

# PART IV

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## HELMINTH INFECTIONS AND GLOBAL HEALTH

Ensuring public health on a global scale is of benefit to all countries.

— MINISTERS OF FOREIGN AFFAIRS OF BRAZIL, FRANCE, INDONESIA,  
NORWAY, SENEGAL, SOUTH AFRICA, AND THAILAND.  
OSLO MINISTERIAL DECLARATION—GLOBAL HEALTH:  
A PRESSING FOREIGN POLICY ISSUE OF OUR TIME. (1)



Health is a precious human asset without which all other hopes for prosperity, learning, and liberty will be incomplete. (2)

Richard Horton

Complications of helminthic infections are serious, costly, predictable and preventable. (3)

John E. Fincham et al.

## HELMINTH INFECTIONS PROMOTE POVERTY WORLDWIDE

Humans in low-income countries are affected by a number of neglected tropical diseases, among which helminth infections in general are the most common. These helminth diseases include hookworm, ascariasis, schistosomiasis, leishmaniasis, trichuriasis, lymphatic filariasis, onchocerciasis, guinea worm (dracunculiasis), *Taenia solium* cysticercosis, and food-borne trematodiasis. Helminth infections produce a global burden of disease that exceeds better-known conditions, including malaria and tuberculosis. (4) Approximately one third of the almost three billion people that live on less than two US dollars per day in developing regions of sub-Saharan Africa, Asia, and the Americas are infected with one or more helminths. (5)

In low-income countries, these helminth infections are medically recognized but politically neglected diseases. In well-organized and wealthy societies of the world, helminth infections are probably limited to *Taenia* and *Toxocara* larval tissue infections transmitted from dogs and cats and may be termed medically neglected diseases. However, these helminth infections probably affect people in the rest of the world as well and increase the burden of helminth diseases among people in low-income countries.

Preschool and school-aged children (including adolescents) tend to harbour the greatest numbers of intestinal worms and schistosomes and, as a result, experience growth stunting and diminished physical fitness, as well as impaired memory and

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3. Fincham JE, Markus MB, Appleton CC, Evans AC, Arendse VJ, Dhansay MA, Schoeman S. Complications of worm infestation—serious, costly, predictable and preventable. *S Afr Med J* 1998;88:952-3.

4. Hotez PJ, Brindley PJ, Bethony JM, King CH, Pearce EJ, Jacobson J. Helminth infections: the great neglected tropical disease. *J Clin Invest* 2008;118:1311-21.

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cognition. (6) Worm infections cause about 200 million years of lost primary schooling. (7) Hookworm and schistosomiasis are also important diseases during pregnancy, causing reduced neonatal birthweight and increased maternal morbidity and mortality. (8) In the adult population, lymphatic filariasis, onchocerciasis, hookworm, and schistosomiasis are major determinants of reduced worker productivity. (9) Helminth infections translate into enormous poverty-promoting effects and represent a major reason why poor people and poor or low-income countries remain mired in a downward cycle of destitution. (4,10)

## HELMINTH INFECTIONS IMPAIR THE INNATE IMMUNE RESPONSE AND THE ADAPTIVE CELL-MEDIATED IMMUNE RESPONSE

The immune system functions properly when challenged by an infection if it successfully clears the infection and resumes a state of readiness to challenge a new infection. The analogy between the immune system and a fire brigade is widely used in immunological textbooks: like the immune system, the fire brigade functions properly when it puts out fires and resumes a state of readiness to fight a new fire. If the fire brigade is permanently occupied with limiting a fire that is impossible to put out and a new fire breaks out, the chances of successfully extinguishing the flames of the new fire are reduced. Similarly, a permanently ongoing immune response to a chronic infection will reduce the ability of the immune system to clear a new challenging infection.

Helminths are biologically the most advanced microorganisms infecting humans. These animal parasites have developed remarkable mechanisms to establish chronic infections in the host. To circumvent the host immune system, helminths may

- Camouflage their own antigens by coating themselves with host proteins
- Develop resistance by biochemical alterations of their surface coat
- Shed their antigenic coat
- Change their surface antigens by antigenic variation
- Develop a surrounding cyst to limit access to the immune response
- Modulate host immune responses in many different ways

When the helminth larvae pass the anatomical barriers and invade the tissues, they are first exposed to the innate immune system, which includes the complement proteins, the professional phagocytes, and the natural killer cells. If the helminth

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10. Eppig C, Fincher CL, Thorhill R. Parasite prevalence and the worldwide distribution of cognitive ability. *Proc R Soc* 2010;277:3801-8.

larvae overcome the innate immune response, they will be exposed to the adaptive immune response induced by the innate immune system.

