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The Role of Helminthes in Human Evolution
Implications for Global Health in the 21st Century

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Introduction

Although physiological and behavioral responses are often reported in animals with high worm burdens, or helminthes,[1*] the adaptive significance of these responses is unknown.[3,4] Similarly, although the field of biomedicine and medical anthropology is replete with publications on the short-term physiological and health effects of helminthes on their hosts, the evolutionary causes and consequences of those responses that might shed light on present-day human global health patterns are also unknown.

Our ignorance is due in part to assumptions that are pervasive in the fields of human biology and biomedicine. The first is the assumption that hunting and gathering humans have throughout history been much less infected with helminthes than their horticultural or agricultural counterparts. A recent review of the literature suggests that relatively few long-term co-evolutionary relationships between hominins and helminthes emerged early in our history, and for the most part, hominins would have contracted new parasites by coming into contact with or ingesting raw plants, insects, meat, and fish.[5] And the second is that even among humans infested with helminthes, such infections are primarily a nuisance rather than a serious threat to health and life, and are therefore unlikely to exert strong selective pressures on human physiological and immunological responses. The justification for this second assumption is that in most human populations, the primary causes of death are attributed to viral and bacterial infections, trauma, conspecific violence, and chronic health conditions, not helminthes (for examples of main causes of deaths among hunter-gatherers, see Hill and colleagues[6,7]). However, in populations with high worm burdens, such primary causes of death could be in many instances secondary or tertiary to helminthic infection. Epidemiologists have long debated over what constitutes a true cause of death—the heart attack or the viral infection that weakened that individual's heart, the automobile accident or the chronic onchocercosis infections of the eyes that blurred that individual's vision, and so on. Similarly, we will argue here that in populations with high worm burdens, rates of death and illness due to

* *Helminthes are worms that are divided into three types that parasitize human hosts: Digenenan flukes, tapeworms (cestodes), and roundworms (nematodes).[2]

bacterial or viral infection are not independent of the levels of helminthic infection that they harbor.

As we grapple for answers to why infectious diseases now contribute more to human mortality across the globe than does any other health condition, in spite of huge technological and medical advances, researchers have found in recent years, in many different contexts and human populations, that helminthic comorbidity greatly increases the probability of infection and death due to HIV, tuberculosis, and malaria. Therefore, it is now clear that helminths can exert strong selective pressures on human hosts by increasing rates of morbidity and mortality directly or by increasing the probability of mortality and morbidity that is more proximally induced by co-occurring bacteria and viruses in the same hosts. Much less is known about the effects of helminth comorbidity on rates of death due to chronic diseases such as asthma, diabetes, cancer, and cardiovascular disease. Could this have been true as well throughout most of our history? What energetic trade-offs might have been involved? And how is the human immune response implicated?

Thus, we need to approach the study of helminthes in past environments with rigor and ask what the potential role of helminthes may have been in shaping the mortality profiles of our ancestors, what selective pressures they may have exerted on ancestral genotypes that modern humans have now inherited, and what might be the implications of this helminth-focused view of human history for understanding global health patterns in the twenty-first century.

In this chapter, we show that the phylogeny of helminth infection in primates is such that nonhuman primates and extinct and extant nomadic and horticulturalist human groups are heavily parasitized. The very high prevalence of helminthes in nonhuman primates and humans suggests that throughout most of our history, helminthes may have exerted important selective pressures on physiological and immunological phenotypes by imposing substantial and chronic energetic costs on their hosts. Helminthes directly impose costs by draining hosts of nutrients essential to physiological performance. They indirectly impose costs by promoting the rapid loss of host nutrients through diarrhea or vomiting, two of the better-known strategies that helminthes use to ensure transmission between susceptible hosts. Moreover, helminthes cause energetically costly upregulation of host immune defense mechanisms. These direct and indirect costs add up to significant foregone investments in growth, reproduction, and maintenance (that is, opportunity costs).

In order to begin to systematically identify helminth-related selective pressures in past human environments, we minimally need answers to two questions: (1) Is chronic helminthic infection prevalent in our closest mammalian ancestors (nonhuman primates), prehistoric human populations, and extant human populations whose disease ecologies most closely resemble those of our past—indigenous populations? (2) What might have been some

of the energetic costs of helminth infection among humans, and do they ebb and wane across the life course?

Figure 8.1 provides an overview of the chapter. In this figure, we show the disease ecology, physiological and life history components of interest, and the sections in which they will be discussed. We first present data on the distribution of intestinal helminthes in nonhuman primates, prehistoric populations, and indigenous peoples ("Helminthes and Early Humans"). We then summarize some of the immune system–related effects of helminth infection observed in animals and humans ("Costs of Defense against Helminthes"). The implications of the findings for global health in the twenty-first century are then considered ("Implications for Global Health").

Data Compilation Methods

Data compilation for this chapter was conducted through keyword searches in PubMed[8] for roundworm, whipworm, hookworm, helminths, primates, South American Indians and prevalence. The PubMed Mesh system extracts records by using terms that are manually assigned to every article published in journals indexed by PubMed. For example, if an article includes information on any South American indigenous group, regardless of the term that the uathros use to refer to that group, members of the PubMed staff assign to it the term "South American Indians." The PubMed Mesh system is the only electronic search engine that works in this way. We chose these key words because we were specifically inerested in prevalence rates of soil-transmitted helminths in South American indigenous populations and non-human primate populations.[9] Because there are at least 64 species of endohelminthes,[10] we focused our search for evidence of helminths in prehistoric and extant populations on four frequently studied species of soil-transmitted hel-

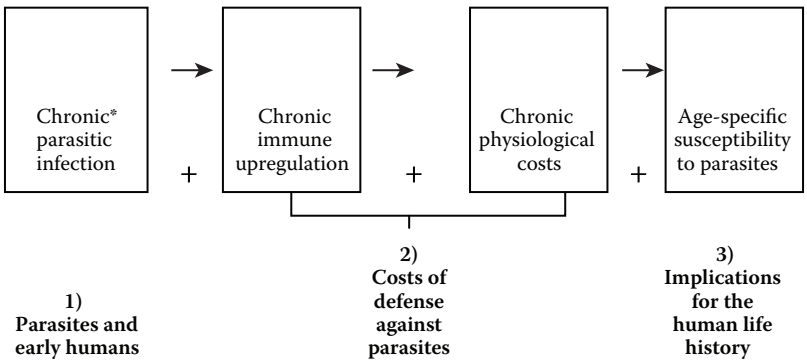

Figure 8.1 Immune system–mediated effects of parasites on health and the human life history.

minths: *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), and two species of hookworm *Necator americanus* and *Anclyostoma duodenale*. Goncalves and colleagues[11] provided a comprehensive review of helminthes discovered in archeological settings, and that information was utilized to form the paleoparasitological tables. For the modern indigenous groups keyword searches of PubMed and Google Scholar include but are not limited to "soil-transmitted helminthes," "macrohelminthes," "prevalence," "hookworm," "ascaris," "paleaoparasitology," and "indigenous." Data on prevalence rates of roundworm, whipworm, and hookworm were systematically recorded into an Excel database. Two samples were generated using data on populations of South America: 125 and 38 studies of indigenous and nonindigenous groups, respectively.

