Chapter 1
Diversity and History as Drivers of Helminth Systematics and Biology

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Abstract Over the years, we have come to recognize that evolution is a dynamic process and a fundamental organizing principle for exploring diversity and the biosphere. Basic knowledge of systematics and phylogenetics within an evolutionary context is essential for gaining a flexible understanding of contemporary parasite diversity and developmental pathways and how these are influenced by environmental perturbation and anthropogenic forcing. Further, an appreciation for historical processes as determinants of modern day geographic patterns and host associations is needed to explore the outcomes of environmental perturbation on parasite evolution. Collectively, these data lead to better predictive capacity for future changes in the distribution patterns and roles that parasites play in animal and human health. In this chapter we highlight how insights from the past and knowledge of current parasite assemblages expose the impacts that accelerated climate warming, habitat perturbation, erosion of biodiversity, and changes in host adaptation have had on the ebb and flow of zoonotic infectious diseases. We further look at how molecular and biochemical studies have advanced systematics, taxonomic stability, and diagnostic capability and are guiding future progress toward understanding parasites, parasitism, and their relationships to global public health.

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1.1 Introduction

Systematics is the foundation for biology. It provides a basic evolutionary map to discover, characterize, and interpret global diversity and our place in the biosphere. It also allows us to explore questions related to host associations, life history, genetics, and patterns of infection and disease, the cornerstones of epidemiology. Systematics reflects the intersection of phylogeny (evolutionary or genealogical relationships of organisms) and taxonomy (a standard nomenclature, the process of species delimitation, and the theory and practice of classification). Significantly, it brings history on the table and links evolution, ecology, and biogeography.

Many operational definitions or "species concepts" have arisen over time, and these concepts have become more convoluted as the number and types of characters and methodologies have increased, including the use of biochemical and genetic information. Scientists seeking to establish and validate helminth systematics are seemingly disadvantaged in that they lack fossil records to support present-day classifications. Instead, they must reconstruct evolutionary history that gave rise to assemblages of considerable diversity predicated on examining characters from extant organisms only. However, with concepts of phylogenies in hand, host and parasite associations can be explored over time and across a global arena that is under dynamic change. Episodic change or perturbation at all levels of history, linking evolutionary and ecological time, introduces uncertainty but also drives the overall structure of complex biological systems including those represented by hosts and parasites (Hoberg and Brooks 2013).

Heisenberg, a German theoretical physicist, conveyed pioneering insight on quantum mechanics, uncertainty and indeterminacy. In his 1927 paper on the Uncertainty Principle, he commented on the relationship between the position and the momentum of photons and the future behavior of an atomic particle. In his discussion he indicated that "...it is not the conclusion that is wrong (determining future behavior) but the premise (predictability)..." He determined that our observations have a direct effect on perceived behavior of quanta or, more generally, on outcomes. His discussion of observer effects on measuring and conveying scientific data is most applicable when trying to understand the concepts of classification, evolution, and the ever-changing role that the environment plays on diversification.

Many philosophies have been put forth on the natural order of things. Smart (1959) suggested that biology is a dynamic entity that neither creates nor refutes but is a manifestation or technological application of the laws of physics and chemistry:

> *...in the (physical type sciences) we are interested in laws, whereas in (the biological type sciences) we are interested in the natural history of structure...and in the explanation of why things with this natural history function as they do.*

Smart's premise was there could be no "laws of nature" that guide biological species because any biological laws like the laws of physics would by definition disallow deviation. Michael Ghiselin (1974) further suggested that biological species and monophyletic taxa are not nominal classes but actual individuals

where multiplicity is not required to define a class. Thus, it behooves us to think of and investigate evolution, speciation, and taxonomy as ongoing processes, producing a more fluid and mutable understanding of species in both space and time. Stable classifications require ample sampling, a valid comparative context, and inclusive consideration of what currently surrounds us, all of which are prone to human interpretation, frailty, and change, much as Heisenberg discovered in the movement of subatomic particles.

A wealth of reviews, chapters, and articles has been written on the taxonomy and systematics of helminths. Inasmuch as specific topics and detailed presentations of the biology of each parasite group constitute other portions of this book, we offer a look at helminth phylogeny from a different perspective. We endeavor to examine why "history matters." A deeper understanding of the historical arena on global to landscape scales contributes to our knowledge of complex host–parasite assemblages. Geographic patterns, host associations, and historical determinants (abiotic and biotic) are foundations for examining the outcomes of perturbation and allow us to predict and anticipate future changes in the distribution of parasites through niche modeling (Peterson 2011) and, by extension, their potential impact on human and animal health (Hoberg and Brooks 2013; Brooks and Hoberg 2013). We highlight how past and current evidence provides a window to explore a future of dynamic change caused by accelerated climate warming, habitat perturbation, erosion of biodiversity, the dissemination of invasive species, changes in host adaptation, and the emergence of zoonotic infectious diseases. Highlighted are recent advancements in molecular identification and population genetics to underscore the value of well-engineered population research to advancing sound taxonomy. Finally, we consider how studies on genomics and phylogenomics have begun to better inform us on the broader "tree of life." In so doing, we hope to help advance and guide future progress in understanding parasitology and its relationship to global public health.

1.2 Complexities Surrounding Helminth Systematics

Helminths that typically utilize humans either as primary or intermediate hosts are represented by roundworms (phylum Nematoda), flukes (Digenea), and tapeworms (Eucestoda), the latter two belonging to the phylum Platyhelminthes. There are no members of the phylum Acanthocephala that commonly parasitize humans. Body form and symmetry among the primary helminths vary widely, although each major phylum is characterized by a general plan and structure. The nematodes are dioecious (either male or female). Those which infect people commonly include gastrointestinal parasites such as hookworms and ascarids (geo-helminths) and lymphatic parasites such as those that cause onchocerciasis and filariasis. All nematodes possess cylindrical bodies, a fluid-filled pseudocoelom, and a complete tubular digestive system in all stages of development. The body is relatively impervious to the external environment because of an outer cuticle that is

synthesized at the end of each larval stage and just prior to molting. In contrast, the Platyhelminthes or flatworms have a soft, solid-tissue body circumscribed by a plasma membrane or tegument. Unlike other bilaterians, the flatworms have neither a coelom nor a complete digestive tract. Specialized organs for circulatory or respiratory systems are to some extent reduced. In the absence of circulatory and respiratory systems, oxygen and other nutrients must diffuse across a permeable tegument. All Platyhelminthes are hermaphroditic except for blood flukes (schistosomes), which are dioecious. In their adult, sexually mature stage, all helminths are considered to be macroparasites and relatively large (>1 mm long), though some adult tapeworms can be measured in meters rather than millimeters. Although there are numerous biological and developmental characters that link these groups, faunal and morphological diversity abounds.