### **Innate immune system evasion by helminth parasites**

Helminth parasites are very large microorganisms and phagocytes alone are not able to ingest them. Complement activation and C3b deposition on the surface of parasitic helminths should theoretically pose a threat to the helminth, but seem to be ineffective in protecting the host against helminth infection. (11–13)

As described earlier in this book, taeniid larvae impair the innate immune system in a number of ways. The larvae first impair monocyte precursor differentiation into immature dendritic cells (DC), rendering them unable to mature, and second, modulate sentinel DC maturation. Taeniid larvae also change macrophage behaviour in order to depress the lymphoreticular response.

### **Impaired activation of the adaptive cellular immune response by helminth parasites**

Most infections engage both the cell-mediated and the humoral aspects of immunity, and in many cases both are helpful in clearing and containing the pathogen. To use these aspects, the immune system must be able to orchestrate an adequate immune response by the different subsets of helper T cells (Th1, Th2, Th17, Tfh, and Treg). Antigen-presenting cells, such as dendritic cells (DC), produce different cytokines depending on the encountered pathogen and in this way direct the production of the different subsets of CD4 T cells. Additionally, there is a complex pattern of cross-regulation between Th1, Th2, Th17, and Treg cells. Interleukin (IL)-4 and IL-10, which are products of Th2 cells, can inhibit the development of Th1 cells by suppressing the production of IL-12 by DC. (14) In this way, a Th2 immune response suppresses the development of a Th1 immune response.

The regulatory T cells are a heterogeneous group of cells with different developmental origins. The natural regulatory T cells (nTreg) develop in the thymus, while the induced regulatory T cells (iTreg) arise in the periphery from naive CD4 T cells. A hallmark of both types of regulatory T cells is the expression of the transcription factor FoxP3, which when activated, prevents production of IL-2. nTreg can secrete IL-10 and transforming growth factor beta (TGF- $\beta$ ), which are cytokines that inhibit T cell proliferation and differentiation of DC. These cytokines inhibit the secretion of IL-12, thus impairing the ability to promote T cell activation and Th1 differentiation. (14) The essential purpose of Treg is to prevent overt reactions to self-antigens and to mediate adaptive responses during infection. (15)

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The Th1 immune response is especially important for fighting viruses and bacteria and those protozoa that survive inside macrophage intracellular vesicles. In the case of viruses, the Th1 response is generally involved in helping to activate the CD8 cytotoxic T cells that will recognize virus-infected cells and destroy them. In the case of mycobacteria, and of protozoa such as *Leishmania* and *Toxoplasma*, the role of Th1 cells is to activate macrophages to a degree that will destroy the invaders. (14)

Helminths are commonly described as masters of regulation of the host immune system. The sum effect of the regulatory activity is to create an anti-inflammatory environment in the host that favours helminth survival. (16) To achieve such a favourable environment, helminths use several different mechanisms.

When the human immune system encounters a helminth infection, DC induce Th2 cell or Treg cell responses or both. The induction of the Th2 response is important to expel intestinal helminths, but despite the response, total clearance of the parasites rarely occurs in humans. (17) The helminths evade and suppress the host immune response by exploiting the host's own system of immune regulation, and the induction of Treg responses is one of the most common mechanisms used to restrain immune responses against the parasite. (18) The canonical Th2 type immune response to helminths involves cytokines IL-3, IL-4, IL-5, IL-9, IL-10, and IL-13; antibody isotypes IgG1, IgG4, and IgE; and expanded populations of eosinophils, basophils, mast cells, and alternatively activated macrophages. (19)

Part of the Th2 response involves tissue repair and if the response is insufficiently counterbalanced by a regulatory response, pathological processes from excessive fibrosis and inflammation will result. Conversely, if the Treg response is too strong, the parasite burden will be enhanced and parasite-associated pathological processes will result. The best compromise for both host and helminth to coexist is a balanced Th2/Treg response. (18)