Helminthes and Early Humans

Molecular genetics and paleoparasitology now allow us to state with some degree of confidence that helminthes have been an essential feature of hominin disease ecologies. Phylogenetic analysis of tapeworm divergence patterns indicates that the human taeniid forms split from the hyaenid, canid, and felid forms during a period of time when hominins appear to have become more dependent on hunting and scavenging, between 0.78 and 1.71 mya.[12] Other paleoparasitological studies, and biomedical studies of nonhuman primates and indigenous peoples also suggest that helminthes were persistent features of past ecologies (see below).

Because there are at least sixty-four species of endohelminthes,[10] we focused our search for evidence of helminthes in prehistoric and extant populations on four frequently studied species of soil-transmitted helminthes: *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), and two species of hookworm—*Necator americanus* and *Anclyostoma duodenale*.

Infection with roundworm, whipworm, and occasionally *A. duodenale* (a hookworm species) originates through ingestion of fully developed eggs in contaminated food or water. Unlike roundworm and whipworm, the two hookworm species enter subcutaneous vessels when human skin contacts contaminated soil. After entrance into the host, the roundworm and whipworm larva burrow through the lining of the stomach, enter the circulatory system, and migrate to the lungs. In the respiratory system the larva pass over the epiglottis to reenter the gastrointestinal tract, where they mature into egg-laying adults.[13–15]

Nonhuman Primates

Helminth infection prevalence rates (i.e., number of individuals infested with helminthes divided by the total number of individuals sampled times 100) are high among nonhuman primates (table 8.1). Based on rates published in three studies by Murray,[16] Michaud,[17] Gillespie[18] and colleagues, it appears

Table 8.1 Prevalence of soil-transmitted helminthes in nonhuman primates

Strata	Primate species	Common name	Parasite species	Prevalence	Country	Reference
<10% prevalence						
	Saimiri sciureus macrodon	Common squirrel monkey	*Trichuris*	1.8	Peru	17
	Pan troglodytes	Chimpanzee	*Trichuris*	5.0	Tanzania	16
	Lagothrix lagotricha	Woolly monkey	Hookworm	8.3	Peru	17
	Lagothrix lagotricha	Woolly monkey	*Ascaris*	8.3	Peru	17
	Pan troglodytes	Chimpanzee	Hookworm	9.0	Tanzania	16
>10% prevalence						
	Cacajao calvus rubicundis	Uakari	Hookworm	20.0	Peru	17
	Cercopithecus ascanius	Redtail monkey	*Trichuris*	21.0	Uganda	18
	Colobus badius tephrosceles	Red Colobus	*Trichuris*	36.0	Uganda	18
	Colobus badius tephrosceles	Red Colobus	*Trichuris*	40.0	Uganda	18
	Papio cynocephalus	Baboon	Hookworm	44.0	Tanzania	16
	Cercopithecus ascanius	Redtail monkey	*Trichuris*	63.0	Uganda	18
	Papio cynocephalus	Baboon	*Trichuris*	66.0	Tanzania	16
	Colobus guereza	Abyssinian Colobus	*Trichuris*	79.0	Uganda	18
	Colobus guereza	Abyssinian Colobus	*Trichuris*	84.0	Uganda	18

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that Old and New World wild nonhuman primates are similarly affected. Values range from 8.1 to 84% for one of three species, whipworm, hookworm, or roundworm. These are probably underestimates of true infection rates since it is very difficult to find worms and eggs in feces in any species and particularly in highly mobile wild communities.

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The total number of prevalence rates reported in these studies is 14, and of those, 5 fell below 10% prevalence and 11 above 10%. New World and Old World nonhuman primates are similarly represented in both groups, suggesting that endohelminthes are a persistent feature of nonhuman primate disease ecology. Perhaps this was also true in hominin species that predated the emergence of *Homo sapiens*.

Prehistoric Populations

In an extensive review of the human paleoparasitological literature, Goncalves and colleagues[11] conclude that "almost all human specific helminthes have been found in ancient feces." With this, in combination with the possibility that hominin species that predated *H. sapiens* were at risk of helminthic infection as the molecular genetics and the nonhuman primate data suggest, it appears that endohelminthes may have been an unvarying feature of *H. sapiens* ecologies until recently.

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Table 8.2 summarizes a subset of key published findings on roundworm, whipworm, and hookworm in prehistoric samples. To our knowledge, the oldest evidence of roundworm was found in fecal samples of early humans over 30,000 years ago in France. All other data are more recent, with the oldest sample dating back to 10,000 years ago and the most recent dating back to 2,700 years ago (see Goncalves et al.[11] for an extensive review of the paleoparasitological data on all helminthes).

The probable early presence of roundworm in France, at over 30,000 years ago, combined with the presence of both roundworm and whipworm at Kruger Cave before the advent of agricultural intensification in sub-Saharan Africa, means these helminthes could survive, if not thrive, in presedentary environments. Hence, soil-transmitted helminthes were likely present in humans before the advent of densely populated, sedentary populations in both South Africa and France.[19,20] Also, in the New World, soil-transmitted helminthes are present from 8,000–7,000 B.P. The pre-Columbian presence of roundworm, whipworm, and hookworm suggests these helminthes were major contributors to the disease load of the Americans since the initial migration to the New World over 12,000 years ago.[11,21]

In spite of the limitations of methods used to detect whole worms, eggs, or their genes in rehydrated coprolites, latrines, or mummified human remains using visual or molecular methods,[30] paleoparasitologists have found strong evidence that roundworm, whipworm, and hookworm were prevalent in prehistoric populations of *H. sapiens*. As methods improve, anthropologists

Table 8.2 Presence of soil transmitted helminthes in prehistoric human coprolites