Revealing the complex tapestry of human helminths and infection relies on clear definitions of faunal diversity, species, and populations. Diversity, encompassing spatial, ecological, and genealogical aspects, can be considered in hierarchical patterns relative to scale. It extends from regional faunas to species, cryptic diversity (e.g., cryptic morphospecies), and populations (Hoberg 1997; Pérez-Ponce de Léon and Nadler 2010). As a gateway to fine-scale relationships, variation in local haplotype diversity is ephemeral and serves as an indicator for landscape epidemiology (analyses of ecosystems) and regional processes. It is the foundation for understanding patterns of emergence (Thompson 2005). Landscape evaluations are essential for understanding basic determinants for occurrence, emergence, and disease. The distribution of disease is often heterogeneous, local, and circumscribed within a more extensive spatial range for a parasite or host–parasite assemblage (Audy 1958; Hoberg 2010). Thus, it becomes important to use molecular phylogenetic and phylogeographic methods to understand the genetic variation within populations, genetic differentiation between populations, and the extent of gene flow among populations (Avise 2000; Criscione et al. 2005; Huyse et al. 2005; Nieberding et al. 2008).

These relationships for spatial and temporal scale highlight the importance of phylogeny and hierarchical order in framing hypotheses and constraining explanations for species diversity, faunal structure, and history. In recent years, we have seen a transformation in how we view the nature of species and a shift from typological and authoritative approaches that characterized much of the twentieth century (Brooks and McLennan 2002) to those that involve hypothesis testing. Modern-day hypotheses emerged from an evolutionary species concept (historical and phylogenetic definitions of species) followed by secondary evaluation relying on aspects of biogeography, ecology, and reproductive isolation (biological species concept) (see Brooks and McLennan 2002; Wiley and Lieberman 2011). Thus, species delineation and the process of speciation (the mechanisms involved in the origins of species) are linked, where history (phylogeny) allows the recognition of species followed by testable hypotheses based upon the biological species concept (Brooks and McLennan 2002; Nadler 2002). Recent examples are analyses exploring diversity among species of *Taenia* and *Echinococcus* (Hoberg 2006; Nakao

et al. 2007, 2009, 2013a, b; Lavikainen et al. 2008), and studies of species richness in *Trichinella* (Zarlenga et al. 2006; Pozio et al. 2009).

1.2.1 Helminth Parasites and the World Stadium

The impact of parasites occurs at the junction of human populations, ecosystem structure, and globalization in a matrix increasingly determined by climatological forces of anthropogenic origin and environmental perturbation (Patz et al. 2000, 2007, 2008; Brooks and Hoberg 2007; Weaver et al. 2010; Brooks and Hoberg 2013). Despite thousands of years of medical and veterinary intervention, helminth parasites remain a considerable regional concern for people, their domestic food animals, and free-ranging vertebrate species. Over the past 10,000–15,000 years, the evolution of agriculture, animal domestication, urbanization, and transformation of natural habitats have all been driving forces for the emergence of helminth and other diseases (Daszak et al. 2000; Patz et al. 2008; Rosenthal 2008; Hoberg 2010; Kuris 2012). These historical processes are equivalent to those in a present-day regime of accelerating environmental change (Brooks and Ferrao 2005; Hoberg and Brooks 2008, 2013). Although the tipping points represented by a burgeoning human population and the development of agriculture and animal domestication have had a direct influence on the occurrence of parasites in humans, many host–parasite associations for extant parasites have considerably deeper origins extending into the Pliocene and Pleistocene (Hoberg and Brooks 2013).

Although parasites are often obscure, they represent in excess of 40–50 % of the organisms on Earth. They are integral components of all ecosystems and have considerable involvement in at least 75 % of trophic links within food webs (Dobson et al. 2008; Lafferty et al. 2008; Kuris et al. 2008). Significantly, 61 % of all pathogens are zoonotic, derived primarily through interactions with free-ranging vertebrate species (Daszak et al. 2000). Human pathogens (primarily viruses and bacteria) are often associated with wildlife (Taylor et al. 2001; Cleaveland et al. 2001; Wolfe et al. 2007). This intricate web of interactions establishes the significance of human parasites as mediators of health and well-being, food sustainability, food security and safety, socioeconomic development, and, more broadly, ecological structure and services that contribute to continuity and connectivity in the biosphere (Patz et al. 2007, 2008; Polley 2005; Weaver et al. 2010).

Based on global estimates, between 75,000 and 300,000 species of helminths infect terrestrial and aquatic vertebrates (Dobson et al. 2008). Among these, 287 are known to occur in humans, 95 % of which are zoonotic (Cleaveland et al. 2001; Taylor et al. 2001). An alternative estimate places this number at 305 helminth species in humans, with 83 identified as prevalent, and 39 able to cause substantial morbidity or mortality (Ashford and Crewe 2003; Kuris 2012) (Table 1.1). Among this larger assemblage, 39 species have patterns of circulation and transmission that are solely dependent on human hosts. Overall, only 44 % of the most prevalent

Table 1.1 Helminth species characteristic of people across the world including those dependent on humans for transmission and some prominent zoonotic parasites [Based on Ashford and Crewe (2003) with modifications from Jenkins et al. (2013) and Nakao et al. (2013b)]

Platyhelminthes-
Digenea (11 human-dependent species)
Schistosomatidae-
Schistosoma haematobium[a]
Schistosoma intercalatum[a]
Schistosoma japonicum[b]
Schistosoma mansoni[a]?
[+ species of *Schistosoma* (8), *Gigantobilharzia* (2), *Trichobilharzia* (4)][c]
Echinostomatidae-
Echinostoma echinatum[b]
[+ species of *Acanthoparyphium* (2), *Artyfechinostoma* (2), *Echinocasmus* (5), *Echinostoma* (11), *Hypoderaeum* (1)][c]
Gymnophallidae-
[*Gymnophalloides seoi*][c]
Fasciolidae-
Fasciolopsis buski[b]
[+ species of *Fasciola* (2)][c]
Gastrodiscidae-
Gastrodiscus hominis[b]
Heterophyidae-
Heterophyes heterophyes[b]?
[+ species of *Apophallus* (1), *Centrocestus* (5), *Cryptocotyle* (1), *Haplorchis* (5), *Heterophyes* (5), *Metagonimus* (4), *Stictodora* (3)][c]
Opisthorchidae-
Clonorchis sinensis[a]?
Opisthorchis fellineus[b]?
[+ species of *Metorchis* (2)][c]
Paragonimidae-
Paragonimus westermanii[b]
[+ species of *Paragonimus* (8)][c]
Troglotrematidae-
[*Nanophyetus salmincola*][c]
Eucestoda (6 human-dependent species)
Diphyllobothriidae-
Diphyllobothrium latum[b]
[+ species of *Diphyllobothrium* (15), *Diplogonoporus* (3), *Pyramicocephalus* (1), *Schistocephalus* (1), *Spirometra* (4)][c]
Anoplocephalidae-
Inermicapsifer cubensis[b]
[+ species of *Bertiella* (2), *Raillietina* (2)][c]
Dilepididae-
[*Dipyllidium caninum*][c]
Hymenolepididae-
Rodentolepis nana[a]
[+ *Hymenolepis diminuta*][c]

