

## Parasites - the uninvited dinner guests

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**I can swim, crawl or fly - But occupy neither sea, earth nor sky  
I am a most uninvited company - Taking without giving a thing  
What am I?**



Helminth worms: *Ascaris lumbricoides*, which had been passed by a child in Kenya, Africa.  
©CDC/ Henry Bishop

We think of living beings as existing in either aquatic or terrestrial environments, but there's a third category: the bodies of other organisms, occupied by life forms termed parasites. From a biological standpoint, parasitism seems to be a fruitful lifestyle; more than half of all species are parasitic at some point in their lifetime. Every free-living, non-parasitic species of plant and animal has its own species-specific parasites but also shares parasites with other species. We, as non-parasites - at least in the biological sense of the word-, are outnumbered!

The word "parasite" has undergone major transformation since its origins as a term for a dinner guest (*parasitos*) in ancient Greece, where it eventually developed into a derogatory term for one who earned his meal by humoring his host. Our modern "uninvited guests" are classically defined as organisms that live on, off or at the expense of another (the host): the parasite benefits, the host is harmed -and not at all amused. However, "benefit" and "harm" are difficult to measure, and predators or micro-predators such as mosquitoes may also fall under this definition. Efforts to fine-tune the definition of parasitism have added notions such as

- the parasite is physiologically or metabolically dependent upon its host
- the reproductive potential of the parasite is greater than that of their hosts (to differentiate from predators) and
- heavily infected hosts are killed

Although they fit under both the classical and the extended definition of parasites, bacteria and viruses have been excluded from the science of parasitology, which concerns itself exclusively with eukaryotic parasites. Three very diverse groups fall under the umbrella "parasite", namely the single-celled protozoa, helminths (worms) and ectoparasites (arthropods).

Parasites are not only diverse, their eukaryotic genomes mean they are inherently more complex than bacteria or viruses. There is, of course, a wide range of complexity among parasites. The protozoan *Giardia lamblia*, for example, is a genetic minimalist, with fewer and simpler genetic components than most eukaryotes. It has a simple life cycle, existing either as hardy and highly infectious cysts in water or, after ingestion, swimming and feeding trophozoites in the gut of the host...just one host. In contrast, many parasites have adopted life styles involving multiple mor-



A flea a common ectoparasite and an important vector for the bacterium *Yersinia pestis*.  
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phological forms in multiple hosts, with intermediate hosts required for some parts of the life cycle, definitive hosts in which sexual maturity is achieved, vectors for transmission (can be intermediate or definitive hosts) and sometimes an optional paratenic (transport) host, in which the parasite undergoes no morphological change. This huge complexity makes the study of parasites an enormous challenge, complicating the development of new drugs, vaccines and other control measures. The stronghold that parasites and vectors have within their environments as well as the immense socioeconomic problems in areas where parasites are most common only make matters worse.

## The human toll of parasitic diseases



A protozoan parasite: Giardia lamblia ©CDC/ Janice Carr

In developed countries the control of insect vector populations, unlimited access to safe water supplies and availability of effective drugs have largely eliminated parasites as a public health concern. Nevertheless, they are still present, infecting hikers who drink carelessly from mountain streams, swimmers at the local pool, small children in daycare. An estimated 30-80% of children in Western Europe and North America are infected with pinworm (*Enterobius vermicularis*), which infects the gut and causes extensive itching as the females lay their eggs in the perianal area. Sexually transmitted *Trichomonas vaginalis*, the most common human protozoan infection in the industrialized world (annual infections in the US approach 8 million), causes a variety of uncomfortable symptoms in infected women and is associated

with potentially serious complications such as preterm birth and acquisition of HIV. And according to the Centers for Disease Control and Prevention (CDC), *Giardia* and *Cryptosporidium* are the cause of gastrointestinal distress in some 2 million and 300,000 individuals, respectively, in the US every year. Then there are the travelers who return from their exotic vacation with undesired souvenirs, perhaps some *Plasmodium* or *Leishmania* to excite the local infectious diseases specialist. And global warming is threatening to increase the threat of “tropical” parasitic infections in temperate climates, as increased temperatures enable the spread of parasites and vectors into new areas (see Perspective: [Coming to a Boil: Climate change encourages the expansion of infectious disease](#)).