Strata	Species	Archeological site	Country	Continent	Oldest approximate date (years ago)	References
Preagriculture	*A. lumbricoides*	Grand Grotte	France	Europe	30,160	19
Postagriculture	*A. lumbricoides*	Kruger Cave	South Africa	Africa	10,000	20
	T. trichiura	Kruger Cave	South Africa	Africa	10,000	20
	T. trichiura	Minas Gerais	Brazil	Americas	8,000	11
	E. vermicularis	Utah	United States	Americas	7,837	22
	Ancylostomid	Pedra Furada	Brazil	Americas	7,230	21
	E. vermicularis	Dirty Shame, Oregon	United States	Americas	6,300	23
	Ancylostomid	Tiliviches	Chile	Americas	4,100	11
	Ancylostomid	Clairvaux, Jura	France	Europe	3,600	24
	A. lumbricoides	Clairvaux, Jura	France	Europe	3,600	24
	T. trichiura	Clairvaux, Jura	France	Europe	3,600	24
	T. trichiura	Swifterbant	Netherlands	Europe	5,400	25
	A. lumbricoides	Arbon, Thurga	Switzerland	Europe	3,384	24
	T. trichiura	Arbon, Thurga	Switzerland	Europe	3,384	24
	T. trichiura	Otzal, Tyrol	Austria	Europe	3,300	26
	Ancylostomid	Minas Gerais	Brazil	Americas	4,905	27
	A. lumbricoides	Somerset	England	Europe	4,100	28
	A. lumbricoides	Chalain, Jura	France	Europe	2,700	24
	Ancylostomid	Chalain, Jura	France	Europe	2,700	24
	A. lumbricoides	Huarmey Valley	Peru	Americas	2,277	29

are likely to find higher prevalences of helminthes in prehistoric populations than those documented to date.

Indigenous Peoples

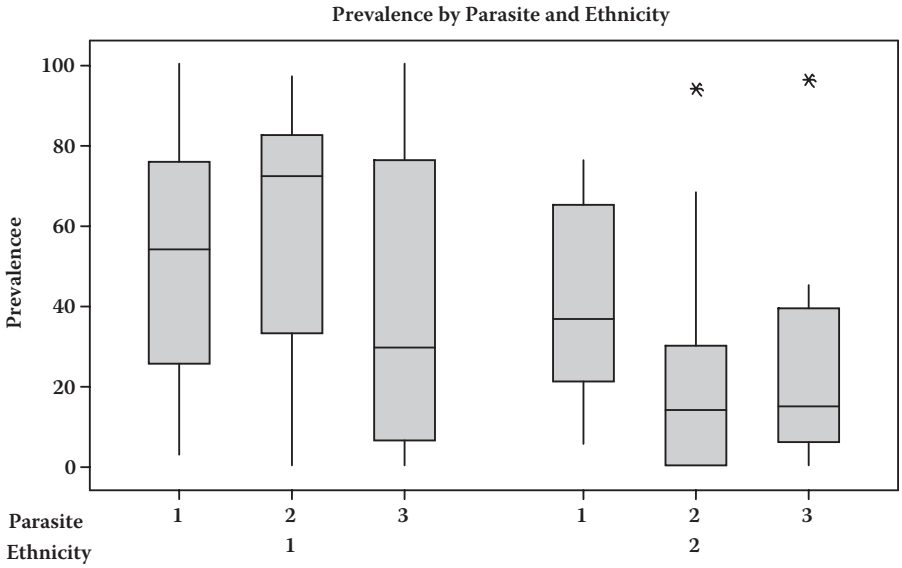
The disease ecologies of indigenous peoples residing in remote areas of the world are the best examples that we have of past human ecologies. Here we summarize data on population and age-specific prevalence rates of roundworm, whipworm, and hookworm among indigenous groups of South America. We use nonindigenous groups residing in similar regions as proxies of later humans. This allows us to compare rates of helminthic infection between populations residing in environments that represent our past and our present.

The foci of this section are two sets of figures (figures 8.2 and 8.3) with data that allow us to answer the following questions: (1) Are the prevalence rates of roundworm, whipworm, and hookworm significantly different between indigenous and their nonindigenous counterparts (figure 8.2)? (2) What are the shapes of the age-specific curves of roundworm, whipworm, and hookworm in South American indigenous groups and their nonindigenous counterparts (figure 8.3)?

Prevalence *and* Intensity

Prevalence rates of roundworm, whipworm, and hookworm are considerably higher among indigenous than among their nonindigenous counterparts. Figure 8.2a shows that although the distributions of roundworm, hookworm, and whipworm overlap between the two ethnic groups; in fact, we found two outlier values for urban groups that were as high as the highest prevalence rates for indigenous groups (close to 100% prevalence). However, the median values are consistently higher for roundworm, whipworm, and hookworm in indigenous groups (n = 125; 29.6–72%) when compared to nonindigenous groups (n = 38; 16.1–36.8%). For hookworm, the difference is considerable; 72 versus 13.9 for indigenous versus nonindigenous. It is less so for roundworm (54.1 versus 36.8%), and much less so for whipworm (29.6 versus 16.1%).

Another way to evaluate differences in helminthic infection between indigenous and other groups is to measure prevalence rates in groups of individuals with light, moderate, and heavy worm burdens. Figure 8.2b shows prevalence rates stratified by group, and then by group and degree of infection intensity.[38] Interestingly, in the indigenous sample, 88% of those surveyed were infected with roundworm, compared to 12.5% of the urban population. Within the urban sample, a larger percentage (7.3) had light infections, with lower percentages in the moderate (5.8) and heavy (2.9) infection groups. This Poisson distribution is typical in nonindigenous communities.[49] However, in Scolari's study,[38] 44% of the individuals under study



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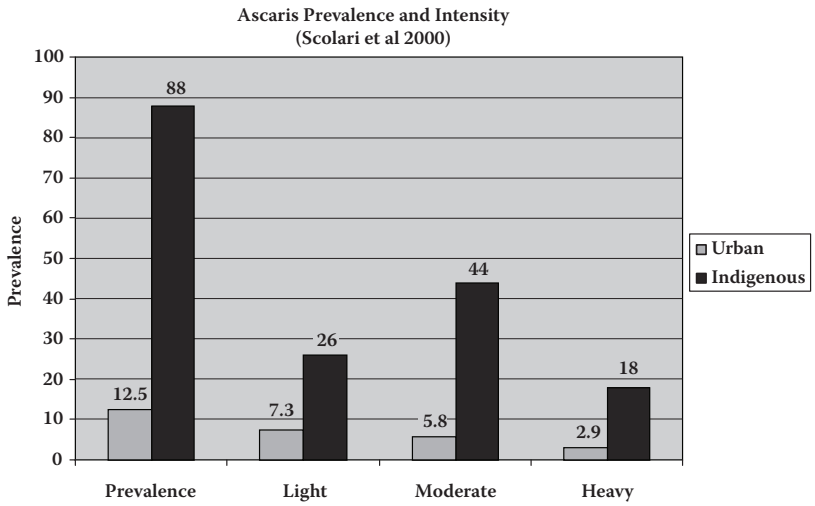

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Figure 8.2 (a) Prevalence rates stratified by parasite species and ethnicity.[15,29–45] (b) Prevalence of roundworm stratified by intensity and ethnic group (urban = nonindigenous and admixed urban populations) (based on Scolari et al.[38]).