(continued)

Table 1.1 (continued)

Taeniidae-
Taenia asiatica[a]
Taenia saginata[a]
Taenia solium[a]
[+ species of *Echinococcus* (6), *Taenia* (7)][c]
Mesocestoididae-
[species of *Mesocestoides* (2)][c]
Nematoda (22 human-dependent species)
Strongyloididae-
Strongyloides fuelleborni fuelleborni[b]
Strongyloides fuelleborni kellyi[a]
Strongyloides stercoralis[a]
Ancylostomatidae-
Ancylostoma duodenale[a]
[+ species of *Ancylostoma* (4)][c]
Necator americanus[a]
Chabertiidae-
Oesophagostomum bifurcum[b]
Ternidens deminutus[b]
Trichostrongylidae-
Trichostrongylus colubriformis[b]
Trichostrongylus orientalis[b]
Angiostrongylidae
[species of *Parastrongylus* (2)][c]
Oxyuridae-
Enterobius gregorii[a]
Enterobius vermicularis[a]
Ascaridae-
Ascaris lumbricoides[a]
[+ species of *Baylisascaris* (1), *Toxocara* (2), *Toxascaris* (1)][c]
Anisakidae-
[species of *Anisakis* (2), *Pseudoterranova* (1)][c]
Dracunculidae-
Dracunculus medinensis[a]
Gnathostomatidae-
[species of *Gnathostoma* (6)][c]
Gongylonematidae-
[*Gongylonema pulchrum*][c]
Onchocercidae-
Brugia malayi[b]
Brugia timori[a]
Loa loa[a]
Mansonella ozzardi[a]
Mansonella perstans[a]
Mansonella streptocerca[a]
Onchocerca volvulus[a]
Wuchereria bancrofti[a]

(continued)

Table 1.1 (continued)

[+ species of *Dirofilaria* (5)][c]
Trichuridae-
Trichuris trichiura[b]
[+ *Calodium hepaticum*, *Eucoleus aerophilus*, *Paracapillaria philippinensis*][c]
Dioctophymidae-
[*Dioctophyme renale*][c]
Trichinellidae-
[*Trichinella spiralis*, *T. britovi*, *T. murrelli*, *T. nativa*, *T. nelsoni*, *T. pseudospiralis*][c]
Acanthocephala (Ø human-dependent species)
Macracanthorhynchus hirudinaceus[c]
Macracanthrohynchus ingens[c]
Moniliformis moniliformis[c]

[a]Parasites completely dependent on human transmission
[b]Parasites that occur among humans and other definitive hosts, and for which people are not required for transmission, but may be involved in circulation
[c]Parasites that represent prominent regional to local zoonoses, and in which humans are not involved in transmission or circulation
? = exact relationship as obligate human parasite requires elucidation
Ø = denotes "none"

micro- and macroparasites are considered zoonotic. This more conservative estimate denotes parasites as zoonotic because they cannot be sustained in humans as definitive hosts (consistent with $R_0 < 1$) and includes helminths for which humans may be infected by larval stages such as the metacestodes of certain taeniid tapeworms (species of *Taenia* and *Echinococcus*) or larvae of nematodes such as *Baylisascaris*, *Anisakis* and *Pseudoterranova*, and *Toxascaris* and *Toxocara* (Polley 2005; Kuris 2012). Consequently, species of *Taenia* utilizing people as definitive hosts (*T. saginata*, *T. solium*, and *T. asiatica*), but requiring domestic ungulates for transmission, are not regarded as zoonotic. Among these, only *T. solium* is considered highly pathogenic as the causative agent of human neurocysticercosis.

Approximately 25 % of the world's population is infected with helminth parasites. Among these, there are 100–150 million suffering substantial morbidity. Not all parasites exact equivalent costs in human health as they vary in virulence, prevalence, abundance, and pathogenicity (Kuris 2012). For example, the soil-transmitted *Ascaris lumbricoides*, *Trichuris trichiura*, *Necator americanus*, and *Ancylostoma duodenale* are cosmopolitan and cause greater morbidity in humans than any other parasitic disease except malaria (Murray and Lopez 1996; Weaver et al. 2010). Further, the distribution of diseases and the impact of parasitic helminths are often heterogeneous. Local factors related to history, climate, land use, food habits, demographics, human behavior, and sanitation play prominent roles as determinants of human infections (Patz et al. 2007; Kuris 2012; Brooks and Hoberg 2013; Hoberg and Brooks 2013). An emerging challenge is seen in the disruption of socioeconomic controls on the occurrence and impact of infection. Warfare, changing climate as it affects food distribution and water resources, movement of refugees, and a breakdown in medical infrastructure all facilitate

new patterns of infection and disease (Patz et al. 2007, 2008; Weaver et al. 2010; Brooks and Hoberg 2013).

1.2.2 Host-Switching Drives Helminth Evolution

History is a defining factor in exploring and understanding contemporary distributions and disease risks posed by helminth parasites in human populations. Traditionally, explanations for host occurrence, biogeography, and diversity have been linked to coevolutionary histories (cospeciation/association by common descent of host and parasite lineages) (Brooks and McLennan 1993, 2002; Brooks and Hoberg 2013) wherein parasite faunas of humans and other vertebrates are largely derived from historical ancestor–descendant relationships with other primates (Kuris 2012). This coevolutionary/cospeciation perspective extends to present-day ideas with regard to the difficulty for parasites to undergo host-switching with unrelated vertebrate lineages (Brooks and Ferrao 2005). It behooves us to explore this apparent paradox for cospeciation, host specificity, and colonization in the arena of pathogenic human parasites and emerging infectious diseases (Agosta et al. 2010; Brooks and Hoberg 2013).