Nevertheless, the toll of parasite infection is by far the highest in tropical and subtropical developing countries. Malaria kills approximately 1 million people each year, making it the deadliest of parasitic diseases, but *Plasmodium falciparum* is only one of a host of parasites that wreak havoc on the human populations of many developing countries. The World Health Organization (WHO) has compiled a list of 15 Neglected Tropical Diseases (NTDs), 9 of which are parasitic. They are termed “neglected” because they endure only in the poorest areas, those with poor sanitation and limited access to safe water and health care. Compared to HIV/AIDS, tuberculosis and malaria, these diseases are also “neglected” in the sense that little money goes into research. An estimated 1 billion people, one-sixth of the world population, are affected by one or more NTDs, with an annual mortality of 500,000 and an even larger burden of morbidity (DALY= disability-adjusted life years: Measure of morbidity and socio-economic impact: missed work/school, impairment of growth and cognitive ability in children...).

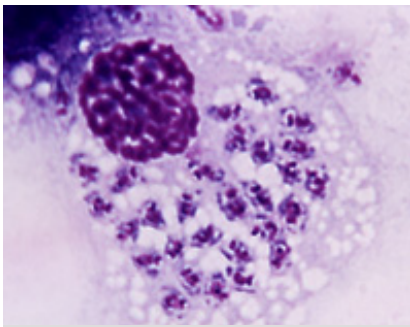
The Parasitic Neglected Tropical Diseases				
Disease	Causative agent	vector	distribution	No. Infected
American trypanosomiasis (Chagas disease)	<i>Trypanosoma cruzi</i> (flagellate protozoan)	“kissing bug”	South America, Central America, Mexico	9 million <sup>d)</sup>
Dracunculiasis (Guinea-worm disease)	<i>Dracunculus medinensis</i> (nematode)		Sub-Saharan Africa	~25,000 <sup>e)</sup>
Fascioliasis	trematodes <i>Fasciola hepatica</i> (common liver fluke) and <i>Fasciola gigantica</i>		Worldwide	2.4 million <sup>d)</sup>
African trypanosomiasis (Sleeping sickness)	<i>Trypanosoma brucei</i> (flagellate protozoan)	tsetse fly	Sub-Saharan Africa	50,000–70,000 <sup>e)</sup>
Leishmaniasis	genus <i>Leishmania</i> (protozoa)	sand fly	88 countries on 4 continents	350 million <sup>d)</sup>
Lymphatic filariasis (elephantiasis)	Filarial nematodes: <i>Wuchereria bancrofti</i>	mosquitoes	S-S Africa, Asia, Latin America, West Pacific	107 million <sup>d)</sup>
	<i>Brugia malayi</i> and <i>Brugia timori</i>		India, Indonesia, Philippines, S.E. Asia, S. Ch	13 million
Onchocerciasis <sup>a)</sup>	<i>Onchocerca volvulus</i> (nematode)	black fly	Africa (99% of cases) <sup>d)</sup> ; Yemen, Latin America	17.5 million <sup>c)</sup>
Schistosomiasis <sup>b)</sup>	<i>Schistosoma</i> sp. (flukes)		S-S Africa (80%); Asia, Latin America	200 million <sup>d)</sup>
Soil-transmitted helminthiasis	<i>Ascaris lumbricoides</i> , <i>Trichuris trichiura</i> , hookworms ( <i>Ancylostoma duodenale</i> and <i>Necator americanus</i> )		Worldwide, developing countries; most in S-S Africa, Americas, China, E. Asia	<i>A. lumbricoides</i> 1 billion <sup>d)</sup> <i>T. trichiura</i> 795 million hookworms 740 million

a) world's second leading infectious cause of blindness

b) second only to malaria in public health impact and socioeconomic devastation of a parasitic disease

c) Crompton, D.W.T. How much human helminthiasis is there in the world? (1999) *Journal of Parasitology* 85: 379–403 (S-S Africa: sub-saharan Africa; C.S. America: Central and South America)

d) WHO; [http://www.who.int/neglected\\_diseases/diseases/en/](http://www.who.int/neglected_diseases/diseases/en/)