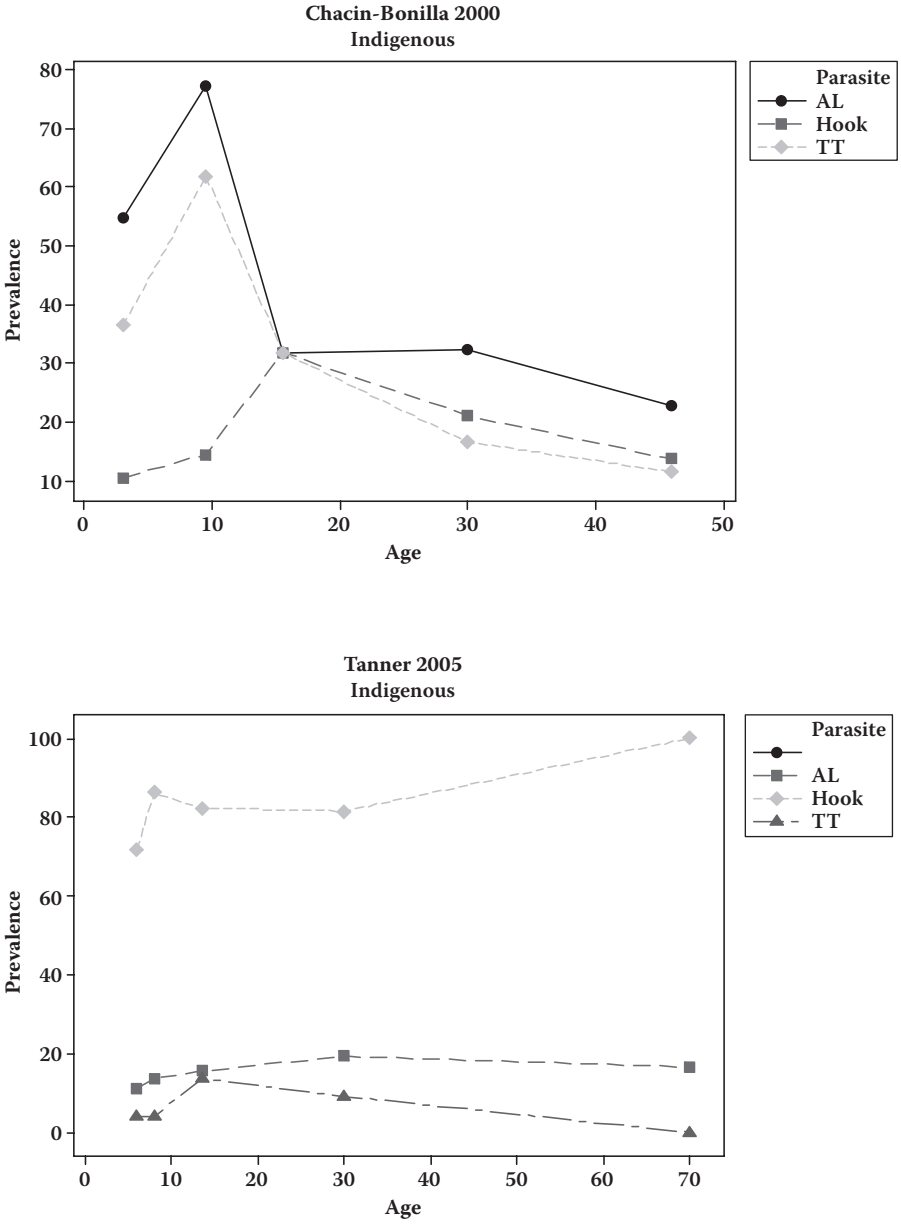
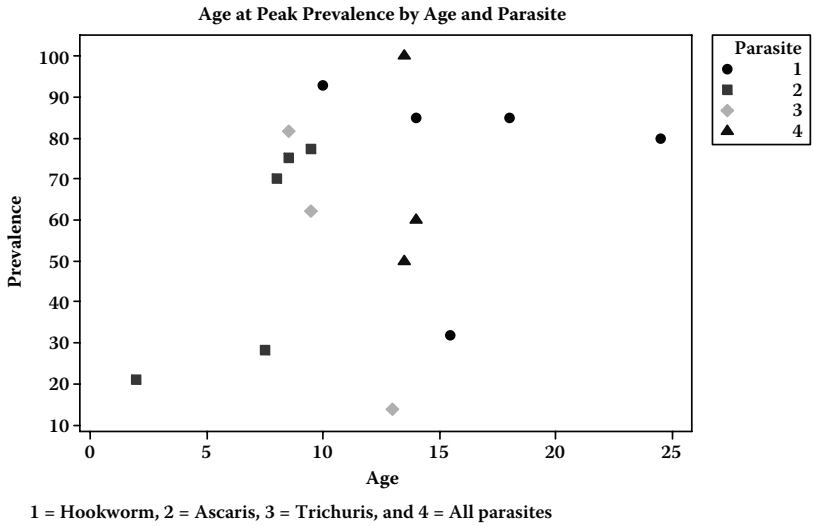


Figure 8.3 (a) Age-specific curves of roundworm, hookworm, and whipworm in two South American indigenous groups (based on Chacin-Bonilla and Sanchez-Chavez[37] and Tanner[45]).



