

1 General Aspects of Parasite Biology

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1.1 Introduction to Parasitology and Its Terminology

1.1.1 Parasites

Parasites are organisms which live in or on another organism, drawing sustenance from the host and causing it harm. These include animals, plants, fungi, bacteria, and viruses, which live as host-dependent guests. Parasitism is one of the most successful and widespread ways of life. Some authors estimate that more than 50% of all eukaryotic organisms are parasitic, or have at least one parasitic phase during their life cycle. There is no complete biodiversity inventory to verify this assumption; it does stand to reason, however, given the fact that parasites live in or on almost every multicellular animal, and many host species are infected with several parasite species specifically adapted to them. Some of the most important human parasites are listed in Table 1.1.

The term parasite originated in Ancient Greece. It is derived from the Greek word “parasitos” (Greek *pará* = on, at, beside; *sítos* = food). The name parasite was first used to describe the officials who participated in sacrificial meals on behalf of the general public and wined and dined at public expense. It was later applied to minions who ingratiated themselves with the rich, paying them compliments and practicing buffoonery to gain entry to banquets where they would snatch some food.

Table 1.1 Occurrence and distribution of the more common human parasites.

Parasite	Infected people (in millions)	Distribution
<i>Giardia lamblia</i>	>200	Worldwide
<i>Trichomonas vaginalis</i>	173	Worldwide
<i>Entamoeba histolytica</i>	500*	Worldwide in warm climates
<i>Trypanosoma brucei</i>	0.01	Sub-Saharan Africa (“Tsetse Belt”)
<i>Trypanosoma cruzi</i>	7	Central and South America
<i>Leishmania</i> spp.	2	Near + Middle East, Asia, Africa, Central and South America
<i>Toxoplasma gondii</i>	1500	Worldwide
<i>Plasmodium</i> spp.	>200	Africa, Asia, Central and South America
<i>Paragonimus</i> sp.	20	Africa, Asia, South America
<i>Schistosoma</i> sp.	>200	Asia, Africa, South America
<i>Hymenolepis nana</i>	75	worldwide
<i>Taenia saginata</i>	77	Worldwide
<i>Trichuris trichiura</i>	902	Worldwide in warm climates
<i>Strongyloides stercoralis</i>	70	Worldwide
<i>Enterobius vermicularis</i>	200	Worldwide
<i>Ascaris lumbricoides</i>	1273	Worldwide
<i>Ancylostoma duodenale</i> and <i>Necator americanus</i>	900	Worldwide in warm climates
<i>Onchocerca volvulus</i>	17	Sub-Saharan Africa, Central and South America
<i>Wuchereria bancrofti</i>	107	Worldwide in the tropics

Source: Compiled from various authors.

*many of those asymptomatic or infected with the morphologically identical *Entamoeba dispar*.

The result was a character figure, a type of Harlequin, who had a fixed role to play in the Greek comedy of classical antiquity (Figure 1.1). Later, “parasitus” also became an integral part of social life in Roman antiquity. It also reappeared in European theater in pieces such as Friedrich Schiller’s “Der Parasit.” In the seventeenth century, botanists were already describing parasitic plants such as mistletoe as parasites; in his 1735 standard work “Systema naturae,” Linnaeus first used the term “specie parasitica” for tapeworms in its modern biological sense.

The delimitation of the term “parasite” to organisms which profit from a **heterospecific** host is very important for the definition itself. Interactions between individuals of the same species are thus excluded, even if the benefits of such interactions are very often unequally distributed in the colonies of social insects and naked mole rats, for instance, or in human societies. As a result, the interaction between parents and their offspring does not fall under this category, although the direct or indirect manner in which the offspring feed from their parent organism can at times be reminiscent of parasitism.



Figure 1.1 Parasitos mask, a miniature of a theater mask of Greek comedy; terracotta, around 100 B.C. (From Myrine (Asia Minor); antiquities collection of the Berlin State Museums. Image: Courtesy of Thomas Schmid-Dankward.)

The principle of one side (the parasite) taking advantage of the other (the host) applies to viruses, all pathogenic microorganisms, and multicellular parasites alike. This is why we often find that no clear distinction is made between prokaryotic and eukaryotic parasites. With regard to *parasites*, we usually do not differentiate between viruses, bacteria, and fungi on the one hand and animal parasites on the other; we tend to see only the common parasitic lifestyle. Even molecules to which a function in the organism cannot be assigned are sometimes described as parasitic, such as prions, for example, the causative agent of spongiform encephalopathy, or apparently functionless “selfish” DNA plasmids that are present in the genome of many plants. Many biologists are of the opinion that only parasitic protozoa, parasitic worms (helminths), and parasitic arthropods are parasites in the strict sense of the term. Parasitology, as a field, is concerned only with those groups, while viruses, bacteria, fungi, and parasitic plants are dealt with by other disciplines. This restriction clearly hampers cooperation with other disciplines, something that seems antiquated in today’s modern biology, where all of life’s processes are traced back to DNA; it is gratifying that the boundaries have relaxed in recent years. However, eukaryotic parasites are distinguished from viruses and bacteria by their comparatively higher complexity, which implies slower reproduction and less genetic flexibility. These traits typically drive eukaryotic parasites to establish long-standing connections with their hosts, using strategies different from the “hit-and-run” strategies used by many viruses and bacteria. For these reasons, and for the sake of clarity and tradition, only parasites in the stricter sense of the term, that is, parasitic protozoa, helminths, and parasitic arthropods are dealt with in this book.

1.1.2

Types of Interactions Between Different Species

The coexistence of different species of organisms involves interactions among them that take many different forms in which the benefits and costs are often very unevenly distributed. Both partners benefit from mutualistic relationships, while in antagonistic relationships the advantage lies with only one side. However, a direct relationship between two species is seldom completely neutral. Different types of interactions are not always easy to distinguish, such that transitions between them are often fluid and the differences subtle. The spectrum of the partnerships between different organisms can be best illustrated by the use of concrete examples.

1.1.2.1 Mutualistic Relationships

If different partners rely on their coexistence and are limited in their viability or even nonviable when separated, this close association is described as a **sympiosis** (Greek: *sym* = together, *bios* = life). For example, Lichens – a combination of fungi and photosynthetically active algae – can only colonize completely new habitats in this combined form. Another example is the partnership of termites with cellulose-digesting protozoa, which live in the intestinal blind sacs of the hosts. The metabolites of the protozoa complement the hosts' rather unbalanced diet.

When the two partners benefit from coexistence without losing the ability to live independently, it is known as **mutualism**. A close mutualistic relationship exists between clown fish (anemone fish) and sea anemones: the fish can gain protection from predators by snuggling into the tentacles of the sea anemones without being attacked by the latter's poisonous stinging cells (Figure 1.2) and always returns to the anemone when danger threatens. The sea anemone benefits in turn

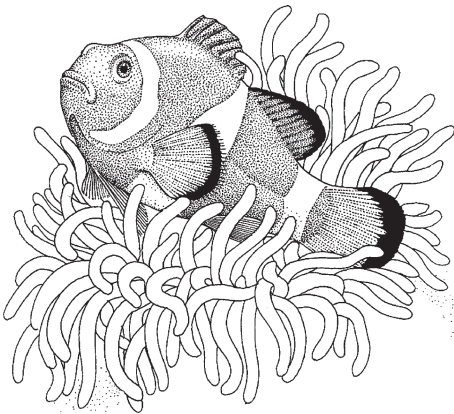


Figure 1.2 A clown fish in the tentacles of a sea anemone. The partners form a mutualistic symbiosis, but they can also survive independently. (Image: Richard Orr, courtesy of Random House Publishers, Munich.)

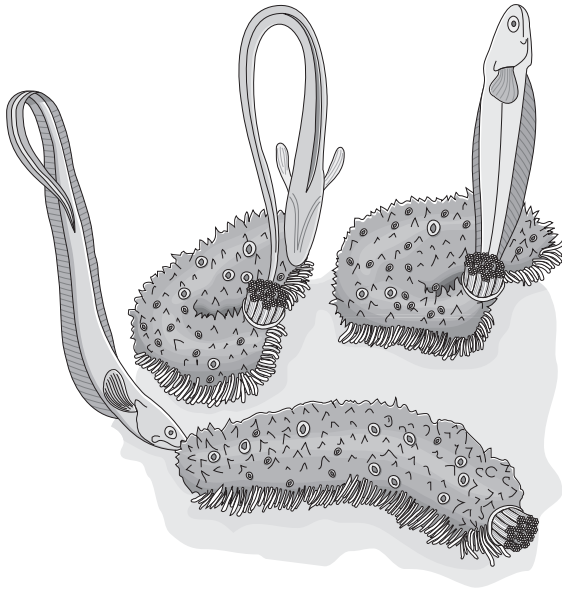


Figure 1.3 The pearlfish *Carapus* (syn. *Fierasfer*) *acus* lives in the water lungs of sea cucumbers. (Edited from Oche G. (1966) "The World of Parasites", Springer-Verlag Heidelberg.)

from the food remnants of the fish. Another example of a less intimate mutualistic association is the interaction between Cape buffalo and the cattle egret. While grazing, a buffalo flushes out insects, which are then snapped up by the egrets – and the danger-sensitive birds warn the buffalo by flying up when they spot big cats approaching.

Commensalism describes a feeding relationship, in which one partner benefits without providing any reciprocal benefits nor imposing any cost to the other. The commensal draws sustenance from the host's waste materials or from the components of the host's food, which are of no value to it. The flagellates that reside in the anal canals of arthropods provide an example, because these are areas of the digestive system where no more food absorption takes place.

However, there are symbiotic relationships in which a host is merely used as a living place. This involves organisms settling on the external surfaces of a different species (e.g., barnacles on crabs and shellfish), or even inside the host's body. One example of this is the pearlfish, a member of the cod family, which can grow to a length of approximately 20 cm. The fish lives in the water lungs of sea cucumbers into which it skillfully wriggles, pointed tail first (Figure 1.3). Pearlfish only leave their hosts to forage and reproduce.

1.1.2.2 Antagonistic Relationships

When a guest organism extracts nutrients from its host – and the host incurs a cost from the relationship – it is known as **parasitism**. Parasites can also cause damaging effects such as injury, inflammation, toxic metabolite, and other factors,



Figure 1.4 Coexistence of a typical parasite with its host. Tapeworms draw nourishment from their host and exploit the host in the long term – they are, however, only moderately pathogenic. (De bouche à Oreille by Claude Serre © Editions Glénat 2016)

and result in reduced evolutionary fitness of the host, even if the effects are only slight. Adult tapeworms may be regarded as typical examples here: they absorb nutrients from the digested food in the small intestine of the host, thereby harming the host, but do not attack its tissues. The host is thus weakened a little, but not killed, and the parasite lives of the interest without touching its capital. Claude Serre expresses all these qualities very aptly in his cartoon (Figure 1.4). Parasites are usually smaller and more numerous than their host, whereas predators are larger and less numerous than their prey. When one parasite settles on another, we call this **hyperparasitism**. *Nosema monorchis*, for example, a single-cell organism of the phylum Microspora, parasitizes the digenean *Monorchis parvus*, which is itself a parasite of fish.

We usually expect an intimate, physical relationship between parasite and host. Intimate contact like this exists in endoparasitism and (in many cases) ectoparasitism. There are also forms of parasitism in which the physical contact between the partners is less intimate, where the parasite does not exist as a pathogen, but exploits the host in other ways. The exploitation of interactions between members of social organisms is defined as **social parasitism**. In the case of social insects such as ants, the interactions of a host species are exploited by a parasitic species. The spectrum of social parasitism ranges from food theft to slavery and the targeted assassination of the queen, which is then replaced by the queen of a parasitic species. One specific form of social parasitism is the exploitation of a different species to rear one's own offspring, which is known as **brood parasitism**. A well-known representative of the brood parasites is the



Figure 1.5 Brood parasitism: A young cuckoo is fed by a warbler. (Image: Courtesy of Oldrich Mikulica.)

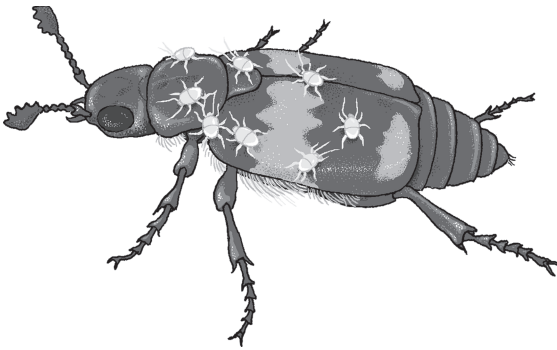


Figure 1.6 Phoresy: Mites latch on to a sexton beetle, “hitching a ride” to the nearest carrion. (Drawing from a photo by Frank Köhler.)

cuckoo (*Cuculus canorus*). The female of the species lays its eggs in the nests of smaller songbirds to have them raise its young ones (Figure 1.5). The cuckoo bee’s behavior is very similar. Cuckoo bees account for 125 of a total of 547 species of bees in Germany – a fact that says much for the success of this form of parasitism. Not only food but also functions such as transportation can be exploited by parasites. For instance, some mites and certain nematodes latch on to insects for transportation. In this type of parasitism, **phoresy**, the carriers are referred to as transport hosts (Figure 1.6).