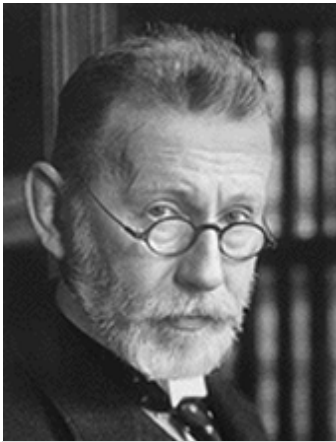
Trypanosoma cruzi, a protozoan parasite, causing "Chagas disease", during its leishmanial stage of development. © CDC/ Dr. A.J. Sulzer

Most NTDs could be prevented, and Guinea worm disease is on the way to becoming the first parasitic disease to be eradicated - without a vaccine or drug. Internationally supported efforts (CDC, WHO, UNICEF, Carter Center) to identify all infections and modify behavior, such as filtering water and preventing reinfection of water, have proven very successful: Guinea worm disease, as e.g. infection with *Dracunculus medinensis*) affected some 3.5 million people in more than 20 nations in Asia and Africa in the mid-1980s. Today it is endemic in only 5 countries in Sub-Saharan Africa. The infection is rather easy to combat, as there is no animal or environmental reservoir of *D. medinensis*: it is only necessary to break the chain of human infection. Tackling other parasites is more difficult; attention given to prevention measures may not be enough, effective drugs are also necessary.

The very nature of a neglected tropical disease makes it unattractive for pharmaceutical companies; there isn't much money to be made with drugs heading only to developing countries. Between 1975 and 1999, less than 1% of the 1393 newly registered drugs were for tropical diseases. In the United States, the government has created incentives for companies to invest in drugs and vaccines for neglected tropical diseases. On an international level, the Drugs for Neglected Diseases Initiative (DNDi), a non-profit drug development organization, is organizing and supporting research efforts, particularly in the developing world, to find drugs for neglected diseases. DNDi is currently focusing on human African trypanosomiasis (Sleeping Sickness), leishmaniasis and Chagas disease (American trypanosomiasis). In 2007, they announced the development of a new drug to treat malaria, ASAQ, which fuses two existing treatments into one.

Key to the development of new drugs and vaccines is basic knowledge about how the human immune system responds to parasite infection and how the parasite thwarts the response. Almost all major parasite infections are chronic; parasites need time in the host to complete their complex development, reproduce sexually and enable vector transmission. Despite their exquisitely developed immune system, humans and other host organisms are frequently unable to rid themselves of the parasite. It's not that there is no immune response to parasites: prevalence of infection with some parasites decreases with age (indicating development of immunity), immunity has been demonstrated in animal models, and immunocompromised individuals are very susceptible to infection. However, for the thousands of years that humans and parasites have been -quite literally- living together and co-evolving, parasites have been searching for the right balance between hiding from and suppressing the immune system without killing the host or making it susceptible to another deadly infection.

## Masters of hiding, masters of control



Paul Ehrlich

The concept of immune evasion began with the demonstration of antigenic variation in African trypanosomes by Paul Ehrlich (1854–1915; Nobel Prize, 1908). Trypanosomes are covered by one glycoprotein that induces immunodominant antibody responses – that is, one glycoprotein at a time.

They are able to switch the glycoprotein regularly, a process involving up to 2000 genes (10% of its DNA!), and thereby escape antibody detection. *Plasmodium* and *Giardia lamblia* also use antigenic variation to trick the immune system, and this is only one of the games that parasites play. Immune evasion by parasites is ubiquitous, and many different mechanisms are involved.

### Parasites undercover – immune evasion strategies

#### Antigenic variation

**Anatomical seclusion/immunologically privileged site.** *Trichinella spiralis* in muscle cells become surrounded by a host capsule. *Ascaris lumbricoides* living in the lumen of the intestine provokes little or no immune response.

**Intracellular localization.** Intracellular protozoa such as *Toxoplasma gondii* and *Plasmodium falciparum* undermine host cell processes to avoid detection yet obtain all the “necessities of life”.