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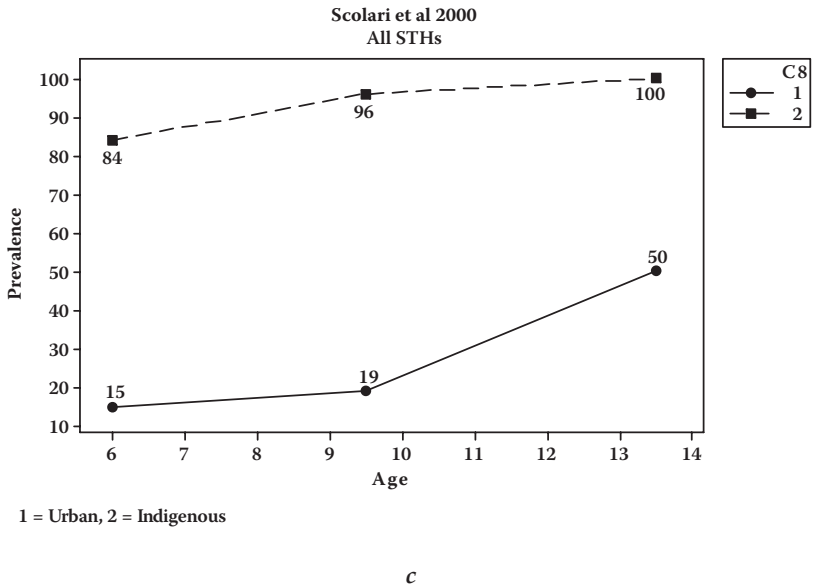

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Figure 8.3 (b) Age at peak prevalence among indigenous groups of South Americans stratified by parasite.[34,36–38,40,45–48] (c) Age-specific prevalence of parasite infection stratified by ethnic group (urban = nonindigenous and admixed urban populations). Based on Scolari et al.[38]

had moderate intensity infections, compared to 26% with light and 18% with heavy infections. This bell-shaped distribution in intensity of infection is unexpected and shows that relative to the urban population, when indigenous groups are infected with roundworm, not only do they have higher overall prevalence but also a higher percentage of individuals harbor larger worm loads.

Age-Specific Curves

If prevalence rates of roundworm, whipworm, and hookworm are generally higher among indigenous groups than the nonindigenous, then it must also be the case that in every age group indigenous individuals also have higher rates.

Figure 8.3a shows two panels with data on indigenous groups of Venezuela and Bolivia. The first panel shows the age distribution of prevalence rates of roundworm, whipworm, and hookworm among 433 indigenous individuals from two villages of Southern Venezuela.[37] For both roundworm and whipworm the prevalence rates increase throughout childhood and eventually reach a peak between 7 and 12 years of age at 77.3 and 62%, respectively. Then, prevalence of infection decreases during adolescence and tapers down to 28% for roundworm and 15% for whipworm in adulthood. Hookworm prevalence peaks later in life at 31% between the ages of 13 and 18 before decreasing in adulthood.

The second panel shows the age distribution for a sample of 317 Tsimané, an indigenous population of lowland Bolivia. The hookworm prevalence peaks at 86.2% between the ages of 6 and 9 years and remains at a steady high level until old age. In this study, 100% of elderly individuals (70 years old or older) were infected with hookworm (n = 6). In contrast, roundworm and whipworm were much less prevalent across all ages, although the rates are not biologically insignificant. Between 10 and 17 years of age, the Tsimane in the sample had a prevalence of 13.7%. And infants had infection rates of 21% for roundworm and 16% for hookworm.

When we compare the two studies, we find that in both groups at least one soil-transmitted helminth has a prevalence rate of over 70% at one or more stages of the life course. We also find that in Venezuela, a dramatic increase occurs from infancy to adolescence, followed by a long period of resistance into old age. In contrast, in Bolivia susceptibility to roundworm, whipworm, and hookworm appears to be high at all ages, particularly in the case of hookworm.

From these two studies, it appears that risk of helminth infection increases in indigenous groups during periods of brain and body growth, mainly from infancy to adolescence. Other studies support this conclusion. Figure 8.3b shows the distribution of age at peak prevalence for hookworm, roundworm, and whipworm among indigenous groups of South America. Most values fall between 5 and 17 years of age, and within this age range, the prevalence rates are greater than 50%. The Tsimané of Bolivia are an exception to

this pattern; by 2 years of age, individuals reach a peak of 21% prevalence of roundworm. In addition, in groups of Itagua, Paraguay, and American-inhas of Brazil, the age at peak prevalence for hookworm is delayed into the 20s.[36,45,46] We also learn from figure 8.3b that roundworm and whipworm tend to peak in prevalence at earlier ages than does hookworm.

In summary, the age distributions of prevalence rates of roundworm, whipworm, and hookworm are similar in some ways but different in others when compared across indigenous groups. But how much do they differ from the age curves of indigenous groups?

Figure 8.3c shows that they can be extremely different in both magnitude and shape between the ages of 5 and 15. A study on the prevalence of roundworm, whipworm, and hookworm infection among indigenous and urban schoolchildren in Ortigueira, Brazil,[38] shows that the overall prevalence of those infections was significantly higher in the 100 indigenous children compared to the 136 urban children in the sample. The main culprits of infection in the urban and indigenous samples were roundworm (88 versus 12.5% for indigenous and urban) and hookworm (38 versus 5.8%). In both samples, collected by the same team of researchers using the same methods in two locations, the prevalence rate increased throughout childhood and peaked between 12 and 15 years of age. However, the urban prevalence peak was only 50%, compared to 100% among indigenous children between 12 and 15 years of age. While in the indigenous sample, susceptibles are close to being completely exhausted before the age of 10 (i.e., 96% of the children were already infected with at least one helminth), in the urban sample, only 19% of the children were infected.

Costs of Immune Defense against Helminthes

If endohelminthes, as the previous sections on nonhuman primates, prehistoric populations, and indigenous peoples suggest, were a major feature of the disease ecologies of early humans, what costs did they incur across the life course, and across generations?

Based on a review of the literature on immune system-related effects on health, we learned that immune upregulation due to helminthic infection has at least three short-term effects and five long-term effects (figure 8.4). Over the short and long term, helminth-induced immune upregulation is associated with hypermetabolism, an exaggerated increase in metabolic rate, and catabolism, or destructive processes by which cells convert complex molecules into simpler compounds. These include lipolysis, protolysis, and glycolysis, or the decomposition of lipids, proteins, and carbohydrates.

Over the short term, these physiological responses in turn lead to increases in body temperature and fever, weight loss, and loss of skeletal muscle (figure 8.4). And over the long term, as these physiological responses become chronic, hosts continually invest in the synthesis of new proteins; suffer from

immunopathologies, impaired neurological function, and viral and bacterial disease; and develop morphological traits that are asymmetrical (figure 8.4).