Parasitoidism occurs when the death of the host is almost inevitable following parasitic exploitation. One typical example of this involves ichneumon wasps, which lay their eggs on caterpillars. When the young wasps hatch, they feed on the host’s tissues (Figure 1.7). The parasitic wasp larvae first devour the body fat, and then eat the muscle tissue and finally kill their hosts by consuming the neural

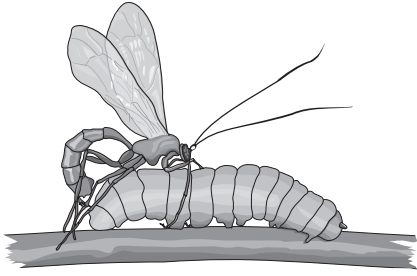


Figure 1.7 Parasitoidism: A parasitic wasp of the genus *Ichneumon* lays its eggs in a caterpillar. (From a photo in “The Animal Kingdom,” courtesy of Marshall Cavendish Books Ltd.)

tissue. The larvae finally break out of the caterpillar and pupate. A parasitoid like this attacks the capital, rather than living of the interest. However, it does exploit the host for a relatively long period of time and only kills it when the parasitoid is finished with it.

The interaction between parasitoids and their host shows some similarities to **predator–prey relationships**, for example, between a lion and wildebeest (Figure 1.8). However, whereas the parasitoid only kills its host after eating most of it, the prey is immediately killed by the predator and then eaten. In addition, predators are typically larger than their prey, and consume more than one prey in their lifetime, two features that separate them from parasites.



Figure 1.8 Predator–prey relationship: A lion attacks a wildebeest. (Image: Ingo Gerlach, www.tierphoto.de.)

1.1.3

Different Forms of Parasitism

Organisms, which can live as parasites, but are not necessarily dependent on the parasitic mode of life represent **facultative parasites**. One example is the bloodsucking kissing bug, *Triatoma infestans*. It can also live as a predator by sucking out the hemolymph of smaller insects. **Obligate parasites** have no alternative other than their way of life. In the case of some organisms, only one sex lives parasitically. In mosquitoes, for instance, only the females need a meal of blood to produce eggs; the male feeds on the sap of plants. **Permanent parasites** are parasitic in all stages of their development, while **temporary parasites** spend only certain phases of their life in a host.

An **ectoparasite** attaches to the skin or other external surfaces (e.g., the gills) of its host, where it subsists on hair or feathers, feeds on skin, or sucks blood or tissue fluid substance. Included among ectoparasites are numerous **temporary parasites** (sometimes called micropredators), which only seek out their hosts to feed (e.g., bloodsucking mosquitoes), and many **permanent parasites** that remain in constant contact with their hosts (e.g., lice, or the monogeneans parasitic on fish). Parasites that live inside their hosts are known as **endoparasites**. The worms living in the gut lumen of vertebrates illustrate the simplest form of endoparasitism. The difference between rotting substances in the outside world and the contents of the digestive tract is not particularly significant and it is relatively common to find organisms that have adapted to endoparasitism of this type. One example of these residents of the gut lumen is the nematode *Strongyloides stercoralis*, the life cycle of which illustrates that it has the option of either the free-living or the parasitic modes of life. Other endoparasites either live in organs (such as the great liver fluke *Fasciola hepatica*), live freely in the blood of their hosts (such as *Trypanosoma brucei*), or inhabit body tissue (such as the filarial nematode *Onchocerca volvulus*). **Intracellular parasites** induce very pronounced changes in the host cell: using these highly specific mechanisms, these parasites (e.g., *Leishmania* and *Plasmodium*) invade host cells, reorganize them to fit their own needs, and exploit this extreme ecological niche due to a multitude of adaptations.

As an adaptation to their modes of life, many parasites have evolved complex life cycles, which include switching between multiple hosts and sexual and asexual reproduction (Figure 1.9). In the simplest forms of parasitism, only one host is exploited; these parasites are referred to as **monoxenous** (Greek *mónos* = single, *xénos* = foreign). In this case, transmission from one host to the next takes place among members of the same host species, and is referred to as **direct transmission**. By contrast, **indirect transmission** occurs when the parasite switches between two or more host species. These parasites are known as **heteroxenous** (*hetero* = differing); their complex cycles require two or three, sometimes even four, host species, depending on the parasite. By switching hosts from one stage of their life cycle to the next, heteroxenous parasites achieve greater overall fitness, or transmission efficiency, than they would by utilizing a single host per generation. For example, the use of bloodsucking mosquitoes

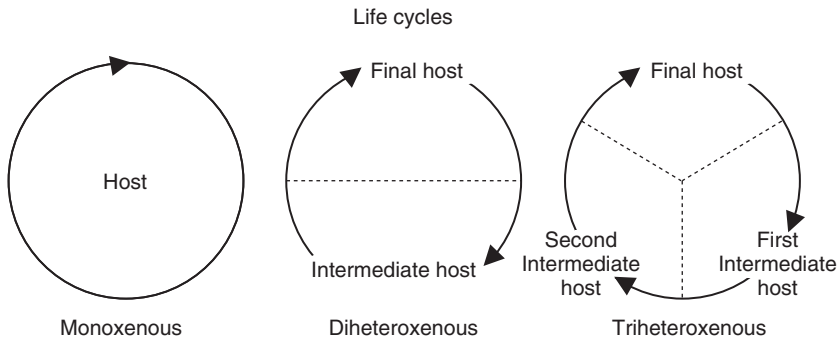


Figure 1.9 Life cycles of parasites. *Left:* Monoxenous cycle with one host, for example, *Ascaris lumbricoides*. *Center:* Heteroxenous cycle with final and intermediate hosts, for example, *Trypanosoma brucei*. *Right:* Heteroxenous cycle with final host and two intermediate hosts, for example, *Dicrocoelium dendriticum*.

as **vectors**, that is, carriers of the parasite between vertebrate hosts, results in a much higher level of efficiency in the transmission of malaria than has been measured in highly contagious viral diseases transmitted through direct transmission. The evolution of complex life cycles from what originally were simple ones has occurred in several unrelated parasite lineages, ranging from microorganisms to multicellular parasites, through the stepwise addition of a new host whenever this was favored by natural selection.

Modes of reproduction vary greatly among parasites, and many parasite species can switch from one reproduction mode to another during their life cycle. When a parasite alternates between sexual and asexual reproduction, this is known as **metagenesis**. The Apicomplexa, alternating between schizogony (asexual), gamogony (sexual), and sporogony (asexual), is a good example of metagenesis. Switching from sexual to asexual reproduction (i.e., parthenogenesis = virgin birth) is also seen in some intestinal nematodes, such as *Strongyloides stercoralis*, for instance; its life cycle illustrates a change between generations of parthenogenetically reproducing parasitic females and free-living sexually reproducing worms. Among sexually reproducing parasites, hermaphroditism is a common strategy, in which individual parasites possess both male and female reproductive organs. This is the case among platyhelminths such as tapeworms and flukes (except the blood flukes, or schistosomes). Hermaphrodites have the great advantage of being capable of reproduction even if they cannot find another member of their species in a host, by self-fertilization.

1.1.4

Parasites and Hosts

In heteroxenous life cycles a distinction is first made between the final host and intermediate host. Sexual reproduction takes place in the **final (definitive) host**. Some confusion in terminology can occasionally arise with this definition;

for plasmodia, for example, the more important host from an anthropocentric viewpoint is the human being. However, fertilization takes place in the mosquito, and hence the insect must be regarded as the definitive host. Another part of the life cycle of parasites takes place in the **intermediate host**, where significant developmental processes or asexual reproduction occur. This is the distinguishing factor between intermediate hosts and pure transmission agents (vectors), which transmit pathogens mechanically (e.g., through the stylets of bloodsucking insects). Several intermediate hosts may be exploited in succession during a life cycle, and these are known as first or second intermediate hosts. In some life cycles, a host individual plays the roles of the final and intermediate hosts simultaneously, as observed in the case of the nematode *Trichinella spiralis*. The trichina reproduces sexually in the gut of its host (final host function), and then forms resting stages in a completely different compartment, the muscle cell (intermediate host function). In many cases, transmission from intermediate to definitive hosts occurs by predation of the former by the latter. The larval stages of some parasites can also be transmitted from smaller to larger intermediate hosts through the food chain, without any significant morphological changes occurring. Such hosts, known as **paratenic hosts**, accumulate the larvae, and their insertion in the life cycle facilitates transmission of these larvae to the definitive host.

At each stage of their life cycle, many parasites are optimally adapted to a particular host species, which may represent their main host in fat, that is, the one they have coevolved with for a long time. On this host, growth and reproduction are optimal and the parasite enjoys a long life cycle. By contrast, living conditions are worse for the parasite in alternative host in fat that nonetheless allow the survival of the parasite, with the result that these hosts play a less significant role in the perpetuation of the life cycle. These alternative hosts, however, may serve as **reservoir hosts** in fat and be of major epidemiological importance – when control measures have been used on the main host, for example, chemotherapy on farm animals, the parasite cycle in wild reservoir hosts cannot be eradicated and a reinfection may take place via these hosts. By contrast, parasite development stages can sometimes occur in a **wrong host** or dead-end host, where no further transmission can take place (e.g., *Toxoplasma gondii* in humans).

One indispensable basis for the establishment of a host–parasite relationship is the **susceptibility** of the host. Susceptibility is essentially determined by the behavioral, physiological, and morphological characteristics of the host, and also by the host's innate and adaptive immune responses. Within a population, therefore, the host genotype often determines the individual degree of susceptibility – certain hosts may thus be predisposed for infection. Acquired characteristics, such as physical condition or age, can also affect an individual host's susceptibility to parasites.

Host **resistance** to a parasitic infection can depend on the immune responses of the host. This becomes clear when a host only becomes susceptible when elements of the immune system are disabled. For example, *Aotus* monkeys – used as experimental animals in malaria vaccine research – can only be reliably infected

after splenectomy. However, resistance can also be defined by biochemical factors. *T. brucei*, for instance, is killed by a protein in human serum, which is associated with high-density lipoproteins. **Immunity** is the term used when a past infection leaves behind protective immune responses. In the case of parasitic infections, an existing infection often provides immunity to further infections. A **concomitant immunity** (premunity) like this permits already-established parasites to survive, but leads to the elimination of new infective stages trying to infect the host. This situation can cause parasite density to be downregulated to a tolerable level for the host. Hosts with defective immune systems are often more susceptible to parasites; these hosts may consequently be colonized by **opportunistic pathogens**, which are present only in low densities or not at all in immunocompetent individuals. Such opportunistic parasitic infections are common in AIDS patients – and in many cases, these infections are the direct cause of death. Examples of this are the frequent occurrence of *Toxoplasma gondii*, *Cryptosporidium parvum*, and *Leishmania* species in AIDS patients and other immunocompromised persons.