A prevailing assumption describing complex host–parasite assemblages is that parasites coevolve with their hosts (Brooks and Ferrao 2005 and earlier papers cited therein). The interdependence of these phenomena discounts host-switching by otherwise narrowly distributed helminths. A challenge to this orthodoxy is that host-switching is common, has directly influenced parasite faunal structure for humans, and is the basis for what are recognized as emerging infectious diseases (Cleaveland et al. 2001; Wolfe et al. 2007; Brooks and Hoberg 2013). Cospeciation as the driving force behind complex host–parasite associations and faunas has had limited explanatory power. It has also hindered studies on geographic expansion, ecological perturbation, and host colonization as prominent processes in faunal assembly and diversification. Invasion is pervasive; episodes leading to the breakdown of ecological isolation and barriers to host colonization have important implications for the distribution and evolution of helminth faunas and emerging infectious diseases (Wolfe et al 2007; Hoberg 2010; Brooks and Hoberg 2013; Hoberg and Brooks 2013).

Whereas coevolutionary history can explain some helminth faunas in great apes and humans (e.g., pinworms, species of *Enterobius*, and hookworms, species of *Oesophagostomum*) (Brooks and Ferrao 2005), the reality is considerably more complex and fascinating. A contemporary helminth fauna in humans has been cumulative, serving to indicate the rich temporal, spatial, and ecological connectivity that *Homo sapiens* have had across the biosphere in space and time (Hoberg et al. 2001; Hoberg 2006). The diverse helminth fauna among humans denotes dynamic and episodic shifts in climate, habitat, and ecological structure during the late Pliocene and Quaternary (Hoberg et al. 2012). These changes occurred in migratory/dispersal capacity and in foraging behavior among our initial hominoid

(Brooks and Ferrao 2005; Folinsbee and Brooks 2007) and immediate human ancestors (Hawdon and Johnston 1996; Jenkins et al. 2013), and among our contemporary worldwide population. Emphasized is the importance of history and scale, and the connectivity of processes for geographic and host colonization in evolutionary and ecological time. Many human parasites have origins linked more to shared trophic relationships and host-switching among carnivorans than to associations with other mammals and birds that are either carnivores or piscivores (Hoberg et al. 2001; Ashford and Crewe 2003; Kuris 2012). As such, geographic proximity and ecological structure and continuity among foraging guilds are key drivers of parasite acquisition and diversification. Events such as these account for numerous host-specific parasites in humans such as species of *Taenia*.

Shared trophic resources are also the basis for many contemporary zoonotic infections, and less involved in the process of parasite speciation (Kuris 2012). For example, species of *Diphyllobothrium* and diphyllobothriid tapeworms known to parasitize marine mammals at high latitudes of the Nearctic also parasitize humans (Jenkins et al. 2013). Also, the considerable diversity of heterophyid, echinostomatid, and other trematodes transmitted through freshwater and marine fishes and crustaceans promotes their circulation among assemblages of vertebrates, including humans, throughout the world (Marty and Andersen 2000).

1.2.3 Anthropogenic Translocation of Parasitic Helminths

Sorting out which parasites are our coevolutionary legacies (distributed out of Africa or other regions with hominid expansion), and which were acquired through ecological dynamics, provides a nuanced understanding of the mechanisms involved in faunal assembly. Contemporary global expansion (from Africa and Eurasia into North America) has led to a breakdown of geographic and ecological isolation and an increasingly broad exposure of humans to "exotic" helminths and other parasites (Daszak et al. 2000; Harcourt 2012; Jenkins et al. 2013). Global invasion and secondary distribution of parasites (anthropogenic translocation) coincided with early Eurasian trade routes, European expansion, colonial occupations, and the slave trade. As a result, a rich temporal (chronological) and spatial (geographic from landscape to regions) mosaic for acquisition, introduction, and establishment of helminth assemblages has emerged (Hoberg 2010; Hoberg et al. 2012). In a contemporary setting, anthropogenic drivers increasingly influence invasion and the distribution of parasites and pathogens with attendant threats across a matrix linking environments, economies, and societies (Pimentel et al. 2005). The character and evolution of geographic expansion for both free-living and parasitic species have also been influenced by a series of thresholds and tipping points in human history beginning with our expansion out of Africa nearly 40–60 Kya. Further, the advent of agriculture and animal husbandry 10–11 Kya, the age of European exploration ensuing around the year 1500, and the industrial revolution have all represented irreversible points of change for people and our

interface with the environment (Riccardi 2007; Hoberg 2010; Hoberg and Brooks 2013). Today, human influence is a pervasive force in evolution as seen in natural systems and in the diverse assemblages of pathogens in both free-ranging and domesticated hosts (Palumbi 2001). These emerged from a burgeoning population and a transition from a slow and large world dominated by isolation and local effects to a rapid and small world resulting from globalization, homogenization, and integration of fragmented environmental networks (Hoberg 2010; Hoberg and Brooks 2013).

1.3 Defining Diversity

Accurate definitions of diversity are vital to understanding the role of parasites in human and animal diseases. In addition, defining diversity is critical to studying epidemiology, developing management practices to limit transmission, and designing treatment regimes to reduce, mitigate, or eliminate infections. Over the past 200 years, species-level identification of specimens has relied on comparative morphology and is often dependent on examining fully developed adult worms. This is best exemplified by the challenges in diagnosing zoonotic helminths in human infections (Jenkins et al. 2013). In the absence of mature or gravid specimens, authoritative morphological identification has often not been possible due to the absence of reliable structural attributes in other parasitic stages. It was not until the advent and application of reliable and rapid molecular-based diagnostic methodologies (Polley and Thompson 2009; Jenkins et al. 2013) that these problems have begun to resolve themselves. Although molecular-based diagnostics can now supplant preparation and microscopic examination of whole specimens, such approaches remain directly tied to definitive identification of adult parasites through linkage to a morphospecies name and concept. Validation of molecular data from multiple authoritatively identified adults, held as archival vouchers in museum collections, is the gateway for applying sequences and appropriate molecular markers to diagnosing life history stages including eggs and larvae.

Continued reliance on archival museum collections as resources for biodiversity, informatics and our study of the biosphere, including history and structure, is apparent (Cook et al. 2013). Museum collections and specimens are the self-correcting records for biodiversity that document the geographic occurrence and host associations for parasites. As such, they remain highly relevant to understanding diversity and the changing patterns of distribution over time. Deposition and full documentation of specimens and their environmental niche in appropriate archives should be the expectation from ongoing programs for host–parasite surveys and strategic monitoring for particular spectrums of pathogens (Hoberg 2010; Cook et al. 2013). In this manner the influence of accelerated climate change, ecological perturbation, human activities and invasion, and other factors that determine the distribution of pathogens and disease may be tracked in space and time through the application of comparative baselines. Specimens combined with

molecular protocols as described below have become the foundations for exploring patterns of cryptic diversity (Pérez-Ponce de Léon and Nadler 2010) and for understanding the nature and structure of emergent infectious diseases (Thompson 2005; Hoberg et al. 2012).