These are the general features of immune responses to helminth infections. However, it is most important to distinguish between *intestinal* helminth infection and *tissue* helminth infections. Even though the Th2 immune response is (usually) insufficient to clear an intestinal helminth infection, it is still the best option for expelling intestinal helminths. The Th2 immune response is, nonetheless, rather inefficient at combatting tissue helminth infections. The greatest immunological threat to helminths dwelling in the tissues would be a Th1 immune response. Tissue-dwelling helminths evade such a damaging immune response through a number of mechanisms. The most obvious mechanism is the cross-regulation of immune responses that suppress the Th1 response by inducing a Th2 immune response. Furthermore, tissue-dwelling helminths may impair Th1 immune responses in several ways.

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19. Allen JE, Maizels RM. Diversity and dialogue in immunity to helminths. *Nat Rev Immunol* 2011;11:375-88.

First, cysteine proteases secreted by helminths may act on the innate immune response and in this way prevent adaptive cellular immune responses. Exposure of immature DC to helminth tegumental antigens may fail to induce DC maturation or only partially induce DC maturation. (20,21) Hamilton et al. reported that treatment of DC with *Fasciola hepatica* tegumental antigen rendered the DC hyporesponsive to a range of Toll-like receptor (TLR) ligands with significant decreases in cytokine production (IL-12p70, IL-10, IL-6, tumour necrosis factor-alpha (TNF- $\alpha$ ), and nitrite) and co-stimulatory marker expression (CD80, CD86, and CD40). (22) Hamilton et al. therefore hypothesized that *F. hepatica* tegumental antigen maintains the DC in an immature state, impairing their function and ultimately modulating the development of adaptive T cell responses.

Second, tissue-dwelling helminths may act on the adaptive immune response by secreting cysteine proteinases that actively suppress Th1 immune responses. O'Neill et al. demonstrated that *F. hepatica* cathepsin L1 cysteine proteinase suppressed the onset of protective Th1 immune responses. (23) In this way, the immune system is made more permissive to drive the development of Th2 immune responses. (24) Similarly, *Leishmania mexicana* cathepsin B cysteine proteinase prevents the development of Th1 responses. (25) *Schistosoma mansoni* may provide another example of how cysteine proteinases suppress Th1 responses. (26) The mechanisms include degradation of pattern recognition receptors such as the Toll-like receptor 3 and specific proteolytic degradation of nuclear factor kappa B (NF $\kappa$ B). (27)

Pathogen-derived cysteine proteinases may also act in many other ways in the evasion, suppression, and modulation of the host mammalian immune system and have been extensively reviewed by Donnelly, Dalton, and Robinson. (28) For extensive reviews of the immune responses to helminth infections, I suggest those by Everts, Smits, Hokke, and Yazdanbakhsh and by Allen and Maizels. (18,19)

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Isolated helminth infections usually cause asymptomatic or subclinical chronic infection. Generally, infections are most easily handled one at a time by the immune system and in the laboratory, but in nature, co-infections are the norm. The most important threat to human health induced by helminth infections is probably not the effect of the infection itself, but the effects of co-infections with other pathogens. Helminth-induced impairment of the innate and adaptive immune responses, in other words, a functional immunodeficiency, will result in an impaired ability to clear a number of viral, bacterial, and protozoan infections. It is of utmost importance to understand this relationship to successfully combat the enormous burden of disease in areas where helminth infections are endemic.

## HELMINTH INFECTION EPIDEMIOLOGY AND DISEASE BURDEN

The lack of quality data on the prevalence of helminth infection makes it just as difficult to estimate today as it was in 1947 when Norman Stoll published his paper entitled, “This Wormy World.” (29) The precise morbidity and mortality caused by helminth infections will therefore never be known. (30) The risk of contracting helminth diseases is unevenly distributed around the world and increases dramatically with poor water, sanitation, and hygiene standards in communities. Accordingly, it has been estimated that 4.2 billion people are at risk of contracting soil-transmitted helminth diseases. (31) Helminth infections probably affect 25% of the world’s population. The most common helminthiasis are intestinal helminth infections, followed by schistosomiasis and lymphatic filariasis. Individuals infected by helminths are often chronically infected with several different helminth species and these individuals mostly live in sub-Saharan Africa, Southeast Asia, and Central America.