Parasites can specialize in varying degrees in the way they exploit their hosts. The degree of specialization is expressed in the **host specificity**, which combines the number of host species that can be used at any stage of the life cycle, and the relative prevalence and intensity of infection by the parasite on these hosts. For instance, parasites that can infect only one host species or infect a few host species but achieve high prevalence and intensity on only one of these species have a high degree of host specificity (“narrow host specificity”). Feather lice (Mallophaga, see Section 4.4.2) are one example of highly host specific parasites. They are not only adapted to a particular host species omit – they can only colonize certain parts of the host bird’s body (Figure 1.10). Other highly host-specific parasites include omit the larval stages of digeneans (flukes) for their molluscan first intermediate host. By contrast, parasites with wide host specificity can colonize a wide range of hosts successfully, and often achieve high prevalence or intensity of infection on many of these hosts. For example, certain stages of *Trypanosoma cruzi* and *Toxoplasma gondii* exploit almost all mammals as hosts and invade almost all types of the hosts’ nucleated cells. Relying on the **host range** combined with information on prevalence and intensity of infection as a measure of specialization can be, however, misleading. Let us consider two related parasite species, A and B, each using four host species and achieving almost equal prevalence and intensity in all their hosts. However, the hosts of parasite A belong to distantly related families, whereas those of parasite B all belong to the same genus. Therefore, we can easily argue that parasite B displays higher host specificity than A, since its hosts are restricted to a narrower phylogenetic spectrum. Host specificity is the outcome of colonization of new hosts and adaptation to these hosts over evolutionary time, and the more host-specific parasites are those that cannot make the large jump necessary to colonize animal species not closely related to their main host. In this context, several parasites have made the “jump” from wild or domestic animals to humans; diseases caused by parasites transmitted between vertebrates and humans under natural conditions are referred to as **zoonoses** (e.g.,

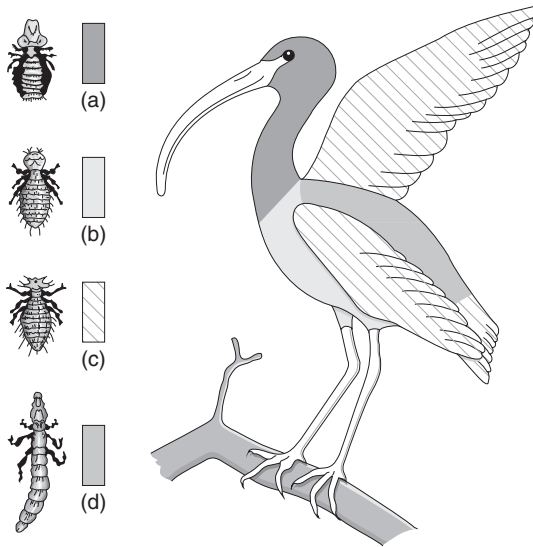


Figure 1.10 Distribution of various Mallophaga species on an Ibis (*Ibis falcinellus*), an example of high specificity for particular habitats on a host individual. (a) *Ibi-doecus bisignatus*. (b) *Menopon plegradis*.

(c) *Colpocephalum* and *Ferribia* species. (d) *Esthiopterum raphidium*. (From Dogiel, V.A. (1963) *Allgemeine Parasitologie (General Parasitology)*, VEB Gustav Fischer Verlag, Jena.)

T. spiralis, transmission between pigs and humans; and *Taenia saginata*, transmission between cattle and humans).

The establishment of parasites in a susceptible host results in an **infection**. In strict context, this term applies only if an increase in the number of parasites occurs by replication of the original parasite within the host, as in the case of protozoa. However, the term is now widely used in the case of helminths (worms) or arthropod parasites, too, where only one mature parasite develops from each infective larva. The term formerly used for these groups is “infestation.” The period during which diagnostically relevant parasite stages appear, such as plasmodia in the blood, is known as **patency**. The period from infection to patency is called **prepatency** or the prepatent period, while the period until the onset of the first symptoms is known as the **incubation period**. For helminth parasites, prepatency corresponds to the period from initial infection of the host to the onset of egg production, when eggs start appearing in the feces or urine of the host; patency then corresponds to the adult life of the worm, from the onset of egg production to its death. In accordance with an international agreement, the infection and the resulting disease are known by the name of the parasite with the suffix **-osis**, for example, toxoplasmosis. However, for many diseases the suffix **-iasis** is in wide use.

The term used when an infection with the same pathogen occurs after a parasitosis has healed is **reinfection**. An infection contracted in addition to

an existing parasitosis and caused by the same species of parasite is known as **superinfection**. Simultaneous infections with multiple pathogen species are known as **mixed infections**. Both superinfections and mixed infections have consequences for host welfare, as the overall harmful effect on the host may depend on additive or synergistic effects between the different infections. If a host infects itself with stages that originate from its own infection, it is called **autoinfection**; an example of this is autoinfection with the pinworm *Enterobius vermicularis*.

The **harmful effect** which the host suffers from parasites may have different causes and manifestations, and is measured in different ways by different groups of researchers. As a measure of the impairment caused by parasites, evolutionary biologists use the reduction in the host's **genetic fitness** attributable to infection. This decrease in host fitness is referred to as the **virulence** of the parasite, and is quantified as the relative difference between the reproductive capacity of the infected host compared to what reproduction it could achieve without the infection. In the assessment of medical importance, the parameters **morbidity** (incidence of disease) and **mortality** (incidence of death) are used. A quantification is determined by calculating the **disability-adjusted life years (DALYs)**; this is a WHO index into which up to 140 individual parameters flow for the assessment of a disease. Finally, the harmful effect of parasitic infections in livestock is calculated by determining the loss of productivity (e.g., milk yield in cows and wool production in sheep) and the cost of infection control.

At a physiological level, parasitic infections usually have a pathogenic impact or effect; this is generally described as **pathogenicity** and the defined molecular factors that are important in this context are called **pathogenicity factors**. The amoebapore protein produced by *Entamoeba histolytica* is a pathogenicity factor, since it plays a crucial role during tissue invasion. The term used for the quantitative expression of pathogenicity is **virulence** (Latin *virulentus* = full of poison), which was originally a means of assessing a pathogen's degree of aggressiveness. Unfortunately, the same term is used by evolutionary biologists to refer to the parasite's effect on host genetic fitness. From a physiological perspective, the host is therefore not only harmed by food deprivation – the destruction of cells or tissues through the action of toxic metabolic products and immune responses that harm the host's own tissue (immunopathology) also cause damage. It used to be thought that phylogenetically ancient parasite–host relationships should be characterized by a relatively low pathogenicity, since parasites which only minimally harm their hosts may persist longer over the course of evolution. However, following both theoretical work and experimental studies with fast-evolving pathogens, it is now accepted that the pathogenicity (or virulence in its evolutionary sense) of parasites can increase over the course of evolution. Indeed, under a range of circumstances, natural selection can favor aggressive exploitation of the host, resulting in high parasite replication and transmission rates, at the expense of long-term host survival.

1.1.5

Modes of Transmission

Due to the different varieties of parasitic organisms, modes of transmission are very diverse. The simplest form of transmission is **by direct contact**, for example, through contact with the skin, such as in mites or lice. One special case of contact infection is **sexual transmission**, as in the case of infections caused by *Trichomonas vaginalis* and *Trypanosoma equiperdum*.

Many life cycles of parasites are based on **oral infection**, that is, the intake of infective stages via the mouth. Intake can occur via the food chain and food-stuff – a process known as **alimentary infection**, or in ecological terms, **trophic transmission**. Some of these cycles are based on a predator–prey relationship between the intermediate and definitive hosts (e.g., catching of mice by the final host, the fox, which simultaneously ingests metacystodes of *Echinococcus multilocularis*, the fox tapeworm). Transmission from an intermediate host to a plant-eating definitive host requires a slight adjustment; here, the parasite stages leave the intermediate host to encyst on food plants (*Fasciola hepatica*: encystment on wetland plants). Infection by **fecal-oral contamination** occurs when infective stages derived from feces (e.g., amoeba cysts, coccidia oocysts, and nematode eggs) are ingested orally; diverse media such as contaminated water, food, and air (airborne transmission) can be used as transmission media. Since transmission is usually left to chance in fecal-oral infections, large numbers of infective stages are typically produced by parasites using this route (e.g., several billion *Cryptosporidium parvum* oocysts per kilogram of cattle dung). Infections occurring through other body orifices such as the nose, ear, eye, rectum, genital apertures, and wounds are less common. One important decisive factor in whether or not infective stages are successful in transmission is their **persistence** in the external environment, that is, the infective stages' resistance to environmental influences such as extremes of temperature, desiccation, salinity, and the effects of chemical exposure.

Percutaneous infection or skin penetration plays an important role, particularly in helminth infections. In these cases, infective stages in the soil or water actively bore into the skin of the final or intermediate host (e.g., the cercariae of schistosomes and other digeneans, the infective larvae of the hookworm *Ancylostoma duodenale*).

One highly targeted and therefore extremely efficient mode of transmission occurs through the use of **vectors** (Latin *vectus* = carried) in the life cycle of many parasites, mostly those living in the blood of vertebrates. This may be purely mechanical, such as the transmission of *Trypanosoma equinum* via the lancets of tabanid flies. More commonly, however, the transmitting organisms have a function as hosts, for instance bloodsucking arthropods that ingest the parasites with their blood meal, with part of the parasite's development occurring inside the vector (e.g., malaria parasites inside the mosquito). Other bloodsucking animals can also serve as vectors of parasites, including leeches and vampire bats.

Many of the aforementioned transmission modes (direct contact, sexual transmission, fecal-oral contamination, transmission by vectors) enable transmission

from one host individual to any other within a population, which is known as **horizontal transmission**. By contrast, **vertical transmission** occurs when the infection is passed on to the offspring from the mother, that is, across generations. In **congenital infection**, parasites infect the offspring of a host in the womb or during birth. For example, some parasites migrate through the placenta to the fetus (e.g., *Toxoplasma gondii*).

The transmission pattern characterizing the spread of diseases and the quantification of all processes associated with transmission of parasites are studied in the science of **epidemiology** (Greek *epí* = via, *dē mos* = people). If a specific study involves animal diseases, the veterinary term **epizootiology** (Greek *zō on* = living creatures) is used. One commonly used measure of infection is its **prevalence**, that is, the proportion of individuals in a population that are infected at a particular point in time. The **incidence** of an infection refers to the number of new cases occurring over a period of time. The **intensity of infection** indicates the number of parasite stages per host. In recent years, the science of epidemiology has relied increasingly on mathematical models to predict the spread of diseases through a population, given some basic parameters such as host population density and parasite transmission efficiency. This growing theoretical framework provides us with the means to forecast the potential effects of climate change and other environmental factors on the future dynamics of diseases.

Further Reading

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| <p>Goater, T.M., Goater, C.P., and Esch, G.W. (2014) <i>Parasitism: the Diversity and Ecology of Animal Parasites</i>, 2nd edn, Cambridge University Press, Cambridge.</p> <p>Loker, E.S. and Hofkin, V. (2015) <i>Parasitology: A Conceptual Approach</i>, Garland Science.</p> | <p>Mehlhorn, H. (ed.) (2007) <i>Encyclopedia of Parasitology</i>, Springer-Verlag, Berlin, Heidelberg, New York.</p> <p>Poulin, R. (2007) <i>Evolutionary Ecology of Parasites</i>, Princeton University Press, Princeton, NJ.</p> <p>Poulin, R. (2011) The many roads to parasitism: a tale of convergence. <i>Adv. Parasitol.</i>, 74, 1–40.</p> |
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Test Questions

1. How is the term parasite defined?
2. Which major groups of eukaryotic parasites are generally recognized?
3. What is the difference between symbiosis and parasitism?
4. Give examples of temporary parasites and permanent parasites.
5. What is the difference between monoxenous and heteroxenous parasites?
6. Which phase of a life cycle takes place in the final (definitive) host?
7. What is a paratenic host?
8. Does a parasite with narrow host specificity infect many or a few species?
9. How do we refer to the phase during which parasite stages are detectable in the host, like in the blood, for instance?
10. What is a zoonosis?
11. What is the difference between horizontal and vertical transmission?

1.2

What Is Unique About Parasites?

1.2.1

A Very Peculiar Habitat: The Host

Parasites, in contrast to free-living organisms, occupy a very special ecological niche, namely a living host. On closer inspection, the host is, particularly in the case of endoparasites, an **extreme habitat**, which, in relation to its inhospitality, can doubtlessly be compared to a salt spring or deep-sea vent. The environment of the small intestine, for instance, in which tapeworms and other parasites live, is characterized, among other things, by oxygen deficiency, high concentration of active digestive enzymes, high osmolarity, and immune responses of the host. Yet, apparently compensating for these harsh conditions is the high abundance of nutrients. In order to be able to exploit such a habitat in the long run, morphological, physiological, and other adaptations are necessary. Such adaptations either existed as **preadaptations** before the ancestral switch from a free-living existence to a parasitic one, or they evolved rapidly after the transition to parasitism, through intense natural selection. Preadaptations would have originally evolved in free-living organisms in response to the demands of their particular habitat; they may have included morphological structures allowing attachment inside the host intestine, a tough cuticle to resist immune attack, or a metabolism capable of handling low oxygen availability. Further evolution after switching to a parasitic mode of life has led to a **strong specialization** for parasitism, a universal feature of parasites. As specialists they exhibit a close relationship with their host. Therefore, the evolution of parasites proceeds jointly with that of their hosts, while the hosts, too, are reciprocally influenced by their parasites. This closely coupled evolution of two species is termed **coevolution**.

The distinctive feature of parasite–host coevolution is the fact that hosts respond to infection with parasites, for instance, by developing defense reactions. This is the reason why parasites not only have to adapt to inhospitable surroundings, but additionally have to evade the host’s defense reactions if they are to survive and reproduce. Thus, an especially strong evolutionary pressure is exerted on parasites. As they are adapted very specifically to their hosts, they cannot easily evade this pressure by, for instance, infecting other host species with lesser defense reactions. Therefore, parasites are forced not only to adapt to the particular physical and physiological conditions associated with the host, but also to evade its defensive attacks that are flexible and change over the course of time (see Section 1.6). Hence, a typical feature of parasite–host interactions is the **antagonism** between the partners.