1.3.1 Molecular Epidemiology, Diversity, and Helminth Systematics

The application of molecular taxonomy, phylogeny, and population genetics to epidemiological problems has become known as molecular epidemiology (Foxman and Riley 2001). For human helminths, recognizing genetically based variation has helped identify species or populations of epidemiological concern, recognize factors that promote transmission to human hosts, and trace the evolution and spread of physiological characters such as drug resistance (Steinauer 2009; Norton et al. 2010; Blanton et al. 2011). Unique DNA sequences or molecular markers are identified using state-of-the-art methodologies and then used to characterize neutral genetic variation. These markers can be employed to study population-based demographic parameters and processes such as dispersal, mating systems and effective population size. In addition, markers can be developed for regions of the genome that respond to selective forces stemming from interactions with the environment, hosts, or other parasites. Both sets of markers have been used to study the relationship between mass drug administration programs and the evolution of drug resistance (Lustigman et al. 2012).

The molecular epidemiology of human helminths has been strongly influenced by advances in biotechnology, especially DNA sequencing technologies. DNA sequencing platforms are continuously being developed to produce higher quantities of data and with better quality that ultimately improve our ability to accurately and precisely measure genetic variation (Pareek et al. 2011). In human helminths, early work employed a few isoenzyme markers to detect whether genetic variation existed among geographic isolates of single species or between species (e.g., Coles (1970) with *Schistosoma mansoni*, Flockhart et al. (1982) with *Trichinella* spp.). Recently, more informative DNA approaches (gene sequences, single nucleotide polymorphisms (SNP), and microsatellites) have become widely used to infer how different aspects of parasite biology influence the population genetics of human helminths. In human *Ascaris* (Peng and Criscione 2012), *S. mansoni*, (Steinauer et al. 2010), and *Trichinella* (Rosenthal 2008; Rosenthal et al. 2008), population genetic approaches using DNA-based genetic variation have elucidated transmission cycles and the role of hosts and geography in structuring populations. New sequencing technologies have and will continue to facilitate marker discovery at the genomic scale, wherein the cost and time associated with developing and using markers will continue to decline. For example, 61,547 microsatellite loci were found in the *Brugia malayi* genome using modern techniques (Castagnone-Sereno

et al. 2010), whereas only two microsatellite loci were identified using older sequencing approaches (Underwood et al. 2000). Such a large number of loci distributed across the genome can be used for a variety of population genetic applications including linkage mapping, which can identify genes associated with phenotypic traits such as virulence, drug resistance, or host specificity. Despite the utility and epidemiological significance of these applications, to date the only human helminth with a linkage map is *S. mansoni* (Criscione et al. 2009).

In concert with sequencing technologies, advances in molecular biological methodologies such as whole genome amplification, in particular, multiple displacement amplification (MDA), have allowed us to generate microgram quantities of DNA from small amounts of tissue (Dean et al. 2002). MDA has been validated as providing unbiased whole genome amplification in single *B. malayi* microfilaria (McNulty et al. 2008) and in single *S. mansoni* miracidia (Valentim et al. 2009). This advancement has enabled hundreds of microsatellites or SNPs to be genotyped from single parasites, which is especially relevant when only helminth larval stages can be sampled for molecular epidemiological studies. For instance, only the zoophilic strain of *B. malayi* can be maintained in the laboratory; thus, to understand the population genetics of the anthropophillic strains, larval parasites (e.g., microfilariae 200–275 μm in length) must be sampled directly from human blood, tissues, or insect vectors with the luxury of culturing (McNulty et al. 2008). Prior to MDA, sufficient amounts of DNA could not be obtained from a single individual for multilocus genotyping, and therefore several thousand microfilariae had to be pooled into a single extraction in order to amplify just two microsatellite loci (Underwood et al. 2000). Using aggregates of individuals in population genetic analyses has several drawbacks, in particular, the inability to characterize the tremendous genetic variation that can and does exist between individual organisms even within a single population. Perhaps most significantly for taxonomy, pooling precludes several analyses which help estimate the genetic differentiation between populations such as linkage disequilibrium and Hardy-Weinberg-based *F* statistics (Silva et al. 2006; Steinauer et al. 2010). Other drawbacks have been described in more detail by Steinauer et al. (2010).

As molecular biology and technology have advanced, they changed our ability to assess the genetic variation of helminths relating not only to taxonomy and phylogeny but also to individual populations at ever increasing genetic scales (i.e., from enzymes to whole genomes). Despite these advances, many molecular studies of human helminths are often phylogeographic in nature. Among the 39 human helminths recognized by Ashford and Crewe (2003), there is a clear predominance of studies that utilize only a few genes to assess genetic variation across a large geographic scale (e.g., see below under Sect. 1.4). This is likely driven in part because of the difficulties associated with recognizing parasite species. Parasites are small and live in or on hosts making aspects of their biology not directly observable. In addition, there is currently no consensus as to what constitutes appropriate discovery methods and analytical approaches for defining species, particularly in the context of cryptic diversity (Pérez-Ponce de Léon and Nadler 2010). Regardless of the interpretation, phylogeographic studies provide a first

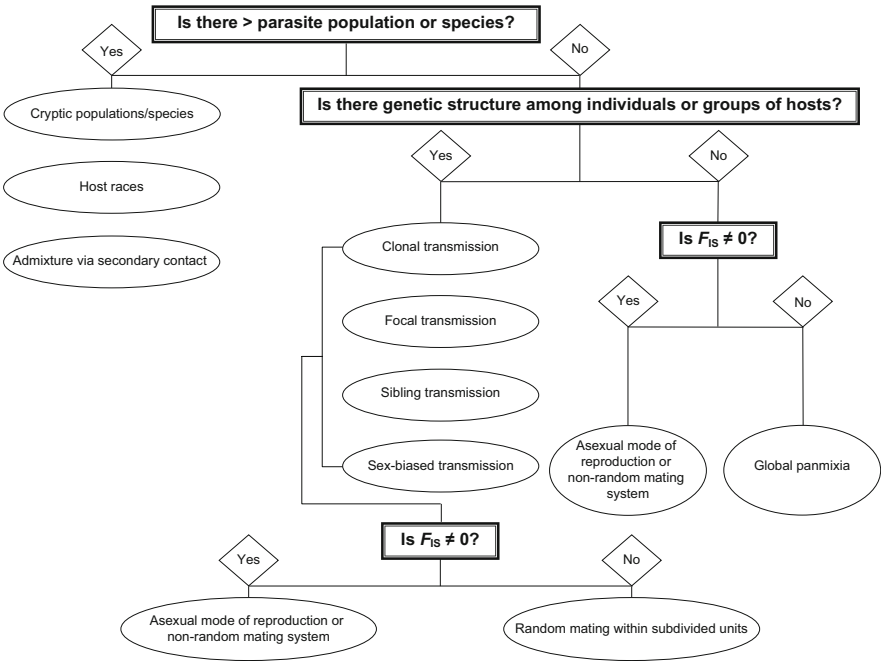

Fig. 1.1 Categorizing genetic variation among helminth parasites (From Gorton et al. 2012)

glimpse into the extent of genetic variation across broad geographic scales. In a recent review, Gorton et al. (2012) provided a flow diagram that describes the practical process of categorizing inter- and intraspecific variation for helminth parasites (Fig. 1.1).