The predictor variable in the figure is helminth-induced immune system upregulation, which in humans involves significant increases in the production of immunoglobulin E (IgE) and eosinophils. In helminth-endemic regions of the world, high IgE and eosinophil levels are associated with resistance to reinfection.[50–52] In helminthic infection, IgE, the immunoglobulin with the lowest circulating concentration, relies on the high affinity of mast cells for IgE via their e-heavy-chain Fc receptors (FcERs) to clear endohelminthes. Mast cells degranulate upon binding to IgE, and release histamine, which in turn activates eosinophils. The latter then release cationic granule proteins with activities known to be cytotoxic, or toxic to the cells of endohelminthes, including eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase.[53]

The upregulation of IgE and eosinophils is significantly greater in populations whose disease ecologies most closely resemble those of early humans, mainly extant indigenous groups residing in remote regions of the world.[54] Moreover, IgE and eosinophils are not the only cells that are upregulated during helminthic infection. The concentration of other immune cells such as T-lymphocytes is also elevated in tribal populations of West Africa and Papua New Guinea.[55–58]

We did not find any studies that measured the effects of hyper-IgE, eosinophil production, or any other immune cell on the health of indigenous peoples. Instead, we found studies in the animal literature and the medical literature on nonindigenous peoples that systematically measured some of the relationships of interest summarized in figure 8.4. This published work is a useful starting point for thinking about how helminth-induced mechanisms can exert strong selective pressures on the expression of genes that regulate differential energetic investments into helminth clearance across the life course.

Short-Term Effects

Over the short term, the initial immune upregulation associated with helminthic infection requires mobilization of protein and energy to combat infection.[58] Even brief infections are sufficient to instill protein malnutrition within a few days in hospital patients with sepsis.[59] In bumblebees and caterpillars, these protein and energy requirements have especially devastating effects during periods of starvation because hosts have to rely on their own tissue for nutrients, and thus frequently succumb to death.[60,61] In humans, similar phenomena are observed in patients suffering from trauma or sepsis, a health condition that also elevates the production of IgE and eosinophils.[62] The high glucose and glutamine requirements of immune cells like IgE and eosinophils require the breakdown of protein (proteolysis), carbohydrate (glycolysis), and lipid (lipolysis) reserves in septic hospital patients.[63,64] And

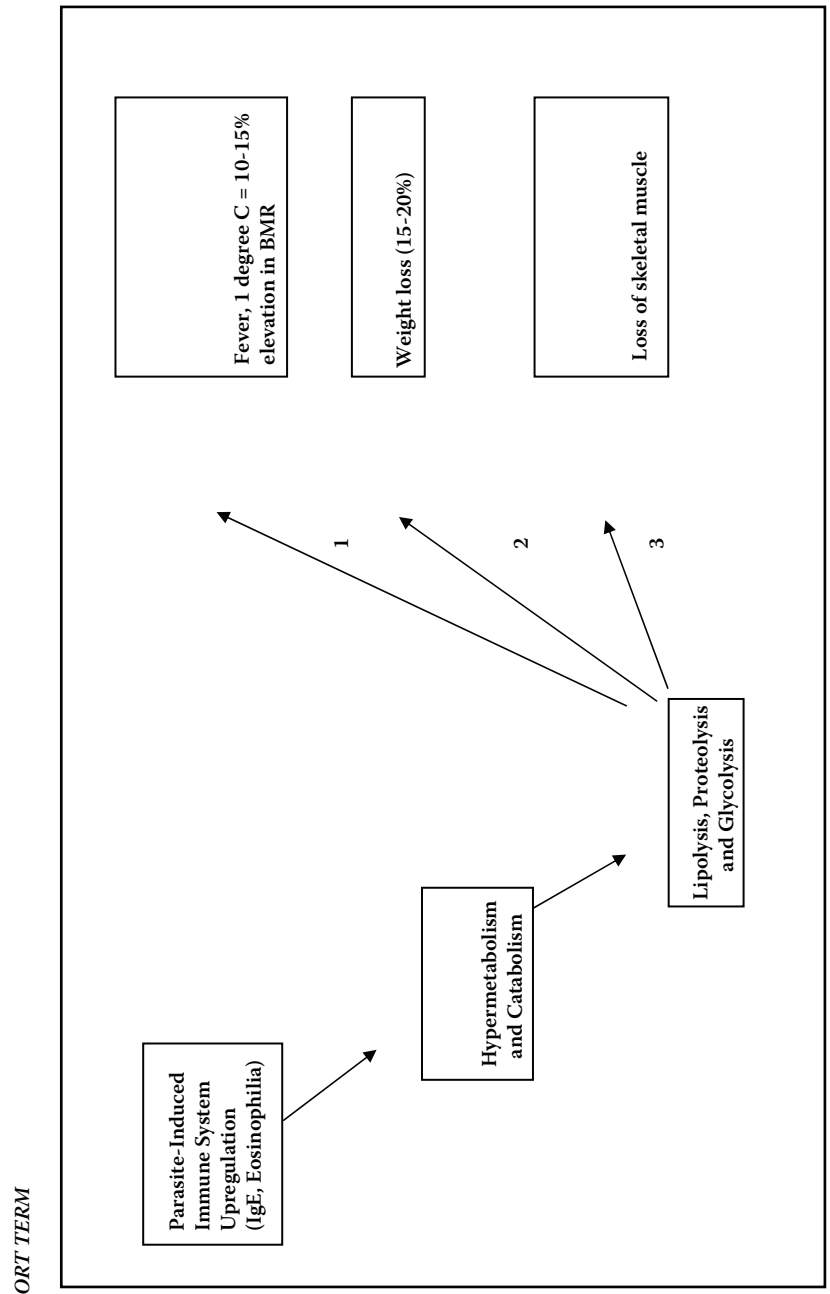

Figure 8.4a The costs of parasite-induced immune system upregulation on (a) short-term.