Parasites lower their hosts’ genetic fitness and quality of life, acting as competitors for nutrients and exerting pathogenic effects due to lesions, inflammations, toxic metabolic substances, or merely by occupying space within the body cavity of the host. In contrast to most viral and bacterial pathogens exploiting their host only temporarily, the typical eukaryotic parasites **persist in their hosts for long**

periods of time. For example, intestinal nematodes often live several years in their hosts, hardly inducing any pathology as long as the worm burden is low. For such parasites, a **high prevalence** is typical, meaning a high percentage of infected individuals within a host population over a long time. By contrast, in flu epidemics, the susceptible individuals of a population become infected, produce viruses for a short time, and transmit these to their conspecifics, until the germs are eliminated by the immune system. As soon as protective immunity has developed in a sufficiently large number of individuals, the transmission practically ceases and the pathogen disappears from the population, only to perhaps reappear later, usually in an altered form.

The typical long-term strategy of parasitic worms, therefore, is in contrast to the hit-and-run strategy of many smaller pathogens. However, it should be mentioned that the persistence of parasitic worms in their host is not a singular feature, as there are also multicellular parasites relying on short-time exploitation, while some viruses and bacteria live for a long time in their hosts.

Still, why do typical eukaryotic parasites prefer long-term strategies? It is often claimed that protozoa and particularly helminths, due to their larger body size and complex genome, have long replication times and thus are less flexible genetically than viruses and bacteria. Although there are counterexamples, it is evident at first glance that organisms with a small genome and body size replicate more rapidly – and consequently can also change their genome more rapidly – than very large creatures (Figure 1.11). As a rough estimate, typical viruses usually possess several dozen genes, bacteria a few thousand, and eukaryotes around 10,000 or more (see also Table 1.2). While *Escherichia coli* has a generation time of 20 min, trypanosomes divide only every 6 h and some nematodes need more than 1 year to attain sexual maturity. Such a long development is not compatible with a hit-and-run strategy, but instead favors a long-lasting exploitation of the host.

A parasite's optimal level of virulence may be completely altered when the parasite encounters a novel host species. For instance, an infection with *T. brucei*, the causative agent of "Nagana," usually proceeds asymptotically or with only few symptoms in wild ungulates, in which the parasite experienced a long coevolution. By contrast, the infection often leads to death in horses and donkeys to which the parasites are not adapted, as these host species have been relatively recently introduced into the endemic regions.

The regulation of the parasite population density prohibiting an overcrowding of the host is another requirement for the long-term exploitation of the host. It has been suggested that some unicellular parasites (e.g., plasmodiids and trypanosomes) self-regulate their population density to achieve an optimal utilization of the host, although the underlying mechanisms and molecules are not yet known. In many species of tapeworms, there exist density controlling mechanisms, which govern the number or size of the worms. These operate either by induction of host immunological responses or via molecules secreted by the tapeworms themselves, which act against their conspecifics. The outcome is that infections by few worms generally produce of large ones, whereas infections by many worms result mostly in very small individuals (**crowding effect**). Besides, it

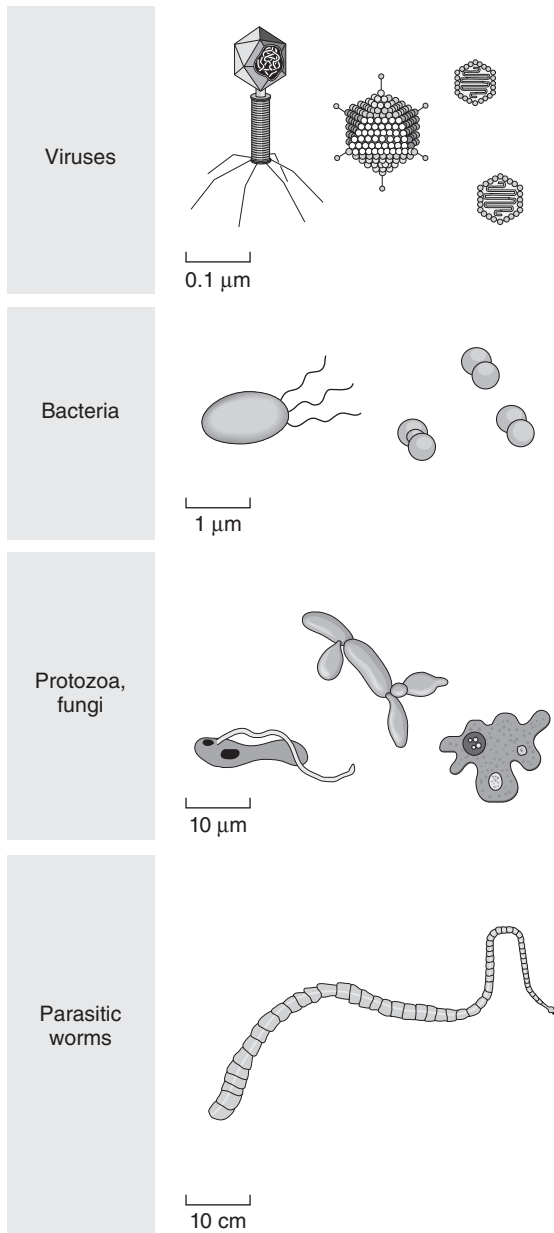


Figure 1.11 Dimensions of various parasitic organisms.

Table 1.2 Genome size and number of protein-encoding genes of some viruses, bacteria, and eukaryotes.

Organism	Number of protein coding genes	Genome size
<i>Hantavirus</i>	3	12.2 kb
<i>Herpes simplex</i>	74	152 kb
<i>Smallpox</i>	187	186 kb
<i>Escherichia coli (K12)</i>	4377	4.6 Mb
<i>Bacillus subtilis</i>	4221	4.2 Mb
<i>Helicobacter pylori</i>	1589	1.6 Mb
<i>Encephalitozoon cuniculi</i>	1997	2.9 Mb
<i>Giardia lamblia</i>	5012	11.7 Mb
<i>Entamoeba histolytica</i>	9938	24 Mb
<i>Trypanosoma brucei</i>	9068	36 Mb
<i>Leishmania major</i>	8311	32.8 Mb
<i>Cryptosporidium parvum</i>	3807	9.1 Mb
<i>Plasmodium falciparum</i>	5268	22.8 Mb
<i>Babesia bovis</i>	3671	8.2 Mb
<i>Theileria parva</i>	4035	8.3 Mb
<i>Schistosoma mansoni</i>	>11 809	363 Mb
<i>Caenorhabditis elegans</i>	21 733	100 Mb
<i>Haemonchus contortus</i>	23 610	320 Mb
<i>Brugia malayi</i>	~11 500	90 Mb
<i>Anopheles gambiae</i>	13 683	278 Mb
<i>Mus musculus</i>	24 174	2.8 Gb
<i>Homo sapiens</i>	~24 000	3.3 Gb

has been shown in many worm infections that established adult parasites induce immune reactions to repel superinfections without themselves being damaged. This premunition (“concomitant immunity”) protects already-established parasites against conspecific competitors and simultaneously spares the host from overwhelming damage.

An infection of long duration requires the correct balance between exploitation of host resources on the one hand, and parasite growth and reproduction on the other. Highly pathogenic parasites that quickly kill their hosts have no chances to exploit them for prolonged periods of time, although they may achieve high replication rates during their brief use of the host. By contrast, parasites hardly impairing their host are more likely to prevail for a long time, but their less aggressive exploitation of host resources may only support modest replication rates. The evolution of parasite virulence toward its host may settle anywhere between these extremes, depending on the host–parasite association, as natural selection favors the combination which yields the highest overall transmission success.

Even if many parasites are amazingly well adapted to their hosts, infection results in a considerable burden for the host, as measured by reduced fitness (Section 1.3). Consequently, **hosts strive to eliminate their parasites**. They have evolved complex defense systems, for instance, innate immune responses or the

adaptive immune system, which, however, cannot provide a complete protection. Yet, a small number of parasites may not critically diminish host fitness. On the other hand, parasites are absolutely dependent on their hosts and have to be able to cope with their defence systems. Thus, the parasite–host relationship is an **asymmetric arms race**, in which the benefits of staying ahead appear greater for the parasites than for the host. As stated earlier, the necessity to adapt to their host has led to such a pronounced specialization of parasites that life with another host species is not possible any more, let alone a return to a free-living existence (with very few exceptions). Hence, for most parasites, the way back is blocked and they depend on the host for better or worse.

1.2.2

Specific Morphological and Physiological Adaptations

Parasites have specialized very successfully and accomplished some remarkable feats of adaptation while doing so. However, these achievements cannot often be measured accurately against the current benchmarks, so they are seldom appreciated. Konrad Lorenz proposed that parasites do not need to acquire properties which have been developed by their hosts. They do not have to sing well, for example, or look attractive or be successful in capturing prey – they have more *subtle* skills which, upon closer inspection, are just as impressive as those of their hosts. For instance, a detailed look at the antigenic variation of trypanosomes or the induced behavioral changes of the intermediate host, which enable the transmission of the lancet fluke *Dicrocoelium dendriticum* to its definitive host, reveals that these parasites deserve the same level of interest as the evolutionary achievements of higher organisms. Parasites have often abandoned the features required by their free-living ancestors, because the host has taken over the relevant tasks for them. For instance, consider the loss of the intestinal tract of tapeworms and acanthocephalans; they can absorb their food from the host in solubilized form via their outer surface. This **loss of features** has often led to the assumption that parasites were simplified versions of their free-living relatives. Indeed, genome projects have actually shown that increasing specialization is often accompanied by a reduction of the genome size and the number of protein-coding genes, and hence well-adapted parasites transfer more tasks to the host. However, there are counterintuitive examples as the one of *Trichomonas vaginalis*, with one of the largest known parasite genomes, coding for 59 681 predicted protein genes. Given the complex mode of life of certain parasites, we may assume that a general tendency toward a reduction of genomic complexity is accompanied by the acquisition of new functions by the expansion of certain gene families. Any accurate statement about a possible genomic simplification of multicellular parasites will only become possible when sufficient genomes have been sequenced to enable us to compare the complexity of parasites and their free-living relatives with one other.

In the course of coevolution with their hosts, many parasites have lost structures that their free-living ancestors still required. The more intimate and prolonged is a

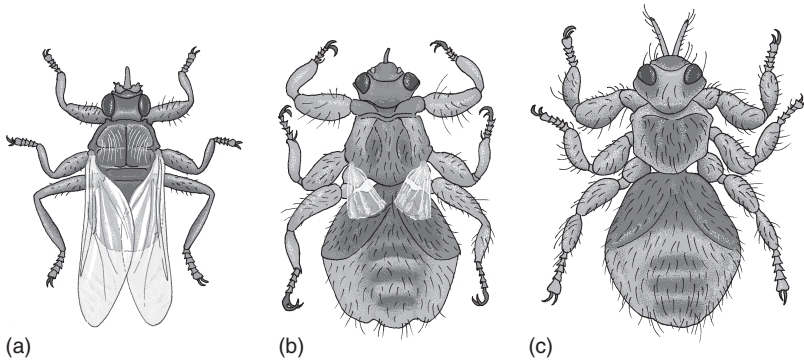


Figure 1.12 Louse flies with varying degrees of wing reduction. (a) *Lynchia maura* (continuously flight-capable). (b) *Lipoptena cervi*, sheds its wings when it has alighted on a host. (c) *Melophagus ovinus*, wingless. (Compiled from various authors.)

host–parasite association, the more pronounced are the changes. Among insects, temporary ectoparasites generally have all of their nonparasitic relatives' locomotor organs, while permanent ectoparasites tend to possess reduced wings and their legs have either been modified into clasping organs or lost completely. Louse flies are an example of this type of evolutionary change. While *Lynchia maura*, the pigeon louse fly, remains winged throughout its life, transferring among hosts at the adult stage, the deer ked or deer fly, *Lipoptena cervi*, sheds its wings immediately after finding its host. The sheep louse fly, *Melophagus ovinus* is stationary, completing its entire development on the host. It is transmitted by direct contact and therefore develops no wings at all (Figure 1.12). Similarly, the extremities of arthropods can be modified and are eventually largely lost with increasing intimacy of the host–parasite association. This can be seen in *Demodex folliculorum*, commonly referred to as the eyelash mite, whose grub-shaped body possesses extremely stubby limbs (see Section 4.2.4.1).

