homogenetic effects of high gene flow, in association with the high dispersal capacity of the definitive cetacean hosts. Indeed, high levels of gene flow among populations, indirectly estimated from allele frequencies and *Fst* values have been observed (Mattiucci and Nascetti, 2008). Preliminary data from genetically monitoring anisakid populations over temporal scales indicate that the loss of polymorphism, i.e., "genetic erosion," could have affected their gene pools. This seems to be the case for populations of *A. pegreffii*, a sibling species of the *Anisakis simplex* complex widespread in the Mediterranean Sea, but also present in the Austral region (Mattiucci et al., 2014). Loss of heterozygosity has been found in the Mediterranean populations of *A. pegreffii* recently collected from fish hosts relative to that estimated from samples collected 20 yr earlier. In contrast, the Austral populations (South African coast and New Zealand sea waters) of *A. pegreffii* have maintained the same level of heterozygosity at the same gene loci through time despite the high level of gene flow estimated from allozymes ($Nm = 15.0$) (Mattiucci et al., 1997). Again, this can be attributed in part to human activity. The genetic diversity of the same populations of *A. pegreffii* inferred from mtDNA *cox 2* revealed genetic substructuring of *A. pegreffii* along its geographical range, including the Austral populations (South African coast, New Zealand sea waters, and the Mediterranean Sea) ($Fst = 0.025$ among the Boreal and Austral populations). In contrast, genetic variation obtained from π revealed 3× higher levels of variation in Austral populations relative to Mediterranean populations along with a higher number of haplotypes (Mattiucci and Nascetti, unpubl. obs.). The story was quite different in the more pristine Antarctic anisakid populations, where mean *He* levels at the same allozyme loci have remained invariant over a wide temporal scale, in *C. osculatum* D and *C. osculatum* E sampled in 1994 and again in 2012. Recently, it was noted that the reduction of *Contracaecum* in cod that was observed 20 yr ago because of a decrease in the host population in the Baltic Sea, has been reversed. Haarder et al. (2014) documented an increase in *Contracaecum osculatum* infections in Baltic cod (*Gadus morhua*) livers (1982–2012), but this was in association with a notable increase in the grey seal (*Halichoerus-grypus*) population.

As noted above, human activity has altered the population genetics of aquatic nematode parasites either by affecting the

parasites directly or by altering the diversity and population size of the hosts they infect. Continuing to assess the genetic diversity and abundance levels of anisakid nematodes in hosts from different geographical areas subject to dissimilar levels of habitat disturbance over temporal and spacial scales, is important for monitoring the effects of habitat disturbance on food web stability and the biodiversity and health of marine ecosystems at both the species and genus levels. Given that many of the anisakid nematodes are host specific, an ecosystem rich in anisakid parasites and their genetic diversity is likely to reflect a healthy ecosystem.

PROTOZOANS

Human impact on the structure of protistan parasite populations

Although the greatest impact in molecular epidemiology of parasites has occurred in the realm of diagnosis and differentiation among species and strains, notable progress has been achieved when these tools have been applied to questions of population diversity and the degree of uniformity among regional communities (Criscione et al., 2005, 2011; de Meeûs et al., 2007; Prugnolle and de Meeûs, 2008).

The most complete data for protozoan parasites are available on *Plasmodium falciparum*, the agent of severe malaria. *Plasmodium falciparum* occupies particular foci of transmission in certain tropical regions, which have connections to sub-Saharan localities. These areas harbor notably the greatest genetic diversity and are, therefore, considered the origins of this parasite (Rich and Ayala, 2000; Lum et al., 2004; Tanabe et al., 2010). Given this parasite's known antigenic diversity and its success in acquiring resistance to chemotherapies, it was long held as the embodiment of a genetically diverse biological species. In spite of such phenotypic plasticity, global samples of falciparum malaria were subsequently shown to harbor limited variability in synonymous sites of protein-coding genes (Rich et al., 1998) or in introns (Volkman et al., 2001). The absence of such "silent" variation indicated that these far-flung isolates shared very recent common ancestry. It further demonstrated that subsequent differentiation among regional populations was minimal, and restricted to sites undergoing exceptionally rapid differentiation, i.e., microsatellite repeats, or to sites experiencing strong selective pressure, i.e., drug resistance and immune evasion alleles (Rich and Ayala, 1998, 2000; Mita et al., 2009a, 2009b; Vinayak et al., 2010; Mita and Tanabe, 2012; Mallick et al., 2013; Pacheco et al., 2013). These findings illustrate the need for a proper context in interpreting patterns of genetic variability or, in this case, what seemed a notable lack of variability. Were the right types of genes being sampled? Could a global "brake" on the rate of mutation bias the expected level of variability downwards? Were inferences being skewed by poor sampling? Could the notable preponderance of A and T in the genome mask true rates of synonymous substitution?