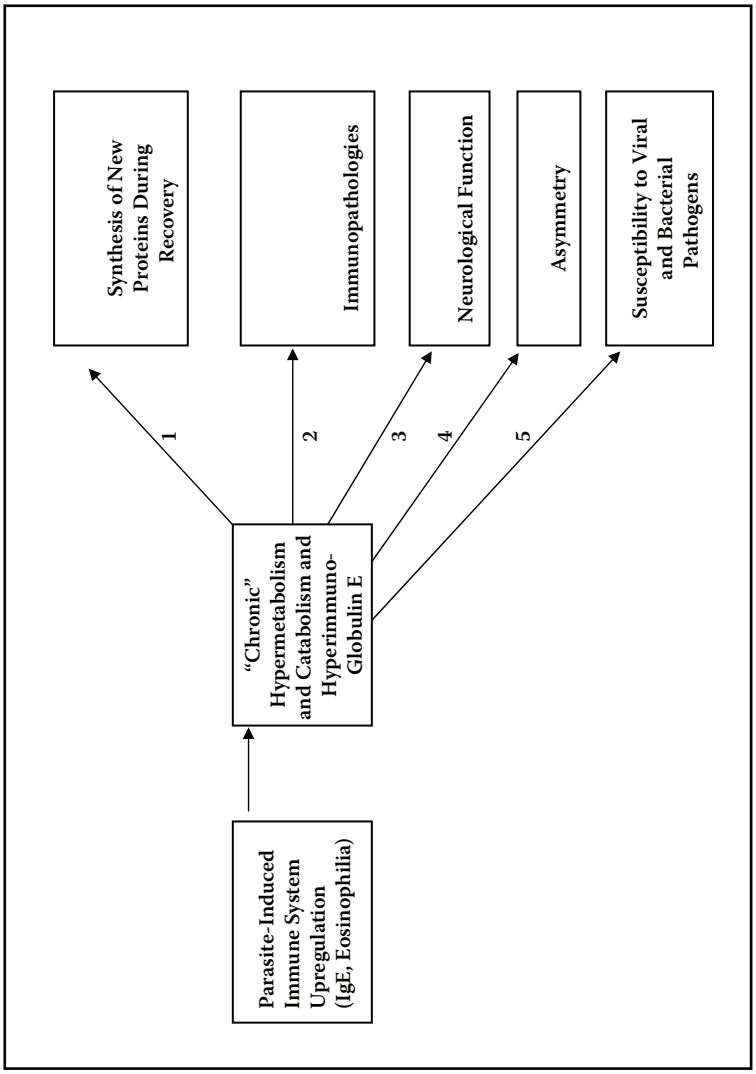

Figure 8.4b The costs of parasite-induced immune system upregulation on (b) long-term physiological function, morphology, and health outcomes.

lipolysis, proteolysis, and glycolysis have been found to reach exaggerated levels in trauma patients and must be quelled quickly with therapeutic interventions to prevent disability and death.[65–67]

Lypolysis, proteolysis, and glycolysis are also associated with an increase in body temperature in hospital settings.[66] In at least one study of patients suffering from major trauma, researchers found that with each 1°C in fever, BMR increased by 10–15%.[68] Even a typhoid vaccination can raise the metabolic rate of human hosts between 15 and 30%,[69] and metabolic rate can increase 20–25% during septic infections.[70] Moreover, an increase in metabolic rate leads to weight loss and loss of skeletal muscle such that in some studies researchers found that humans suffering from infections or severe trauma, and birds infested with ectohelminthes, experienced a dramatic decrease in weight.[65,71,72] In humans, severe sepsis infections can lead to a loss of 15–30% of overall body weight.[59]

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Few studies have measured the energetic costs of infection by specific groups of pathogens. That is, for example, are the costs similar or different for bacteria, viruses, or helminths? This is a difficult question to answer because it requires experimentation that requires controlling for factors other than "type of pathogen," such as pathogen virulence factors, host susceptibility, pathogen load, and replication rates within hosts. Thus at present we are unable to provide a summary of differences in costs between helminths and other microbial agents such as viruses and bacteria. For the time being, we can only guess that the energetic costs of helminth infection must be significant for individuals who are infected because, unlike many of the better known pathogenic viruses and bacteria that afflict humans, helminth infections are never completely cleared, reinfection is chronic throughout the life course, and the complex interplay of cells involved in humoral immunity that is associated with helminth clearance is less effective than is the more specialized cell-mediated immunity responsible for the defense against viruses and bacteria.[73]

Long-Term Effects

Extended periods of hypermetabolism require the synthesis of new proteins to make up for their loss in injured humans as well as septic infections in humans and rats.[74,75] The cost of synthesizing new proteins can be substantial, requiring an additional 24 kcal intake in human hosts to replace each gram of protein lost during the period of infection.[76] Under conditions of limited or fluctuating food availability, hosts may never be able to make up for lost tissue even after elimination of the infection.

In addition, chronic immune attacks against helminthes throughout the life course increase the probability that cells of the immune system will be less able to discriminate between self and nonself (i.e., immunopathology) for reasons such as (1) the likelihood that some of the molecular arrangements of pathogen cells and host cells will match increases with persistent infection,

(2) mechanisms that downregulate immune cell production become less efficient, leading to unintended attacks on host cells as the immune response continues to fight pathogens unabated, and (3) the immune response becomes increasingly more exaggerated and less discriminating between host and pathogen cells with each subsequent bout of infection, i.e., a superantigenic response (see also [78–80]).

Moreover, chronic helminthic infection throughout the life course forces hosts to compromise investment in important tissues such as brain matter. Thus, in humans, chronic helminthic infection is associated with a decline in the volume of gray matter and in the ability to consolidate memory to long-term storage.[81,82]

Other tissues are also compromised when helminthic infection is persistent and chronic early in life. This compromise is associated with asymmetrical development of morphological traits and growth faltering. Research on birds shows that in some species the feathers of immune-challenged individuals grow more asymmetrically than in controls.[83–87] In addition, in at least one study of a tribal population, the growth rates of children with higher levels of C-reactive protein, an indicator of systemic acute inflammation, was lower than in other children.[88]

Last, chronic immune defense against helminthes can influence susceptibility to viral and bacterial pathogens. This is because helminthes skew immune defense toward Th2 and compromise the effectiveness of Th1 response, which is essential to clearing viral and bacterial infections.[54,84–94]

In summary, if endohelminths were a major feature of the disease ecologies of early humans, what mortality costs did they incur? And can the mortality profiles of indigenous groups today provide a glimpse into the past? Possibly. Currently we find rates of mortality among indigenous groups that far exceed those of their their nonindigenous neighbours and other humans globally who have lower or negligible helminth infestation rates or no exposure to helminths. High rates of mortality among indigenous populations, including those of South America, have been documented in many books and articles. Ribeiro[95] reports that 87 of 230 native groups in Brazil went extinct between 1900 and 1957, and studies estimate that the current native population in Brazil is only 5% of the size estimated size for the 1500s. Contrary to the received wisdom, this dismal picture did not end with the period of conquest. Indigenous groups continue to be vulnerable to all sorts of diseases, and much of this vulnerability could be due to, by current public health standards, high and sometimes extraordinary prevalence rates of helminth loads.