The best example of an extreme loss of morphological characteristics is the parasitic crustacean *Sacculina carcini* of the order Cirripedia (barnacles). They infest the European green crab, *Carcinus maenas*. The female parasite transforms itself into a network of roots, which pervades the entire body of the crab, absorbing nutrients which contribute to the development of the parasite's brood sac, the "externa." This sac-like organ replaces the female crab's egg case under its anal segments. The host keeps it clean and supplies it with fresh oxygenated water as if it were its own egg case (Figure 1.13). Male *Sacculina* larvae penetrate the young externa and change into extremely reduced dwarf males inside the female. In its adult stage, *Sacculina* therefore displays none of the characteristics of a free-living crustacean. This morphological degeneration has long been considered to be typical of parasites and as such has been given the name "sacculinization." However, when we consider the complex life cycle of *Sacculina* – a cycle which has been only fully understood relatively recently – we realize that this animal is not simplified, but highly specialized. The mode of life of *Sacculina* is an extreme form of



Figure 1.13 Beach crab with the externa of *Sacculina carcini*. The brood sac – the only externally visible part of this extremely modified barnacle – juts out under the anal segments of the crab. (Image: Courtesy of M. Grabert)

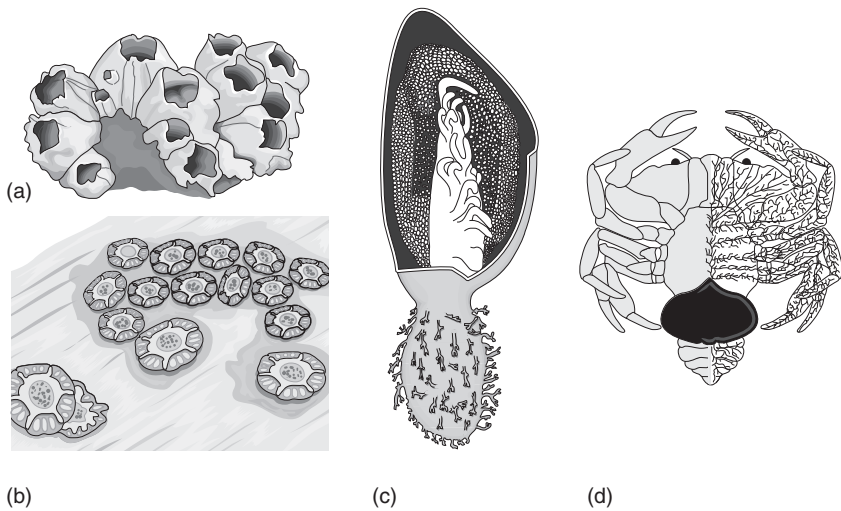


Figure 1.14 Transition to endoparasitism in barnacles. (a) Barnacle on a firm surface. (b) Whale barnacle on whale skin. (c) The shark parasite *Anelasma squalicola*, forming root-like extensions that extend into the host's skin and absorb nutrients. (d) The root system of *Sacculina carcini* runs throughout the entire body of the host; the externa is under the anal segments. (Compiled from various sources.)

a development which can also be found in other Cirripedia (Figure 1.14). Many of these barnacles are stuck to rocks and other objects and strain their food from water, such as the common barnacle *Chthamalus stellatus*. Related species have specialized in attaching to moving surfaces, where they live as external symbionts, such as the “crown” barnacles *Coronula diadema*, on the skin of whales. Other Cirripedia, for example *Anelasma squalicola*, which inhabits the skin of sharks, have evolved into genuine parasites, branching out into the host tissue to absorb food.

The highly specialized endoparasitic lifestyle of *Sacculina* probably developed in similar steps.

Reduction or total loss of organs, however, is not exclusive to parasites, but also occurs in free-living animals. Similar to the gradual loss of wings in ectoparasitic insects, the loss of legs in whales and snakes is an adaptation, not a retrogressive simplification. Even the gut can be reduced among free-living animals, as the example of the Pogonophora illustrates. These marine tube worms are related to the acorn worms. They live in deep-sea vents, where the main food source is chemotropic bacteria. Pogonophora have lost their gut – they absorb their food through a tentacle crown. In addition, the loss of sight organs in endoparasitic flatworms parallels the loss of eyes in fish and crustaceans inhabiting the complete darkness of underground rivers. Thus, basic structures have been reduced in a range of other free-living as well as parasitic organisms – natural selection indiscriminately favors the loss of any feature that has become useless ballast due to a new mode of life. Parasites are not less complex than free-living animals, but are complex in different ways.

Indeed, some structures that have evolved in parasites are not present in their free-living relatives, particularly structures serving for anchoring or attachment to the host. Across all parasite taxa, we find a wide array of impressive hook and anchor structures or adhesive disks and suckers with which parasites anchor themselves to the surface of their hosts, in mucous membranes or within cells (Figure 1.15). The entire body is often flattened to offer as little resistance as possible. Noteworthy in this respect is the formation of analogous structures in very different organisms. The common fish louse or carp louse, *Argulus*, an ectoparasitic crustacean and the single-celled intestinal parasite *Giardia lamblia*, for example, have a plate-shaped flattened body, which is held on the surface of the fish or the lining of the intestine by suction cups or a suction plate. A very different convergent development is found in the prehensile legs of true lice and the ectoparasitic crustaceans (Amphipoda) of whales, the “whale lice.” These analogous structures also reflect the need for the parasite to anchor itself on the host animal. These are just some of the examples of clear morphological convergence among unrelated parasite lineages facing similar challenges.

Another striking feature of many helminth parasites is their **larger body size** than their free-living relatives. While soil-inhabiting nematodes rarely grow larger than a few millimeters in length, *Placentonema gigantissima*, a parasite of the placenta of the sperm whale, reaches a size of between 6 and 9 m. The nematodes *Dioctophyme renale* from the kidney of the dog and the Guinea worm, *Dracunculus medinensis* can grow up to a length of 1 m. In tapeworms, the broad fish tapeworm *Diphyllobothrium latum* (up to 20 m in length) is one of the record holders for length (Figure 1.16, see Section 3.1.2.5). Similarly, a digenean parasitic in the sunfish, *Mola mola*, reaches length of more than 10 m, dwarfing any of its free-living flatworm relatives. This evolutionary increase in body sizes is most apparent in endoparasitic helminths, but is also evident in copepods, where those taxa ectoparasitic on fish are orders of magnitude larger than their free-living relatives. These extraordinary body sizes can only come about if nutrients

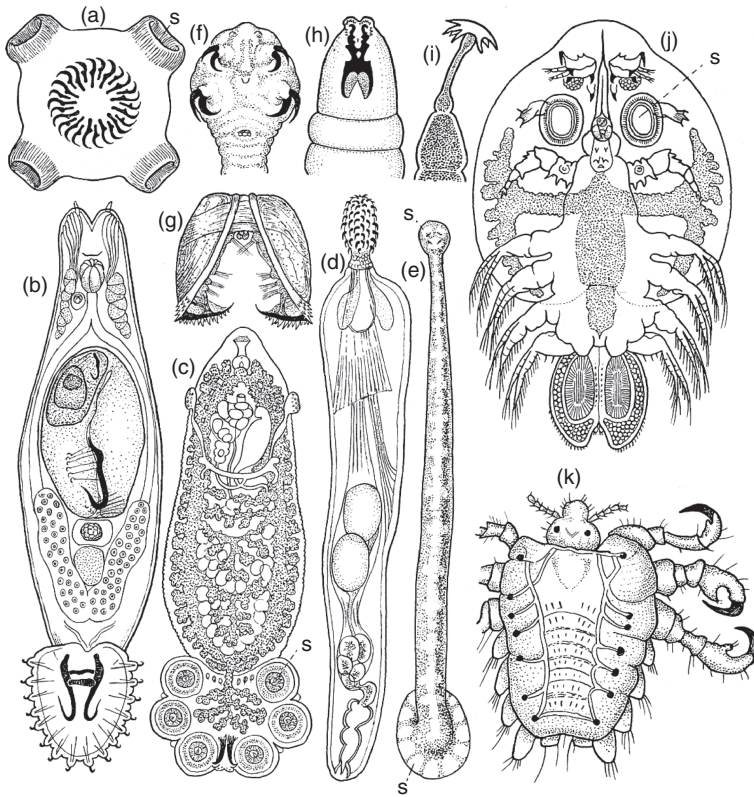


Figure 1.15 Adhesive and clamping organs in parasites. (a) Scolex of the pig tapeworm *Taenia solium*, front view. (b) Monogean *Gyrodactylus elegans*. (c) Monogean *Polystomum integerrimum*. (d) Acanthocephalan, or spiny-headed worm *Acanthorhynchus*. (e) Fish leech *Piscicola geometrica*. (f) Front end of the pentastomid, or tongue worm *Leiperia gracilis* as seen from the abdomen.

(g) Larva of the pond mussel *Anodonta cygnea*. (h) Front end of the larva of a deer botfly (*Cephenomyia*). (i) Front end of a Gregarine (*Stylorhynchus*) from the intestine of a dragonfly larva. (j) *Argulus foliaceus*, a crustacean fish louse. (k) Crab louse (Insecta) of humans (*Pthirus pubis*). s: Sucker. (From Hesse-Doflein (1943) *Tierbau und Tierleben*, Verlag Gustav Fischer, Jena.)

are present in abundance, and they are seemingly the product of strong selection for increased gonad tissue and high reproductive output. Given the high mortality of eggs and larvae that fail to find a host, the reproductive strategy of many parasites is **the mass production of offspring**. Females of the nematode genus *Ascaris* (see Section 3.3.4.6) can each lay up to 200 000 eggs daily – around 70 million every year. This corresponds to 1700 times the female’s body weight – in human terms, a woman weighing 60 kg would have to produce 102 tons of offspring per year – and that represents around 25 000 human babies of 4 kg each.

The beef tapeworm *Taenia saginata* produces up to 10 billion eggs during its 20 years of life, and a large body is necessary for this type of mass production.



Figure 1.16 Length of *Diphyllobothrium latum* compared to a medium-sized woman. (Image: Archive of the Department of Molecular Parasitology, Humboldt University, Berlin.)

Parasites that produce few offspring are usually smaller; one example of this is the intestinal nematode genus *Trichinella*. The female has a maximum length of 3 mm and only produces up to 2500 larvae. In fact, it is the size of reproductive organs in relation to body size that really matters, as shown by the nematode *Sphaerularia bombi* that lives in the body cavity of the bumblebee – the uterus grows outside of the female and becomes huge, while the rest of the body remains tiny. Since size is associated with the production of eggs, this also explains the fact that male worms are often smaller. A well-known example of dwarf males is seen in the nematode *Trichosomoides crassicauda*, which is found in the urinary bladder of the rat; the tiny male is rooted in the uterus of the female. Similarly, in parasitic copepods, the males are often minuscule compared with the females, being nothing more than mobile testes.

1.2.3

Flexible Strategies of Reproduction

Parasites that have found a suitable host are generally guaranteed an abundance of food for the rest of their life. Finding a mate, however, is not always so easy. Given the relative rarity of hosts and the difficulty involved in infecting them, it is common for a host individual to harbor only a single or very few parasites of a given species. A solitary life like this is basically unproblematic for unicellular parasites that can reproduce asexually. For multicellular parasites with sexual reproduction, finding a mate can be a major challenge, and evolution has favored different solutions to this problem in different taxa. For example, in some types of helminth or

arthropod parasite, once two sexual partners encounter each other, they remain together and thus avoid the struggle of finding another mate in the future. In schistosomes (blood flukes), the larger male worm fits the smaller female in a special groove along its ventral surface and keeps it lodged there, allowing the pair to mate continuously. The female may eventually be usurped by another single male, or leave its own, but the long-term pairing nevertheless serves to facilitate mating in conditions where potential mates do not encounter each other often. In some fish parasites, including copepods (family Chondracanthidae) as well as monogeneans (family Diplozoidae) and digeneans (family Didymozoidae), the two mates physically fuse together when they first meet, forming a permanent mating association. There are other adaptive solutions to the problem of rare mating encounters resulting from the uneven distribution of parasites among their hosts. Indeed, some parasites develop into hermaphrodite adults capable of self-fertilization (selfing), whereas others have adopted parthenogenesis. The latter mode of reproduction can also contribute to the rapid development of a population, since there is no investment in the production of males, which do not produce progeny.

Tapeworms are a good example of **hermaphroditism**. As protandrous hermaphrodites, the male sex organs develop first in the young proximal proglottids, while the female reproductive organs only become sexually mature in older, distal proglottids. This is why a single adult tapeworm can mate with itself. In a study of *Schistocephalus solidus*, a tapeworm of the order Diphylobothriidea, the reproductive success of selfing was compared with that of cross-fertilization. The cestode larvae of *S. solidus* produced by selfing individuals were less successful in infecting a copepod intermediate host when compared with parasites produced as a result of cross-fertilization. With regard to infecting copepods, offspring produced from selfing achieved a lower prevalence and intensity of infection and a smaller body volume than that achieved by the progeny produced by cross-fertilization. This difference shows that the genetic quality of offspring produced by selfing is inferior – for a tapeworm isolated in a host without a partner, however, this type of reproduction can serve as a stopgap measure for producing offspring.