Answering these questions required identifying useful population comparisons (Pacheco et al., 2013). Phylogenetic inferences as to the ultimate origins of *P. falciparum* required improved sampling. Where it was once believed that the sister species of this human parasite infected birds, it became clear that the closest relatives of falciparum malaria infected nonhuman primates (Ayala et al., 1999). Relying on a single representative of *Plasmodium reichenowi* as the sister species to *P. falciparum* once supported the notion that the ancestors of humans and the ancestors of chimpanzees had always harbored parasites of this type, resulting in discreet parasites specific to their hosts. This notion was overturned by more thorough sampling and phylogenetic analysis of the parasites of chimpanzees, which showed that the human parasites were more recently derived from a broad assemblage of malarial parasites still circulating among chimpanzees (Rich et al., 2009). These data proved that the uniformity of global populations of *P. falciparum* could not be ignored as simply a departure from theoretical expectations, or as an unavoidable outcome of some technical limitation, but rather contradicted empirical observations of closely related parasites in other hosts. That conclusion was underscored by subsequent sampling, which found parasites even more closely related to *P. falciparum* in gorillas (Liu et al., 2010). Genetic diversity was the rule in this newly discovered assemblage of primate parasites. Genetic uniformity, by any appropriate measure, was notably lacking in the particular parasite lineage that achieved success in human hosts (Rich and Ayala, 1998; Volkman et al., 2001). Since then, that particular parasite can now be found in certain localities where its human and anopheline hosts have gained footing, resulting in a parasite that is less regionally distinct than it otherwise would be, and lacking in diversity that would have accumulated in large and long-lived populations. Studies of the island biogeography of avian malaria have confirmed that such parasites do accumulate mutations at respectable rates (Fallon et al., 2003; Ricklefs and Outlaw, 2010; Bensch et al., 2013). The fact that falciparum malaria has not accumulated mutations over its relevant history ought not sustain doubts about its mutability; instead, the comparative results emphasize the brevity of that historical interval.

The global diversity of *Toxoplasma gondii* is still far from complete, owing to sampling that underrepresents much of Asia and Africa (Sibley et al., 2009; Su et al., 2012). Nonetheless, this parasite has been subjected to enough sampling to warrant preliminary conclusions concerning the human role in shaping that diversity (Sibley et al., 2009). This parasite is capable of infecting a broad array of intermediate hosts, perhaps all warm-blooded vertebrates (Dubey, 1994), with felids providing the sole venue for completing the life cycle. With such a vast array of potential hosts, and recognizing the experimentally validated capacity of parasites to generate genotypic diversity through crosses in cats, one might expect to observe an array of multilocus genotypes.

In recent years, hot spots of diversity have indeed been recognized (including portions of Amazonia, i.e., northern Brazil and French Guyana) (Demar et al., 2008; Dubey et al., 2008, 2010; Mercier et al., 2010). Indeed, the existence of additional genetic assemblages was instantiated by the recent finding of a new major genotype in North American wildlife hosts (Miller et al., 2008; Khan et al., 2011a). In spite of these exciting finds, it bears repeating that there is a lack of diversity present in the vast majority of isolates derived from human beings and from livestock. These generally partition into 1 of 3 major genotypes, which themselves may have derived from only 2 ancestral parents (Grigg et al., 2001; Grigg and Sundar, 2009). In port cities of South America, especially uniform isolates of *T. gondii* have been identified that are most closely related to those that predominate in Europe and North America (Lehmann et al., 2006); high-resolution genotyping has identified a marked contrast between

low-diversity isolates in the coastal agricultural fringe of French Guyana (Mercier et al., 2011) and the high diversity of isolates derived from the jungle interior. By certain markers, those on the coast resemble others isolated from throughout the Caribbean and beyond, whereas each isolate from the interior harbors uniquely distinguishing characteristics. The exceptional uniformity of 1 particular chromosome in otherwise genetically differentiated strains suggests that a selective sweep has further homogenized geographically disparate isolates (Khan et al., 2007, 2011b). As with falciparum malaria, the minimal genetic diversity in "cosmopolitan strains" of *T. gondii* appears more notable once it is contrasted with greater diversity in relevant comparison groups. The role of people in transporting cosmopolitan strains of *T. gondii* (in ourselves, in our domesticated livestock, in our synanthropic pest rodents, and especially in our domesticated cats) deserves far more scrutiny.