For human helminths, the answer to the first question in Fig. 1.1, "Is there >1 parasite population or species?" has often been "yes" or "likely yes, but more investigation is needed." Molecular phylogeny or phylogeographic studies using genetic distance data or reciprocal monophyly often reveal that organisms previously presumed to be one species is likely comprised of two or more, though usually not without some controversy. For example, discussions continue as to whether the cestode *T. asiatica* is a different species from *T. saginata* (Hoberg 2006; McManus 2006). As Yamane et al. (2012) summarized, all researchers have the same morphological and genetic data, but the taxonomic interpretations vary. Other species have been referred to as "species complexes" when a presumed single species is revealed to consist of multiple, closely related but genetically distinct organisms. Species complexes have been recognized among many of the 39 human helminths, including species of *Paragonimus*, *Schistosoma*, *Opisthorchis*, *Echinostoma*, *Fasciola*, and *Taenia*. As studies of the *P. westermani* complex show, members of parasite species complexes are often not formally described as species. For instance, geographic isolates of *P. westermani* from China and India exhibit nearly the same genetic distance (5.1 % derived from partial cytochrome oxidase 1 [cox1],

the nuclear ribosomal second internal transcribed spacer [ITS2], and partial 28S gene sequences) as observed between the sister species *P. harinasutai* and *P. ohirai* (5.2 %). As such, isolates are currently referred to as genotypes or types 1–3 (Devi et al. 2013). It is not overly surprising that new genetic variants are initially described as strains, genotypes, lineages, or forms because the species concept has become more clouded in recent years with the use of molecular, immunological, and biological characters (Edwards 2009; Pérez-Ponce de Léon and Nadler 2010; Nadler and Pérez-Ponce de León 2011). Further, since these variants are new to science, there is typically incomplete information regarding morphology, host use, life cycle, and distribution which could help address proper classification. Despite these difficulties, discovering and characterizing biodiversity is of high epidemiological importance. Ultimately, the relevant question for human helminths is: Are we engaged in a campaign to eliminate one species/population or a complex of many species/populations? (McNulty et al. 2013).

1.3.2 Populations, Natural Hybrids, and Adequate Sampling

The presence of one or several populations can be detected using population genetics analyses. The same approach can be extended to address speciation. Many computer programs for population genetic analyses have been developed to estimate parameters that help infer genetically based differences between or within populations (Excoffier and Heckel 2006). For example, programs like FSTAT and GENEPOP estimate linkage disequilibrium (nonrandom association of alleles among loci), which when present may indicate cryptic species or distinct populations (Gorton et al. 2012). This and other population genetic parameters have revealed complex microevolutionary patterns that can help illuminate the reasons for taxonomic controversy. For example, questions regarding the species status of human (sensu stricto *A. lumbricoides*) and pig (sensu stricto *A. suum*) associated *Ascaris* have persisted in the literature and have prompted calls for population-level sampling (Nadler and Hudspeth 2000). Sequence and microsatellite-based analyses suggest that both geography and multiple host colonization events have influenced the evolutionary histories of human and pig *Ascaris* (Peng and Criscione 2012). Thus, Peng and Criscione (2012) reasoned that in addition to global population-level sampling, more genetic loci should be incorporated because both historical and contemporary dynamics need to be understood to resolve the taxonomy. For instance, mitochondrial DNA haplotypes associated with *Ascaris* from pigs in China (Peng et al. 2005) were found in human *Ascaris* from Zanzibar (Betson et al. 2011). This geographically shared haplotype could be the result of two historical scenarios, either multiple host colonization or a historical introgression event. As such, it certainly does not confirm contemporary cross-transmission. To test for recent cross-transmission (from pig to human or vice versa), samples from sympatric human and pig-associated *Ascaris* should be

sequenced or genotyped with several fast-evolving genetic loci such as microsatellites.

Cross-transmission of parasites between humans and other animals is important to detect because it can promote hybridization between helminth species. Hybridization has important consequences for taxonomy as it can generate intermediate phenotypes, which have historically fueled taxonomic uncertainty regarding the status of particular species (e.g., *Fasciola* spp., Nguyen et al. 2009; and *T. asiatica*/*T. saginata*). Molecular genetic analyses have suggested historical and contemporary hybridization between species of *Paragonimus*, *Schistosoma*, *Echinococcus*, and *Taenia* species (see Table 1 in Detwiler and Criscione 2010). For example, historical introgression between the ruminant and human infecting *Fasciola hepatica* and *F. gigantica* has been inferred with parental taxa-specific markers and nuclear-mitochondrial discordance (see Table 1 in Detwiler and Criscione 2010). Contemporary hybridization was detected between human- and pig-associated *Ascaris*, and between human *S. mansoni* and rodent *S. rodhaini* using microsatellites and Bayesian clustering (Criscione et al. 2007; Steinauer et al. 2008), and between sympatric species and genotypes of *Trichinella* that are freeze resistant (Dunams-Morel et al. 2012; La Rosa et al 2003). Beyond affecting the morphology, hybridization may also impact infectivity, virulence, transmission, host specificity, and drug resistance in natural populations of human helminths. Few studies have investigated the epidemiological importance of hybrids, and much work remains to even understand the frequency of hybridization in natural populations of human helminths. Studies are also lacking on environmental and or host factors that select for fit hybrids. However, the work that has been done suggests that hybridization could be an important factor that influences our interpretations of the systematics and biology of helminths.