Various parasites can make their propagation more flexible through **parthenogenesis**, such as nematodes of the *Strongyloides* genus. These nematodes are an exception to the helminth norm – they are capable of the autoinfection of a host, which means that a self-perpetuating population can persist in the same host. The threadworm (pinworm) of the rat, *Strongyloides ratti*, inhabits the mucosa of the upper small intestine and, depending on current requirements, can change its mode of reproduction from producing parthenogenetic, parasitic females to producing dioecious individuals. At the beginning of the infections, parthenogenetic females are formed almost exclusively; this enables many offspring to be created when food availability is optimal and immune responses are low. The proportion of dioecious worms increases with the duration of the infection. The likely explanation for this is that increasing immune responses require greater genetic flexibility. This has been substantiated in experiments using immunosuppressive treatment with corticosteroids: In immunosuppressed rats, *S. ratti* produces more offspring,

in which the proportion of parthenogenetic forms is significantly greater than that in untreated rats. Parthenogenesis not only solved the potential problem of mate finding in this nematode, but also allowed it to optimally exploit its host thanks to the flexibility of its reproductive strategy.

Asexual reproduction is also a major reproductive strategy in a wide range of parasites. In unicellular organisms, asexual reproduction is often predominant and may lead to large numbers of offspring. For example, an infection with a few sporozoites of *Plasmodium falciparum*, the causative agent of tropical malaria, may give rise to 10^{11} merozoite stages. In other unicellular parasites, asexual reproduction has been considered as the only way of reproduction, but the recent identification of meiosis-associated genes in some of those protozoans challenges this view. Asexual reproduction is not restricted to unicellular parasites. In some platyhelminths, it is used to amplify the number of individuals early in the life cycle, perhaps as an adaptation to counter the losses incurred during the many transmission steps of a complex life cycle. Digeneans use asexual multiplication to increase larval stages in their snail intermediate hosts. In the case of *Schistosoma mansoni*, it has been calculated that one miracidium can produce 40 000 cercariae through asexual reproductive steps. In some tapeworms, the metacestodes have the ability to reproduce asexually, such as the fox tapeworm *Echinococcus multilocularis*. Several thousand protoscolices can occur in its larval mass, each of which will form a very small and relatively short-lived tapeworm in the intestine of a fox that eats an infected field mouse. In these cases, the parasite has thus shifted a significant part of its reproduction to the asexual phase in the intermediate host.

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Test Questions

1. What is the relationship between genome size, and the reproductive behavior of parasites?
2. Which mechanisms regulate the population density of parasites?
3. Give examples of a reduction of morphological structures in parasites.
4. Why is *Sacculina carcini* regarded as being a drastically simplified parasite?

5. An increase in parasitic worms' body size provides them with what kind of advantage?
6. What is the disadvantage of parthenogenesis?

1.3

The Impact of Parasites on Host Individuals and Host Populations

Many ecologists still believe that animal populations are controlled by food abundance, competition, predation, and abiotic factors. They tend to dismiss parasites as unimportant: parasites are small, hardly visible, and therefore assumed not to unduly affect the host. The opposite is true, however, as recent research has shown conclusively. Even parasitoses with low mortality and morbidity, such as flea or nematode infections, can have a massive impact on the host and its reproductive success – and even affect the structure of host populations as a result. Only by realizing the extent of this effect, can we understand the evolutionary pressure exerted by parasites on their hosts – and also understand the coevolutionary processes that have shaped the interaction between parasites and their hosts.

Depending on the particular type of parasite and the intensity of infection, the effects of a parasitosis vary. These effects are essentially determined by the virulence of the parasite, the susceptibility of the host species, the condition of a host individual, and its instant response situation. While some parasitoses, such as sleeping sickness in humans (caused by *T. brucei*), can induce a very high mortality rate, the impact of other parasite infections is usually so slight that it may be unnoticed. The skin of around 30% of all people is home to eyelash mites (*Demodex folliculorum*), for instance – and they are hardly ever noticed. These widely differing impacts on hosts make it extremely difficult to derive any general conclusion on the harmful effects of parasites. In addition, parasites such as helminths and arthropods are not evenly distributed among individual hosts in a population, and thus not all hosts incur the same effects from the same parasite species. Typically, a small proportion of hosts in the population harbor large numbers of parasites, whereas most of the others harbor few or no parasite (see Section 1.4.2). This aggregated distribution of parasites results from behavioral or physiological variability in the host population, leading to differences among individual hosts in either their exposure to infective stages, susceptibility to infection, or ability to mount immune responses following infection. This is why in what follows, we use some examples to illustrate the impact parasites can have on the performance of their hosts and on the hosts' progeny – and how they can consequently affect entire populations. Although these examples do not illustrate universal effects of parasitism, they nevertheless show the type of impact parasites can sometimes have on their hosts.

In a series of exemplary studies, researchers led by H. Richner from Bern, Switzerland, have illustrated the effects of an infection of great tits with the bird flea *Ceratophyllus gallinae*. Great tits are particularly suitable for such studies, because these cavity nesters are often plagued with fleas and the size of their

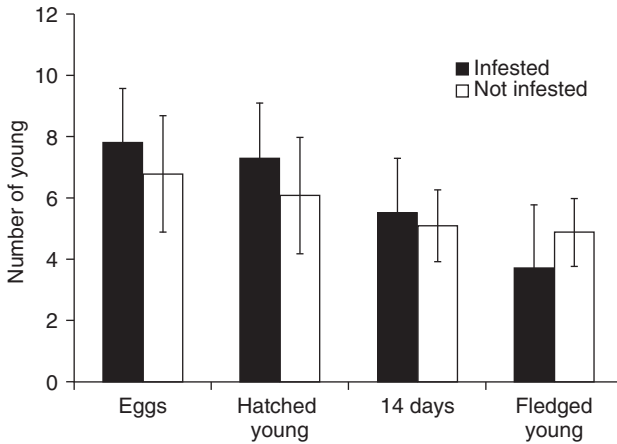


Figure 1.17 Reproductive success of great tits from nests infected/not infected with *Ceratophyllus gallinae*. (According to data from Richner, H., Oppliger, A., and Christie, P. (1993) *J. Anim. Ecol.*, **62**, 703–710.)

egg clutches is easily manipulated. Under natural conditions, the number of eggs varies between 6 and 12, but eggs can easily be removed or added to the clutch. Tits also readily accept artificial nest boxes. The boxes are first placed into a microwave oven to remove any flea that is present. A predetermined number of fleas can then be put into each box for experimental purposes.

The effects of infection by ectoparasites are usually considered to be relatively low. The behavior of tits searching for nesting cavities shows, however, that flea infection in a nest box significantly reduces the box's attractiveness to the birds. In the case of heavily infected nest boxes, fleas surround the entrance hole, forming a dark ring, ready to infect the bird immediately. Tits in search of nesting opportunities try to avoid nest boxes like this. If a shortage of nesting sites forces a tit to accept a flea-ridden nesting site, its offspring will have significantly fewer red blood cells. They are also skinnier and their mortality rate is higher than that of tit offspring from nests with no flea infection (Figure 1.17). In fact, more eggs are laid by adults in flea-infected nests than in clean nests to compensate for the higher mortality of the nestlings, but a significantly smaller proportion of those will survive fledging (Figure 1.17). On average, one more young bird will fledge and leave a clean nest than a flea-infected nest. In infected nests, the breeding success rate (measured by the number of fledged young) was only 53% compared with 83% in clean nests. A pair of great tits which adopts a flea-infected box has therefore significantly fewer offspring; infection by these ectoparasites – contrary to the general opinion that they are relatively harmless – considerably diminishes the fitness of their hosts.

The parent birds also suffer from the consequences of flea infection. In the experiments, the indirect effects of infection were studied after the female tits were stimulated to lay an extra egg, corresponding to the situation in a flea-ridden nest. The additional stress resulted in an increase of 30% (from 20% to 50%) in



Figure 1.18 Scottish grouse, *Lagopus lagopus scoticus*.

the prevalence of avian malaria in the females, suggesting that the combined effects of fleas and increased investments in egg production and care caused a drop in vigilance against mosquito bites or resistance to malaria itself. Similarly, the male great tits significantly expanded their foraging area when the brood was artificially increased by two additional hatchlings. The additional effort involved resulted in the percentage of male great tits infected by *Plasmodium* increasing to 40% for flea-free birds and 80% for flea-infested birds. It appeared that few of the infested males survived through to the following year. They therefore had significantly lower chances of reproduction than birds in nests without fleas. Similar experiments with barn swallows and other birds have shown that the Swiss great tits are no exceptions.

The above experiments show the effect of parasitism at an individual level – but the impact on host populations can also be impressive. One famous experiment on host populations was conducted with the Scottish red grouse (*Lagopus lagopus scoticus*), which are widespread in the mountain heaths of the Scottish Highlands (Figure 1.18). The annual *Red Grouse* hunt is a popular social event. It has always been celebrated by Scottish landowners, as guests and tourists shooting grouse on their land provide a tidy income. Records have been kept of the numbers of birds shot each year, providing long-term data on changes in grouse population abundance. These data show that the population densities of grouse vary considerably over time, making hunting almost pointless during some seasons. A long-term study of 175 populations of grouse in different regions of Scotland showed that population density of grouse goes through a cycle with periods varying between 4 and 8 years (Figure 1.19a). Interestingly, the population density of the grouse was negatively correlated with infection intensities by the nematode *Trichostrongylus tenuis*, which also show variations over time. This parasite is monoxenous, so that transmission depends heavily on the density of the bird population. The parasite

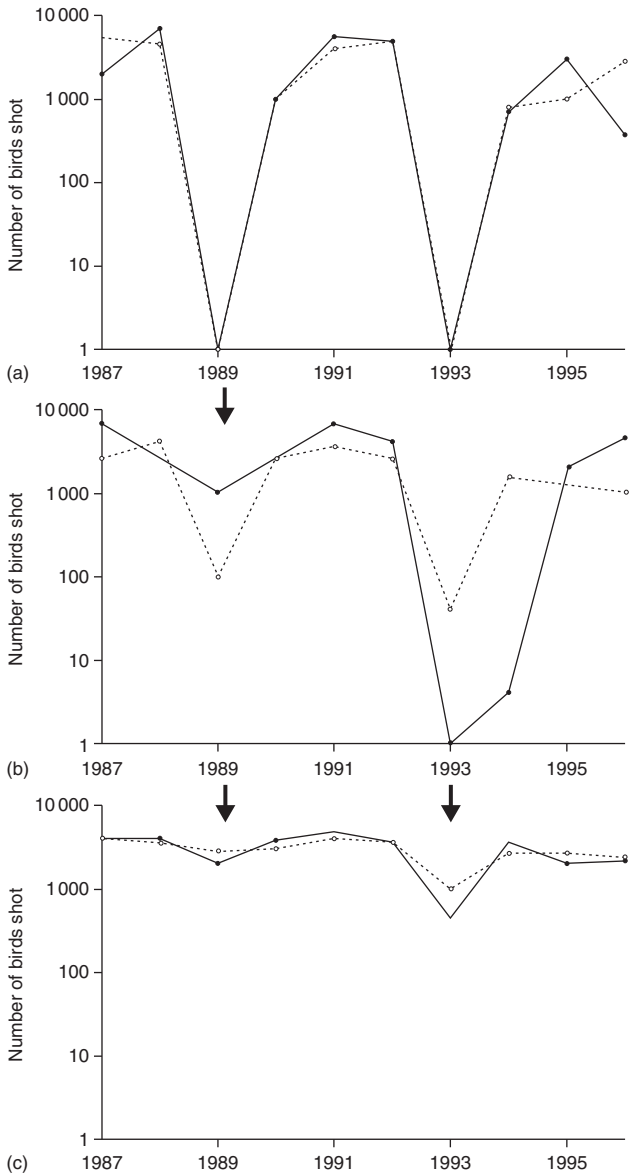


Figure 1.19 Fluctuation in the population of Scottish grouse due to infection with the intestinal nematode *Trichostrongylus tenuis*. Deworming (arrow) of a proportion of the birds prevents the decline of populations. (a) Course of events with two control populations; (b) Course of events in

two populations after a single treatment; (c) Course of events in two populations after two treatments. (From Hudson, P.J., Dobson, A.P., and Newborn, D. (1999) *Science*, **282**, 2256–2258 with kind permission of the publisher.)

load of adult birds had a decisive impact: heavy worm infection – as occurs in dense host populations when transmission conditions are favorable – resulted in a high mortality rate of the young birds. The intensity of infection with *T. tenuis* was obviously reaching a point where the fitness of the birds was decimated, resulting in a population collapse.