Without the luxury of controlled experiments, it will be extremely challenging to determine in future decades the extent to which excess indigenous mortality is primarily driven by the costs that helminths exert on their hosts as opposed to other factors. But for the time being, we can at least propose that helminths may be an important contributing factor, just as have researchers in Africa suggested that the HIV/AIDS and tuberculosis epidem-

ics could be more easily contained if helminths were eradicated from that continent.[96] At least at present it is important to note that that the rates of helminth infestations among indigenous peoples of South America are among the highest in the world, and that even Highland groups that reside in colder climates are not spared.[9] We also know that bacterial epidemics such as tuberculosis take huge tolls on these populations after decades of first contact, even when they are no longer virgin soil epidemics, and the number of susceptibles should be exhausted, at least in principle.[97] In the 1950s, groups like the Southern Kayapo lost 99% of their original population in 50 years. They did not lose the majority of the population at contact: Losses continued through five decades. And, in the 1950s and 1970s, some Xikrin and Yanomamo communities that had had contact with outsiders in previous years declined in numbers by more than 20% within 10–15 years. Equally baffling is the finding that in the 1990s the infant mortality rate among the Xavante was three times higher than among other nonnative Brazilians, decades after first contact, and that life expectancy at birth in 2000 was frequently 20+ years lower among indigenous groups when compared to their nonindigenous counterparts. In fact, the life expectancy of indigenous peopels in Brazil and Venezuela is lower than that for the U.S. population in 1900 and lower than in Sierra Leone in 2000, which has the lowest reported national life expectancy in the world today.[9]

Implications for Global Health in the Twenty-first Century

A review of the literature on the antiquity and on population and age-specific prevalence rates of helminthic infection in humans leads us to conclude that helminthes in general and helminthes in particular were probably the group of pathogens that exerted the strongest disease-related selective pressures on immune system and life history traits in most past human environments. Helminthes appear to be ubiquitous in paleoarcheological remains in spite of our inability to easily detect the presence of worms, eggs, or their genes in ancient feces or guts. Second, they also appear to be ubiquitous among nonhuman primates in the New and Old Worlds, again, in spite of our limited capacity to collect fecal samples from highly mobile, wild primates. And third, they are more prevalent in extant, genetically homogenous, and small human populations that most closely resemble those of early humans, that is, indigenous peoples, than in contemporaneous, genetically heterogenous, and large populations with longer exposure to public health programs and germ theory.

Complementary reviews suggest that helminth-induced immune upregulation is costly over the short and long term during the life of an individual, and that many of these costs are related through metabolic pathways. Thus, if the helminth fauna of prehistoric human populations is similar to that of nonhuman primates and indigenous peoples, then immune upregulation and associated costs, including mortality, was probably the norm in early

humans. Thus, we argue that although indigenous groups have lower overall mortality than do nonhuman primates,[98,99] the higher disease-related mortality that we observe in presanitation, or sanitation absent human environments, compared to sanitized environments[6] is probably primarily caused by chronic and multiple helminthic infection, rather than viral and bacterial agents. Unlike helminthes, these agents wax and wane through virulent and avirulent states over periods that can exceed many human generations.[100]

Taken together, the data on helminth infection suggest that, in the hominin lineage, one of the greatest feats of natural selection was to produce a gracile primate with the largest brain and highest fertility for its body size and the lowest mortality at all ages in spite of multiple chronic, immunologically and metabolically costly helminthic infections throughout the life course. These observations suggest that selection against individuals who could not simultaneously grow a large brain, reproduce at short intervals, and mount effective immune responses against helminthes would have been great during early human evolution (and up to the present time in populations that continue to be heavily parasitized). Moreover, selection against individuals who did not help their kin or establish reciprocally altruistic alliances that would allow them to simultaneously grow, reproduce, keep their children healthy, and mount effective defenses against helminthes must also have been great, particularly during periods of the life course that are most reproductively and immunologically demanding, mainly during childhood and peri-adolescent periods when the probability of helminthic infection is oftentimes highest, the neocortex is not yet fully developed, and reproductive costs increase exponentially (particularly in females).

If our conjectures are correct, then one of the tragic side effects of helminthic infection in hominins is that the physiological and immunological genotypes that we have inherited from our ancestors evolved in hosts with rich, diverse, and chronic helminth faunas. In present-day, highly sanitized environments, these genotypes may be highly maladaptive and may play a causative role in the emergence of a wide range of puzzling conditions, including asthma, diabetes, and acne.[101–104] These conditions are expressed early in life, and as our environments become even more sanitized, the age of onset of these conditions continues to decline.[105] It is possible that immune activity was "programmed" into a developmental schedule millions of years or hundreds of thousands of years ago in response to the age profile of helminthic exposure and defense. The human immunological system may be primed to respond to helminthes early in life, and in their absence, it triggers responses to innocuous substances that damage the host and become chronic. There is no *a priori* reason to believe why responses to innocuous substances should not be acute, and cease to cause morbidity as do responses to other substances, like man-made and natural vaccines. In the future it might be useful to systematically identify differences and similarities between the immunological mechanisms involved in helminth defense, childhood asthma, and childhood diabetes I and II, particularly in light of the exponential growth

of research on the relationship between immunological phenotypes that are expressed early in life and health outcomes later in life.[106,107]

Again, if our conjectures are correct, another tragic side effect of helminthic infection in hominins is that the worms that we harbor today have been with us for thousands if not millions of years. This does not mean that maintaining large worm burdens is not costly to hosts, but rather that the majority of humans have lost, and continue to lose, this host-pathogen arms race. It would be interesting to come up with an approximate number for the total volume of the helminth biomass that humans harbor in their intestines in the world today, to divide that number by the total volume of the biomass of human hosts, and then to do the same calculation for indigenous versus nonindigenous rural and urban groups in developed and underdeveloped countries. This would give us a better appreciation for the energy that helminthes are extracting from humans on a macroscale.

The evolutionary implications of this helminth-centered view of human biology in the twenty-first century are considerable. How much of the energy that humans now invest directly or indirectly in defense against helminthes could be diverted into other fitness- and health-enhancing physiological functions across the life course if helminthes could be eradicated from the planet? How would that affect global health patterns? In addition to the more obvious effects, such as healthier overall developmental trajectories for children, and a longer, healthier life span, the impact of helminth eradication on the rates of emergence of new viral and bacterial infections, and the rates of transmission of their older counterparts, could be significant. If in fact helminthes make hosts more susceptible to pathogenic viruses and bacteria through mechanisms that downregulate the cells involved in the Th1 response, then, on a global scale, eradication of helminthes would in effect lead to a reduction of the number of susceptibles to new and old viral and bacterial infections. Such effects could be modeled mathematically and compared to the effects of immunization campaigns. Second, we are not aware of research on the effects of helminth-induced immunosuppresion on viral and bacterial genetic mutation rates. It would be important to know whether pathogens mutate at faster rates in populations of hosts with a reduced battery of immune attacks than in populations with a more extensive armory. If viral and bacterial mutation rates are higher in populations with high worm burdens, then the eradication of helminthes not only would globally reduce infectious disease morbidity and mortality, but also would potentially slow down the emergence of new diseases for centuries to come.

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