The more recent transformation of disparate landscapes by humans, particularly those in temperate climes conducive to certain forms of agriculture, in conjunction with earlier faunal expansion, has biologically linked regions today that had once been geographically separated for millions of years by the seams of Pangea and prior to the age of European exploration (Crosby, 2004; Diamond, 1997).

There exist additional indications that other livestock parasites, including protists, have enjoyed similar success by virtue of their association with us. Limited data, for example, suggest that *Sarcocystis cruzi*, a parasite cycling between cattle and dogs, is not differentiated among any region yet studied (Rosenthal et al., 2008a). We ought not be too hasty in drawing a conclusion for human intervention because the data are limited to only a few genes; moreover, we lack the sort of comparative data that validate greater regional distinctions among parasites that have shaped more stable populations, and that have not been intentionally or inadvertently moved during the course of (and as a result of) human history. The cases of falciparum malaria and the agent of human and veterinary toxoplasmosis underscore the need for such comparative data.

It may turn out that minimal distinction among geographically disparate populations may also characterize some parasites of wild hosts. A study of *Besnoitia besnoiti*, a parasite of caribou and reindeer, for instance, found genetic variation to be unaccountably lacking (Madubata et al., 2012). Much work remains to be done, therefore, in discerning our overall impact on the structure of protistan parasites (Rosenthal, 2009). However, the current literature married to complementary studies of the dissemination of weeds, viruses, plant pathogens and the entire often unintentional cornucopia of the Anthropocene (Steffen et al., 2011) suffices for a strong statement of the hypothesis: where we have trod, our parasites have followed, and within a time frame too shallow to have permitted establishment of regionally differentiated, endemic forms.

CONCLUSIONS

Herein, we have attempted to raise awareness regarding the global dissemination of parasites resulting from human activities, and to show that this has escalated demonstrably in the past 500 yr. We have noted that movement of parasites is linked to population growth, the advent of agricultural societies to address this growth, range expansion, and to key tipping points in human history. Outcomes of recent human activity on parasite populations can be seen in the translocation of drug-resistant phenotypes, changes in host range expansion and host switching, and the loss of biodiversity (both host and pathogen) and, therefore, refugia as influenced by global warming. Recent work by Dirzo et al. (2014) examined the cost to biodiversity imposed by the explosion of extinction events in the past 500 yr, wherein an estimated 11,000–58,000 species are lost annually and attributed substantially to human activity (Scheffers et al., 2012; Mora et al., 2013). Ironically, it was proposed (Seddon et al., 2014) that the global redistribution and reintroduction of animals should help remedy the loss of diversity and defaunation brought on by such extinction. However, introduction, establishment, and invasion of pathogens are most often associated with a breakdown in mechanisms that maintain ecological isolation. Thus, proposals for the indiscriminant movement of animals, i.e., potential parasite hosts, seem poorly conceived because this can serve to disseminate pathogens, expose naïve animals to pathogens, and provide a context for host switching and the emergence of disease (Hoberg, 2010; Brooks and Hoberg, 2013). The unintended consequences of conservation activities designed to maintain or regain the structure of ecosystems and equivalent faunal assemblages could be detrimental, and an example of the willful but negative impact that human forcing can affect the biosphere. In this arena, actions advocated as beneficial would be the antithesis to controlling the dispersal of pathogens and their concomitant diseases. Indeed, one can surmise that with the continuing human-imposed changes to ecosystems and our environment, the phrase exotic *parasite* may someday become archaic in many regions of the world.

Anthropogenic changes are supported in part by studies in pristine geographical localities unencumbered by human activities, i.e., Antarctica and high-latitude systems of the Arctic, wherein the population structure of parasites and their hosts have remained to a great extent well defined. As such, not only is population structure at local and global scales influenced through direct human intervention via translocation, but indirectly through unintentional, human-imposed changes to ecosystems that can selectively impact the longevity of parasites and their hosts.

Clearly, we have not addressed other matters to which the apparent lack of diversity among populations can be attributed, such as population density and size, mutation rates, and deeper historical processes of expansion and isolation. These are equally important in collating the information before us; nonetheless, human activities have played and continue to play a large role in the globalization of parasite populations.

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