In order to confirm these relationships experimentally, adult birds from six sample grouse populations were caught with nets before the beginning of the breeding season. The birds in some populations were then given a drug orally to rid them of worms, whereas birds from control populations were not treated. The grouse caught amounted to between 15% and 50% of each bird populations. Even this limited action yielded amazing results – in the treated populations, the deworming of some of the birds prevented the collapse of the populations seen in control populations (Figure 1.19). A mathematical model showed that a single annual deworming of >20% of the animals was sufficient to prevent population declines and ensure a relatively high population density. Therefore, there seems to be a critical infection threshold, above which we observe instability in the host population; it is therefore clear that in this host–parasite system, the parasite regulates the density of the host population. A similar periodicity is also found in some insect populations, which achieve high densities, only to collapse when parasitoids enter the equation. These provide real-world examples of the regulatory capacity of parasites predicted by the classical modeling work of Anderson and May in the late 1970s, and echoing back to the earlier demonstration of the potential of predators to control prey populations provided by Lotka and Volterra in the 1920s.

In cases where populations are regulated by parasites, however, the aforementioned marked periodicity is very rare. This is partly due to the influence of factors obscuring the influence of infection, such as climate, vegetation, and human actions. On the whole, however, density regulation by parasites and other pathogens can play an important role in natural animal populations. It is noteworthy that in some cases, relatively minor changes to the balance can have disproportionately strong impact. This finding is important for the design of control programs: if we can keep the prevalence of parasites below a certain threshold and reduce transmission as a result, a significant decline in parasitosis or even its eradication can be achieved – and this perhaps with only a modest effort.

In view of the serious effect of parasitic infections on the fitness of hosts (described above), it is not surprising that the loss of a parasite can be a huge advantage for a population. Introduced species often bring with them fewer parasites than they harbored in their original habitats. The house sparrow, introduced to North America, is infected by only 35 ectoparasite species on that continent – whereas in its home territory of Europe it has 69 species with which it must contend. The potential increase in fitness resulting from the loss of parasites indicates that invasive species are often more successful than in their original habitat and can spread rapidly as a result. One striking example of this is the European green crab *Carcinus maenas* – it has spread all over the world from its original habitat on the North Sea and Atlantic coasts. In Europe, the growth and spread of this crab is mainly restricted by the parasitic castrator, *Sacculina*

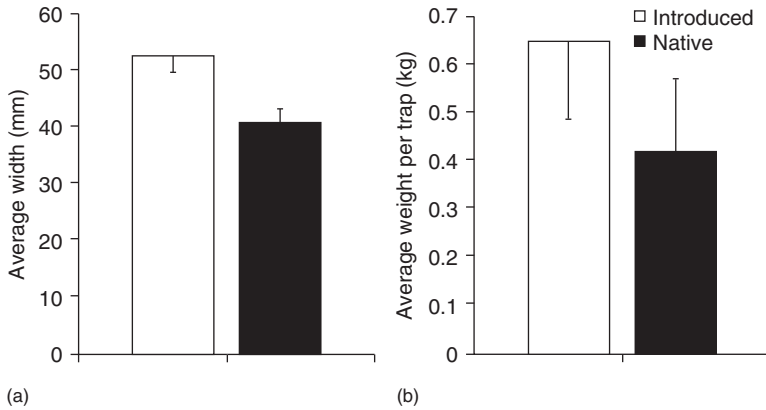


Figure 1.20 Development of green crabs from areas with and without their original parasites. (a) Width of shell. (b) Average weight of crabs in a trap (kg). (From Torchin,

M.E., Lafferty, K.D., and Kuris, A.M. (2001) *Biol. Invasions*, 3, 333–345, with kind permission of the publisher.)

carcini and the feminizing parasitic isopod *Portunion maenada*. These parasites do not occur in the new distribution areas and no native parasitic crustacean has so far switched to exploit *C. maenas*. Certain trematodes, cestodes, and acanthocephalans – the larvae of which exploit *C. maenas* as an intermediate host – do not exist in the new areas of distribution; and copepods and nemertean, which subsist on crab eggs, are also absent. A loss of this diverse parasite fauna is considered to be a key reason why the green crab is about 30% larger, on average, in its new areas of distribution than in Europe, spreading successfully and in some areas even displacing native species (Figure 1.20).

Conversely, the introduction of a parasite can threaten host populations which have not yet been exposed to it. The mite *Varroa destructor* (see Section 4.2.3.3) was originally an ecoparasite of the eastern honey bee *Apis cerana*, which is relatively resistant to infection. Introduced to Europe with Asian bees in the 1970s, *V. destructor* spread rapidly throughout the populations of the highly susceptible Western honey bee, *Apis mellifera*. The mites suck on bee larvae, impairing their development, eventually leading to infection of the entire brood and crash of a hive's population. It has been shown, however, that resistant genotypes can evolve in populations of Western honey bees which have been exposed to the mites for a lengthy period of time. One striking example of this is the "Primorsky bees." These are honeybees that were introduced into the far eastern regions of Russia by European settlers in the mid-nineteenth century. These bee populations acquired resistance against *V. destructor*, with the result that the development of varroaosis in the hives of the resistant bees takes a different course than that of susceptible bees (Figure 1.21). In the United States and other countries where *V. destructor* has now been introduced, attempts are being made to breed *Varroa*-resistant high-performance bees, using Primorsky bees as the source material.

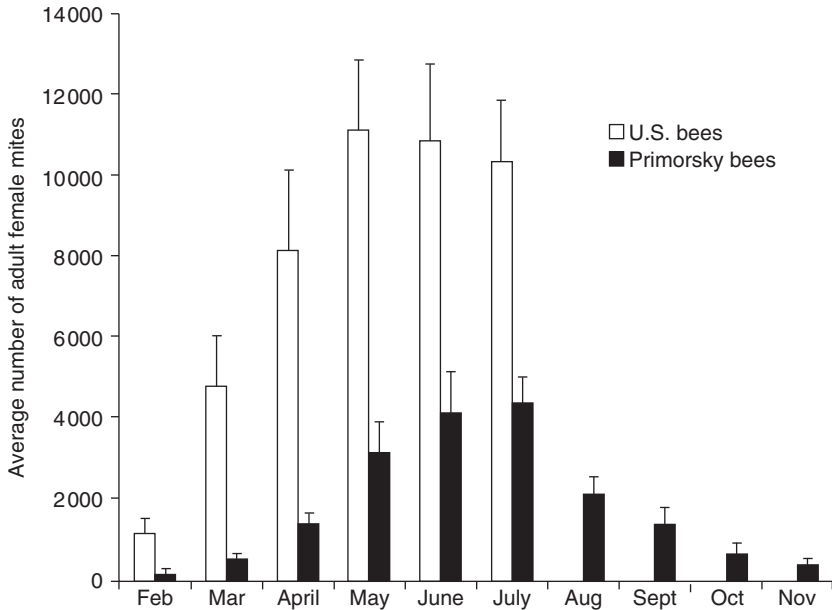


Figure 1.21 Increase of infection with *Varroa destructor* in bees of different susceptibility. White bars: American bees; black bars: Primorsky bees. (Data from Rinderer, T.E., Guzman, L.I., Delatte, G.T., Stelzer, J.A., Lancaster, V.A., Kutznetsov, V., Beaman, L., Watts, R., and Harris, J.W. (2001) *Apidologie*, 32, 381–394, by kind permission of the publisher.)

The eel nematode *Anguillicola crassus* (order Spirurida) is another introduced parasite now part of a novel parasite/host association. Introduced to Europe in the early 1980s from Asia, it has spread very rapidly in the past few decades, threatening the populations of *Anguilla anguilla*, the European eel (Figure 1.22). It has now also invaded North America, where it infects the American eel, *Anguilla rostrata*. *A. crassus* is originally a parasite of the Japanese eel *Anguilla japonica*. In its adult stage, the parasite lives in the swim bladder of the eel. The life cycle of *A. crassus* includes copepods as intermediate hosts. In an experimental study, Japanese eels – having been fed a standardized number of infective larvae – harbored 7.5 worms on average, with a mean dry weight of 11.8 mg/worm. On average, the European eels that had been infected the same way harbored many more and much larger worms – 24 nematodes, each with a mean weight of 98.3 mg – a testament to the significantly better conditions for development in the new host. The pathogenicity of infection is also much stronger in the European eel, so that infection with *A. crassus* is considered to be a factor in the dramatic decline of eel populations. Since the eels have to make use of currents at very different depths, the swim bladder's role in pressure compensation is absolutely vital – especially during the migration to the spawning grounds in the Sargasso Sea. An interesting fact about the threat of an Asian parasite is the fact that the

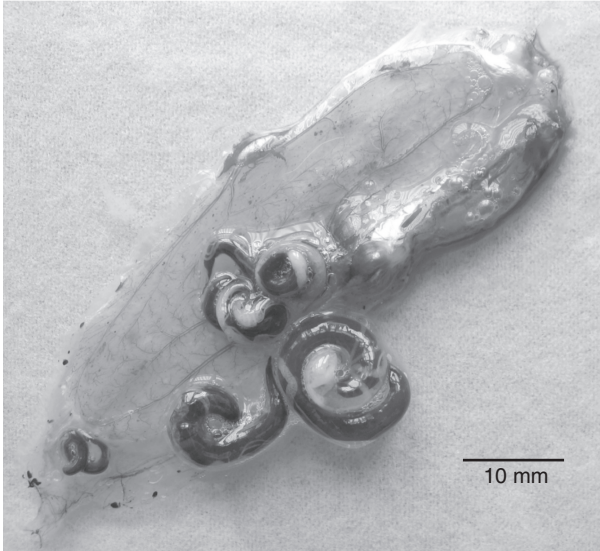


Figure 1.22 *Anguillicola crassus* in the swim bladder of a European eel (*Anguilla anguilla*). (Image: Courtesy of Klaus Knopf.)

radiation of the eel took place from Asia. The European eel diverged from its Asian ancestor and shifted its distribution areas to the west – and it probably lost its nematode parasites during this process. After a considerable delay, *A. crassus* has finally caught up with its host again – and since the eels have largely lost their immune response against these nematodes, this parasite is once again threatening eel populations.

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Test Questions

1. What impact does flea infestation have on the fitness of cavity-nesting birds?
2. Why do grouse populations in Scotland regularly collapse?
3. What is the reason for the fact that some introduced animal species have a survival advantage compared to native species?
4. Why does *Anguillicola crassus* pose a threat to European eels?

1.4

Parasite–Host Coevolution

1.4.1

Main Features of Coevolution

The term “**coevolution**” describes the evolution of different species of organisms which evolve in close association and influence one another. The evolution of a species does not occur in isolation; it takes place alongside the evolution of other species within ecosystems. Imagine a deciduous forest or coral reef – in a habitat like this, plants, animals, protists, fungi, and bacteria and viruses not only live together, they also interact and influence one another. Some of these species are very closely coupled, such as parasite and host, and hence the evolution of one is very strongly influenced by the other, and vice versa.

One often used example of coevolution is the joint development of flowering plants and their pollinators, which has led to very specialized reciprocal adaptations. Certain plants, for example, have evolved flower forms that allow access only to specific pollinators. If these pollinators also specialize in this very plant in their search for food, they will in turn evolve the morphological features necessary to obtain nectar from those flowers. This will result in efficient and specific pollination. Both sides benefit from this partnership, which lays the foundation for a mutualistic relationship (even if conflict can arise regarding the exact extent of mutual services). An **antagonistic relationship** exists between parasite and host, however, because the advantage is mainly on the side of the parasite, while the host tries to eliminate the parasite. This antagonism in the coevolutionary relationship creates a unique selection pressure, one which sustainably shapes both parasite and host and may force the parasite into extreme specialization. Extreme specialization, manifested by strict host specificity, is not the exception, but rather the rule in many groups of parasites. However, it must be said that “generalist” parasites with a very wide range of hosts can also be very successful, like the asexual stages of *Toxoplasma gondii*.

One major difference between free-living and parasitic organisms with high host specificity lies in the fact that the evolution of parasites does not take place in a complex environment that is relatively stable due to the large number of possible partners and food sources. A population of lynx that specializes in mountain hares as prey can switch to grouse or other prey only if the hare population is decimated. By contrast, the environment of many parasites provides only limited opportunities, since most parasites specialize in few or often only a single host species. Switching to a different host species is simply not possible for these highly specialized masters of exploitation – at least not on short time scales – and this is why such parasites are forced to adapt very specifically to their hosts, for better or for worse. Parasites also negatively affect their hosts, indirectly forcing them to develop defense mechanisms that can only be avoided if the parasite “invents” new evasive strategies. The evolutionary changes of one partner therefore exert selection pressure on the other partner in the parasite–host relationship. It is this

reciprocal selection pressure that drives the evolutionary arms race between the two antagonists. The traits of pathogens that are under such a high selection pressure evolve extremely fast. Combined with their short generation times and high reproductive potential, this quality puts parasites among the organisms with the highest speed of evolution.