Prevalence alone is an insufficient measure of the epidemiological situation for helminth infections because morbidity is associated with the number of worms infecting the host (that is, the worm burden) rather than the presence or absence of infection. The worm burden, also referred to as the “intensity of infection,” is commonly measured by the number of eggs per gram of faeces for intestinal helminths. (32) From this measurement and its association with morbidity, individuals are classified by the World Health Organization (WHO) into categories of light, moderate, and heavy infection. (33) However, because egg excretion status alone may be insufficient

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to estimate the prevalence of helminth infection, disease-related immunological variables should also be applied. (34,35)

Furthermore, there is widespread heterogeneity in the worm burden among different individuals infected with the same helminth. A small proportion of hosts are rapidly, frequently, and/or heavily infected. (36) At a given time, 70% of the worm burden may occur in 15% of individuals. (37) High prevalences of mixed infections occur with different helminths. Epidemiological surveys indicate positive associations between schistosomes and soil-transmitted helminths, which appear to depend on the number of different helminth species present and on the intensity of infection in each individual. (38) The bases of heterogeneity and predisposition to helminth infection have yet to be fully elucidated. (4)

The intensity of helminth infections determines the resulting morbidity when these infections occur alone. Additionally, the degree of manipulation of the immune system induced by helminth infections determines morbidity in cases in which viral, bacterial, and intracellular protozoan infections challenge a person who is already infected with helminths. The more impaired an individual has become in executing adequate innate and adaptive immune responses, the more serious the consequences from contracting viral, bacterial, and intracellular protozoan pathogens.

## HELMINTH INFECTIONS PROMOTE INCREASED MORBIDITY AND MORTALITY FROM CHALLENGING VIRAL, BACTERIAL, AND INTRACELLULAR PROTOZOAN INFECTIONS

Increased morbidity and mortality due to helminth-induced cellular immunodeficiency principally applies to all viral, bacterial, and intracellular protozoan pathogens. Among the virus infections, HIV/AIDS is the leading cause of death in regions of the world afflicted with politically and economically neglected helminth infections. (39) In 2011, there were 1.7 million AIDS-related deaths according to UNAIDS.

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Tuberculosis is the most important bacterial cause of death and 1.4 million people are estimated to have died from it in 2011. (40) Malaria is the most important protozoan cause of death, estimated to have caused 1.2 million deaths in 2010. (41) I will therefore use these three infections as examples to illustrate the clinical effects of helminth-induced cellular immunodeficiency during infections.

The following probable assumptions may be induced from the knowledge about helminth-induced Th1 cell immunodeficiency:

Helminth effect 1: Helminth-infected patients have increased susceptibility to HIV infection, tuberculosis, and malaria.

Helminth effect 2: Helminth-infected patients develop more serious infection from HIV infection, tuberculosis, and malaria.

Helminth effect 3: Helminth-infected patients with HIV infection, tuberculosis, and malaria are more contagious than helminth-free patients.

Helminth effect 4: Helminth-infected patients have decreased clinical response to antibiotics against HIV infection, tuberculosis, and malaria.

Helminth effect 5: Resistance to antibiotics against HIV, tuberculosis, and malaria develop more easily in patients with helminth co-infection.

Helminth effect 6: Helminth-infected patients have an impaired response to vaccines dependent on memory CD8 T cells and memory CD4 T cells.

Helminth effect 7: Helminth-infected pregnant women give birth to babies with postnatal Th1 cell immunodeficiency.

Helminth effect 8: Helminth-infected populations increase the risk of emerging zoonotic diseases.

Assumptions along these lines are by no means new, but they have been largely ignored in the fight against HIV/AIDS, tuberculosis, and malaria in sub-Saharan Africa and other regions of the world that are heavily afflicted with helminth infections. As early as 1989, Kilian and Nielsen documented an impaired cellular immune response to Bacille Calmette-Guérin (BCG) vaccination in patients with onchocerciasis. (42) In 1993, Actor et al. reported delayed viral clearance in mice co-infected with *Schistosoma mansoni*. (43) Clerici and Shearer presented evidence

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