**Coating with host proteins.** The tegument of *Schistosoma mansoni* is able to incorporate host blood antigens, making it appear to the host as “self”.

**Shedding of surface antigens.** *Entamoeba histolytica* sheds lectins to avoid detection (recent literature: Baxt, LA, Baker, RP, Singh, U and Urban, S. An *Entamoeba histolytica* rhomboid protease with atypical specificity cleaves a surface lectin involved in phagocytosis and immune evasion. *Genes Dev.* (2008) 22: 1636–1646).

When they're not successful at hiding, parasites can turn to manipulation/suppression of the immune system. Individuals with chronic parasite infections often have high immunoglobulin levels and depressed cellular immunity. And despite their complex and diverse lifestyles, helminths induce remarkably similar immune responses, including Th2-like production of cytokines (including immunosuppressive IL-10) and a strong IgE response. While immunosuppression may also help the host by reducing immunopathology, parasites clearly have developed an arsenal of weapons to directly or indirectly subvert host defenses for their own benefit.

## Parasites taking the controls...a few examples

**Interference with antigen processing.** *Brugia malayi* and other nematodes secrete cystatins (cysteine protease inhibitors) that interfere with presentation via MHC class II. The protozoa *Cryptosporidium parvum* and *Toxoplasma gondii* modulate genes involved in MHC presentation upon infection.

**Modulation of antigen-processing cells.** Prostaglandins and other helminth-encoded products affect APC activity (cytokine secretion, migration...). *T. gondii* uses dendritic cells as a “Trojan horse” to spread through the host.

**Secretion of cytokines/cytokine-like molecules.** *B. malayi* expresses two homologues of TGF- $\beta$ , a cytokine involved in downregulation of immune responses.

**Meddling with effector mechanisms.** Interference with leukocyte migration, chemokine attraction, complement, release of effector proteases/reactive nitrogen and oxygen intermediates; polyclonal/non-specific production of antibodies; killing of leukocytes; the list goes on... (see references below for more information)

Eukaryotic parasites are complex organisms, and our understanding of how they survive in the human host have remained largely descriptive, with advances lagging behind those in bacteriology and virology. However, with the recent publication of a number of complete eukaryotic parasite genomes and advances in the genetic tools used to probe them, the molecular mechanisms parasites use to bypass our defenses and even hijack our cellular processes are starting to be revealed. “We are just scratching the surface of the complexity of eukaryotic parasites,” says researcher Dominique Soldati-Favre, featured in this month’s portrait series: [Have you ever met...?](#) “

The recent identification of ROP18 as a virulence factor in *Toxoplasma gondii* (Saeij et al. and Taylor et al. in *Science*, 2006) is just the tip of the iceberg. With new technologies we can look at the parasite genome-wide, and the next 5 years are promising to bloom with knowledge of the molecular mechanisms parasites use to subvert the immune system”. This information will provide us with potential targets for the development of new drugs and vaccines against eukaryotic parasites that continue to exact an enormous toll, especially in the developing world, in terms of both human suffering and economic development.

The Good, the Bad and the Ugly. The latter two can certainly be used to describe parasites, but can our uninvited guests also be good? Read more in the next Perspective.

## References:

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Plattner, F. and Soldati-Favre, D. Hijacking of host cellular functions by the Apicomplexa. *Annu. Rev. Microbiol.* (2008) 62: 471–487.

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For a list of the completed eukaryotic genomes (parasite and non-parasite), see:  
[http://en.wikipedia.org/wiki/List\\_of\\_sequenced\\_eukaryotic\\_genomes](http://en.wikipedia.org/wiki/List_of_sequenced_eukaryotic_genomes)

## For more information:

Centers for Disease Control & Prevention (CDC), National Center for Infectious Diseases, Division of Parasitic Diseases, DPDx (<http://www.dpd.cdc.gov/dpdx/Default.htm>)

Drugs for Neglected Diseases initiative ([www.dndi.org/](http://www.dndi.org/))

World Health Organization, Control of Neglected Tropical Diseases  
([http://www.who.int/neglected\\_diseases/en/](http://www.who.int/neglected_diseases/en/))