1.4 Genomics, Systematics, and Parasitic Worms

Evolution is a branching process resulting from the diverging of populations over time. This process can be visualized in the construction of phylogenetic trees based upon the order in which these evolutionary events transpired. This in turn generates a historical pattern of species diversification from common ancestry. Inclusion of genomic and molecular data in assessments of relationships within and among parasitic groups has dramatically expanded and has led to new insights across all helminth taxa. A molecular-based phylogenetic revision of the phylum Nematoda began in earnest back in 1998 when Blaxter et al. (1998) used a single gene (nuclear small subunit ribosomal RNA) to construct a tree that was conceptually partitioned into 5 major clades predicated upon data from 53 species. Since that time, the tree has been refined with the addition of key ancestral taxa including nematodes from marine animals (Holterman et al. 2006; Meldal et al. 2007; van Megen et al. 2009). Further refinements to the phylogenetic tree incorporated the major clades originally defined by Blaxter et al. (1998), the minor clades that followed in 2006–2009

(Holterman et al. 2006; Van Mengen et al. 2009), as well as the inclusion of morphological data (De Ley and Blaxter 2002, 2004). Similar comprehensive studies have been performed on the flat worms and cestodes to estimate the phylogeny of the Digenea (Olson et al. 2003) using the complete ssrDNA and partial data from the lsrDNA focusing on expansion segments D1–D3. The analysis included 163 digenean taxa. Extensive analyses using both maximum parsimony and Bayesian inference resulted in demonstrable changes in the membership of higher taxa and thus the construction of new revisions to previously accepted classifications.

Phylogenetics utilizes either biological, morphological, or developmental character states, single genes/protein sequences, or a small number of genes/protein sequences in revealing relationships among organisms. Phylogenetic applications allow development of hypotheses for relationships of lineages, species, and higher taxa and are thus the foundation for exploring complex questions about the history of the biosphere. Single-gene or multigene studies have been utilized extensively to develop phylogenetic inference among members of *Trichinella* (Zarlenga et al. 2006), *Schistosoma* (Attwood et al. 2007), *Taenia* (Nakao et al. 2013a, b), and *Anisakis* (Mattiucci and Nascetti 2008); however, new approaches are being developed to increase the footprint of genes used to explore distantly related organisms. To date, this has been a bit more problematic given the varying rates of evolution. Phylogenomics is a field of science where phylogenetics and genomics intersect and information drawn from whole genome sequencing is used to help decipher the bigger picture, the tree of life (Eisen 1998; Eisen and Fraser 2003; O'Brien and Stanyon 1999). By expanding comparisons to whole genomes or genomic features, variances encountered at the microscale can often be overcome by majority rule (Delsuc et al. 2005; Philippe et al. 2004; Jeffroy et al. 2006). Tree topologies in phylogenomics are less affected by rare genomic changes such as misalignments, horizontal gene transfer, and even missing data (Philippe et al. 2004). As such, it becomes theoretically feasible to resolve deep evolutionary relationships using phylogenomics.

1.4.1 Phylogenomics and Evolutionary Inference

In many instances it is not examining the entire genome that informs us but targeting the portions of the genome that eventually encode proteins, i.e., the transcriptome. Sequence-based comparisons generally involve concatenating multitudes of data into a supermatrix and then evaluating these as a single evolving unit when performing comparisons between taxons. Tree construction can also be based upon individual gene/protein comparisons which are then combined to generate supertrees. These approaches are not unlike the more commonly performed phylogenetic studies but are executed on a much grander scale. Phylogenomics can also be designed so as not to rely directly on sequence comparisons but on genomic features or the character makeup of a genome such as comparing the positions of

introns or intervening sequences (Roy and Gilbert 2005), or the order in which genes appear in a genome (Korbel et al. 2002), among others.

As it relates to parasites, phylogenomics has been substantially relegated to studies on protozoans because of the dearth of whole genome sequence data from more complex parasite assemblages. Still, some work has been performed reconstructing deep evolutionary relationships among nematodes, arthropods, and vertebrates, a question that has plagued those in evolutionary biology for many years. The two prevailing hypotheses suggest that larger clades can be defined either as Coelomata (animals with a coelom or internal body cavity that harbors key internal organs) or as Ecdysozoa (animals that shed their exoskeleton). The Coelomata hypothesis, which is based primarily on morphological and physiological parameters, maintains that chordates and arthropods are more closely related than either is to nematodes which do not possess a coelom. This contrasts with the Ecdysozoa hypothesis where tree topology is predicated upon shared developmental characters. In this case, arthropods and nematodes would form a monophyletic clade independent of chordates because members of these groups undergo a homologous molting process.

In 2004, Wolf et al. (2004) used phylogenomics to address this question by examining greater than 500 protein sequences subgrouped into eight macromolecular complexes. These complexes were then analyzed using both supermatrices from concatenated sequences and supertrees from optimized individual trees, as well as indels, gene content, and protein domain co-occurrence that are all less dependent upon direct sequence comparisons; only six eukaryotic species were used in this analysis. Surprisingly, all analyses converged on a coelomate topology. Using gene content, Dopazo et al. (2004) examined 25,000 amino acid sequences and corroborated the Coelomata hypothesis. However, others showed that when extensive and well-documented character loss was accounted for in the nematode *Caenorhabditis elegans* (Copley et al. 2004) (one of the six eukaryotes used in the analysis), or when fast-evolving sequences in *C. elegans* were removed from consideration (Dopazo and Dopazo 2005), the Ecdysozoa hypothesis was better supported. This work was corroborated by Philippe et al. (2005b). Collectively these studies showed that even if datasets are demonstrably expanded, branch lengths and in particular long-branch attraction biases can substantially impact tree topology when comparing disparately related organisms.

With this as a backdrop, one of the key points of contention between phylogenetics and phylogenomics is whether higher taxon sampling (phylogenetics) or greater gene sampling (phylogenomics) has a more profound impact on tree topology. These types of questions can be difficult to assess because molecular systematics is an evolving and subjective science with few hardcore benchmarks. Large datasets may negate sampling errors, but systemic errors such as compositional biases and misleading data still abound (Jeffroy et al. 2006; Philippe et al. 2005a). As example, in a robust study of yeast phylogeny, whole genome data was analyzed via maximum likelihood (ML) and parsimony. One tree with 100 % bootstrap support was created (Rokas et al. 2003); however, upon analyzing the same dataset using minimum evolution (ME), a different tree was created, also

exhibiting 100 % bootstrap support (Phillips et al. 2004). Recoding the nucleotides as purines or pyrimidines resulted in a new ME tree that aligned with the ML/parsimony tree. Philippe et al. (2005a) later suggested that putative discrepancies such as these should be tested by demonstrating that congruent trees can and will result from both taxon-poor and taxon-rich sampling.

The field of phylogenomics is still evolving, and with any new approach to problem solving, new caveats and challenges will emerge (Philippe et al. 2005a). However, as it becomes easier and less costly to perform whole genome sequencing, the databases of more complex organisms will escalate which in turn will result in a coalescence of benefits from ample taxon sampling and gene sampling. Until that time, comparative genomics will continue to grow as a driving force for using large datasets to study distantly as well as closely related organisms in that comparative genomics looks at the presence or absence of protein sequences in conjunction with systems biology to evaluate similarities, differences, and putative evolutionary links among organisms. As you will see below, much can be gleaned at both the micro- and macroscales when studying evolutionary trends among organisms using comparative genomics.

1.4.2 Comparative Genomics and Evolutionary Inference

In recent years, research on parasite genomes has come of age. Draft genome sequence data are now available for species of *Trichinella* (Mitreva et al. 2011), *Brugia* (Ghedin et al. 2007), *Ascaris* (Jex et al. 2011), *Schistosoma* (Berriman et al. 2009; *S. japonicum* Consortium 2009), and nearly so for the cestodes *Taenia* and *Echinococcus* (Tsai et al. 2013). Other genera encompassing key human parasitic worms are soon to follow. In addition to being used to study evolutionary relationships and processes on a grander scale (phylogenomics), genome sequences have come to better enlighten us on issues like host–parasite interactions, adaptation, and selection and have placed a genetic face to the biological diversity that abounds in this group. Comparative analyses, i.e., comparative genomics, using genome information in conjunction with the transcriptome and proteome data that usually accompanies these studies, have helped us understand the functions of genes and gene products. In essence, comparative genomics has helped link phenotypes to genotypes.

A comparative analysis of the genomes of four tapeworms representing multiple genera, *E. multilocularis* (canine, humans, and rodents), *E. granulosus* (canine, humans, and ungulates), *T. solium* (swine and humans), and *Hymenolepis microstoma* (rodents and arthropods), was recently performed (Tsai et al. 2013). This study showed extraordinary genetic plasticity among tapeworms, how this plasticity contributed to the evolution of the group, and provided insights into the acquisition of parasitism among cestodes. Identification of key heat shock proteins (HSP) in *Echinococcus* and *T. solium* and the massive independent but parallel expansion of this gene family in each species have given rise to theories on the role

that the HSP genes play in the ability of cestodes to cope with change and therefore adapt to new environments and new hosts. Further, gene sets were identified that function to increase the ability of these flatworms to absorb needed nutrients rather than metabolize ingested foods, a genetic finding that corroborates their morphological structure.

A review by Lawton et al. (2011) evaluated the use of comparative genomics in an intragenus study of *Schistosoma* phylogeography. They targeted mitochondrial genome organization, nuclear data, and existing cytogenetic information to gain better insight into the evolution of the genus particularly as it relates to opposing views of its African (Davis 1993) or Asian (Rollinson et al. 1997; Snyder and Loker 2000) descent. Based upon the genomic evidence, they concluded that the genus *Schistosoma* originated in Asia approximately 60–70 million years ago from an avian schistosomatid then switched to ungulates approximately 20 million years ago, giving rise to the *S. japonicum* group. The *S. japonicum* group shares distinct genomic similarities with the avian parasites including but not limited to mitochondrial gene order. Their analysis led to the conclusion that the genus then invaded Africa with the migration of mammals. It is believed this occurred as recent as 2–3 million years ago (Attwood et al. 2007), and on two separate occasions, the second of which gave rise to the *S. mansoni* and *S. haematobium* clades. This was followed by reinvasion of Asia and subsequent evolution of the *S. indicum* clade.

Comparative genomics is not relegated to intragenus studies. Numerous reports have surfaced using genomics to investigate more holistic questions such as parasite lifestyles and mechanisms constituting "parasitism" among nematodes (Blaxter et al. 2012; Heizer et al. 2013; Shinya et al. 2013; Strube et al. 2012; Tsai et al. 2013). As one might expect, there is a large collection of genes that are conserved among metazoa because they harbor functions needed to sustain life in nearly all organisms. There is an equally large collection that constitutes genes archetypical of nematodes and still others that are non-conserved and that uniquely define an organism or taxa; these are likely involved in functional diversification, speciation, and species adaptation. One study examining these subsets of genes was performed in conjunction with sequencing the genome of *T. spiralis* (Mitreva et al. 2011). In this study, the genome of *T. spiralis*, a member of a more ancestral clade in the Nematoda, i.e., Dorylaimia, was compared to other available nematode genomes in the hope of identifying pan-phylum-specific sequences and proteins. The ultimate goal of this type work was to distinguish genes and proteins that can be evaluated as targets for broad spectrum drug intervention. This is significant, principally because of the multitude of people worldwide requiring anthelmintics, the relatively small number of drugs available for this purpose, and the ever increasing threat of resistance to those currently in use (Keiser and Utzinger 2010). Herein lies one very important intersection linking systematics, comparative genomics, and human health, namely, the use of pharmacophylogenomics in the development of prophylactic and therapeutic treatments for human parasites (Caffrey et al. 2009; Jex et al. 2011; Rufener et al. 2010; Swain et al. 2011; Taylor et al. 2013). However, the ultimate success in these types of studies and the breadth

of the gene targets is predicated upon user-defined criteria for culling and grouping sequences.

1.5 Conclusions: Human Helminths in a World Under Change

Parasites have been a fundamental component of the human landscape throughout our history. Contemporary parasite faunas, assembled across disparate time frames and sources, provide an intricate mosaic that reflects historical and ongoing interactions among ecology, evolution, and geographic colonization. Our understanding of historical processes as determinants of faunal structure and parasite distribution is critical for mitigating their impact on human health and well-being in a world where dramatic changes in distribution and the interfaces for infection are being demonstrated and predicted (Hoberg and Brooks 2010; Brooks and Hoberg 2013).

Much of human parasitism has been linked to improper hygiene wherein 35 % of the world's population (2.5 billion people) lacks access to improved sanitation. A similar percentage is infected by intestinal parasites as a direct result of poor hygiene and unwashed food. Within the span of just a few hundred years, we have seen the impact that human travel can have on the dissemination of once exotic parasites (Rosenthal et al. 2008; Hoberg 2010). Thus, interacting challenges between people and the biosphere are apparent and constitute a synergy for crises in biodiversity, climate change, and emerging infectious diseases. Given the extent to which parasitism permeates our ecosystem, parasitological insights must be integrated into any discussion on the unfolding and accelerating effects of climate and ecological disruption because of the potential for new and changing patterns of parasite/pathogen distribution. Within this discussion must come an appreciation for the fluidity rather than rigidity of helminth systematics and phylogenetics and the impact that environmental perturbation and anthropogenic forcing, through human behavior and globalization, imparts on that plasticity.

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