One important aspect regarding coevolution in the antagonistic parasite–host relationship is the fact that for both opponents, the selection pressure comes from several sources:

- On the one hand, parasites are subjected to **selection pressure by the host’s defense mechanisms**. A probable response here is the development of evasion mechanisms in the course of evolution. Such mechanisms would disable, undermine, or otherwise thwart the defenses of the host. The host, however, is exposed to **selection pressure applied by the pathogenicity of the parasite** – and the host will inevitably respond to this with, for example, the development of improved defense mechanisms.
- On the other hand, parasites and hosts, like any organism, are also subject to **evolutionary pressure through intraspecific competitors** competing for the same ecological niche and sexual partners. **Evolutionary pressure through interspecific competitors, predators, and environmental factors** is also acting on hosts and parasites.

The combination of evolutionary pressure applied by the antagonist and generated through competition with competitors has far-reaching consequences, because even slight disadvantages – created by an opponent – will cause an organism to fall behind in the race with its competitors; and this may have a much more drastic effect on fitness than would normally be the case.

In coevolution, the constant threat of falling behind in the arms race with the antagonist drives both parasite and host to change – permanently and swiftly. This is an ongoing process, since each opponent forces the other to adapt and this in turn leads to a counteradaptation. Characteristics that expose an Achilles heel to the opponent must be modified. From the viewpoint of the parasite, if its surface structure is recognized by the host’s antibodies, thereby allowing the activation of host immune responses, it must react and change its surface structure to survive – only parasites that do this will persist. From the perspective of the host, it responds to fitness reductions caused by the parasite by “inventing” improved defense mechanisms to attack the parasite, despite the latter’s new surface structure. Both parasite and host are thus competitors in an evolutionary race, a race in which neither can win a permanent advantage. They are in constant motion, so to speak, without significantly changing their position relative to one another. If one side slackened its efforts, however, the opponent would gain the upper hand. This situation represents the foundation of the **“Red Queen hypothesis,”** coined after a quote from Lewis Carroll’s classic, “Alice through the Looking Glass”; the Red Queen tells Alice that she has to run very quickly to stay in one spot, because the surroundings themselves are moving very fast. It is because of these dynamics that

the coevolution of parasites and their hosts is believed to proceed more rapidly than most other evolutionary changes.

The importance of the host–parasite relationship has, however, a different dimension for the two opponents: a parasite is completely dependent on its host and cannot exist without it – so it cannot afford to make any mistake. A mistake like a failed invasion attempt or ineffective protection against immune mechanisms will usually result in the death of the parasite. Conversely, for the host, just one failure of its defenses against one infective stage of a parasite will not necessarily result in death, but may only entail a small reduction in its fitness. Richard Dawkins, in his book “The Selfish Gene,” described this difference as the “*life/dinner principle*” and compared this situation with the relationship between the hare and fox: While the hare will be eaten if it fails to escape just once, it is just another meal for the fox. This is exaggerated, of course; but it is true that parasites are under a great deal more evolutionary pressure than hosts and are therefore forced to adapt even more rapidly and precisely than their counterparts.

The main elements in the scenario for this antagonistic interaction are the individuals. However, evolution – and consequently coevolution – takes place within populations via the differential survival and reproduction of individuals. In a parasitized population, susceptible host genotypes become scarce due to their impaired fitness, but infection-resistant genotypes come to the fore. In this way, the distribution pattern of the host population’s genotypes changes under evolutionary pressure from the parasites. Parasites must consequently adapt to such change and alter their own genomes through time. Coevolution in the short term is thus determined by changes in the frequency of genotypes within populations.

Although parasite and host are in permanent competition, the dynamics of the evolutionary process can allow a delicate balance to be created under certain conditions. The host contributes to this compromise – after all, it is often less costly, in terms of fitness, to permit some slight infection than to develop solid defenses with no loopholes. On the part of the parasites, there is a tendency for strains with lower virulence to prevail in the long term, especially if high virulence leads to the early death of the hosts, impairing transmission. A relatively balanced equilibrium may become established if parasites adapt very specifically to their hosts through long coevolution and if the transmission rate is also low.

The result of this reciprocal influence is often an extreme specialization of parasites on one host species, with the parasites becoming highly adapted to that particular host’s characteristics. From a phylogenetic perspective, **cospeciation** with their hosts is typical for these species – thus, when subsets of an ancestral host population become segregated and evolve into separate species, the parasites follow their host species by speciating in parallel (Figure 1.23). If new host species are created through geographical isolation or other barriers to gene flow, their parasites adapt to the individual properties of the new host species to such an extent that they themselves form new species during the course of evolution. In such cases, the phylogeny of a group of parasite species becomes a mirror image of that

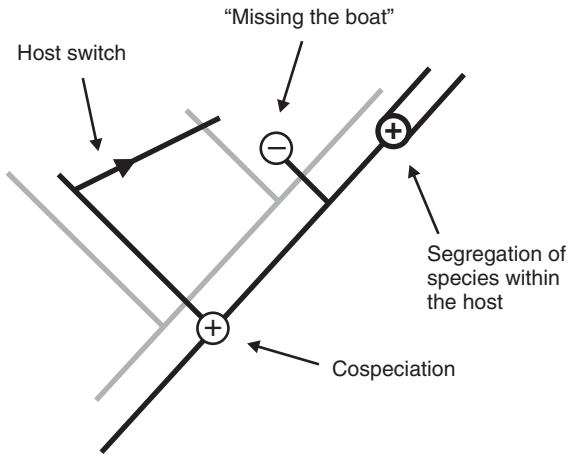


Figure 1.23 Various modes of coevolution of hosts and their parasites. For details see text. Black line: evolutionary line of parasite species; grey line: evolutionary line of host species. (From Paterson, A.M., Palma, R.L., and

Gray, R.D. (1999) How frequently do avian lice miss the boat? Implications for coevolutionary studies. *Syst. Biol.*, **48**, 214–223 with kind permission of the publisher.)

of the hosts they infect. This pattern, combined with the fact that the speciation of the parasites follows that of the host after a short time lag, has been summarized in “Fahrenholz’s rule.” The relationships of parasites should therefore enable conclusions to be drawn about the relationships of their hosts – and before the birth of modern-day phylogenetics, this was indeed the case. The relationships of ducks with flamingos and of old world camels with new world, llama-like camelids were thus substantiated (*inter alia*) by the relationships among their ectoparasites.

However, parasites do not always follow their host species over evolutionary time. Since the distribution of parasites in host populations is not uniform, a few host individuals from a small founder population may be free of one particular parasite. A study on introduction to New Zealand as alien fauna shows that this event occurs very frequently: only three of 18 bird species introduced by humans had the same number of bird lice species as they had in their area of origin; all others had fewer parasite species. Host species that evolve from such founder populations may be free of the corresponding parasite species – or in other words, the parasite has *missed the boat*. Conversely, specialized parasites may also adapt to a new host species, particularly if it is closely related to their own host and offers them similar living conditions. This is termed a *host switch* – it consists of the parasite species colonizing a new host species while remaining capable of exploiting its original host.

Most of our current knowledge of phylogenetic patterns of coevolution comes from studies of ectoparasites such as bird lice, which are extremely specialized for their respective host species. Across all parasite taxa, it remains unclear whether coevolution has proceeded mostly by cospeciation following Fahrenholz’s rule,

by repeated host switching, or through a mixture of both. In particular, we know relatively little about the speciation of parasites which are pronounced generalists, infecting a variety of host species, such as *Toxoplasma gondii*.

Finally, we note that according to many evolutionary biologists, coevolution with pathogens may have decisively contributed to one of the most fundamental aspects of life on Earth. One hypothesis – the subject of some debate – is that selection pressure from pathogens has strongly favored hosts capable of maintaining genetic flexibility and is responsible for the **evolution of sexual reproduction**. According to one rival hypothesis, the genetic recombination generated by sex is mostly beneficial for the purging of adverse mutations.

Whether these hypotheses are correct or not, it can be said that the intermixing of the genome resulting from sexual reproduction provides two different individuals with the opportunity to create offspring with new and unique genotypes through recombination. This is essential for the continued evolutionary refinement of new defenses against pathogens. On the contrary, sexual reproduction has one marked disadvantage: 50% of the population (the males) produces no offspring; essentially, they only make their sperm available, yet require many resources for growth. A population of parthenogenetic females would seem better off, as all offspring could themselves produce offspring. Despite this huge disadvantage, the fact that sexual reproduction has prevailed in most higher organisms indicates the extreme importance of genetic variation, presumably as an important requirement for defense against pathogens.

1.4.2

Role of Alleles in Coevolution

Adaptation occurs gradually through **mutation and selection** in the course of evolution. The mutations, however, evolve in random, undirected manner and usually have a disruptive character; this is why mutants normally have a lower level of fitness than the wild type. The relatively few successful mutations that provide a selective advantage, however, are of great importance. If we consider only short periods of time, stable mutations that provide selective advantages do not occur often enough to explain the rapid adaptation of parasites to their hosts. Moreover, often only a combination of several mutations has a lasting effect on the parasite–host relationship. Combinations like this occur much more rarely than successful single mutations. In addition to the emergence of mutations, their distribution throughout the population is therefore a crucial factor for coevolution. If there are mechanisms that help to spread the relatively rare beneficial mutations efficiently, populations of parasites or hosts can respond quickly to new conditions.

In order to understand the rapid adaptations that occur during the course of a coevolutionary process, it is not enough to simply analyze the genes of individuals – we must study their frequency distribution in populations of parasites or hosts. Such studies show that populations are composed of very different genotypes. Typically, there are different alleles for each single gene. Adaptations to the

coevolution partner arise through the **selection of alleles** within a population, so that **changes in allele frequencies** can be observed, while new successful mutations occur only rarely.

Host populations consist of individuals that exhibit a spectrum of host characteristics that are more or less suitable for any particular parasite of a given species. Similarly, the parasite population is also assumed to consist of a range of different genotypes. It could therefore be argued that the success of infection and the progression of parasite development and reproduction depend on which genotype combinations of the parasite and of the host encounter one another. Experiments involving controlled exposure with bacterial pathogens and other parasites have confirmed the importance of this “matching” of genomes.

If the infection success of parasitic worms (or arthropods) in a population of hosts is examined, clear inequalities among individual hosts will become apparent. A negative binomial distribution of worm loads is typical – while few hosts harbor a large number of worms, most host individuals have few or very few worms, or no worms at all (Figure 1.24). This uneven distribution of parasites among hosts is in part due to chance events, as different host individuals will not encounter the same number of parasitic infective stages. However, high susceptibility to helminth infection is frequently found in certain families and not others, therefore genetic predisposition exists and contributes to uneven worm burdens among hosts. In a host population, there is a pool of different alleles, which define the host qualities of any individual. These hereditary characteristics are modified by other factors, of course, such as environmental conditions and current constitution.

Analysis of the genetic compatibility of a parasite–host combination is complicated by the fact that in most cases, several genes have an influence at the same time. Situations where individual genes play a crucial role are illustrated by the drug resistance of parasites or by host diseases such as sickle cell anemia (see below). In these cases, the spread of the corresponding alleles in a population

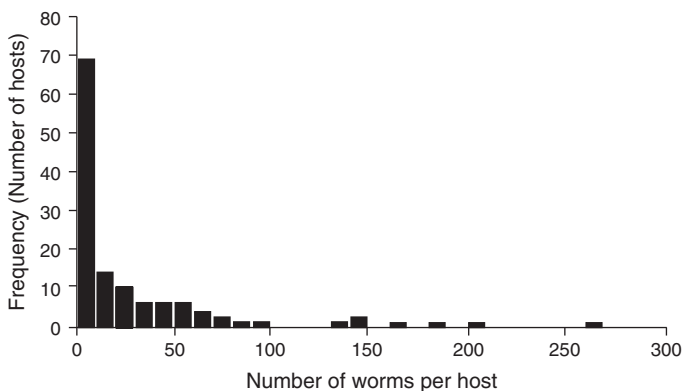


Figure 1.24 Negative binomial frequency distribution of hookworms in a human population in Papua and New Guinea. A few individuals have many worms – but the majority of individuals have few or no worms. (From Pritchard *et al.* (1990), *Parasitology* 100, 259–267.)

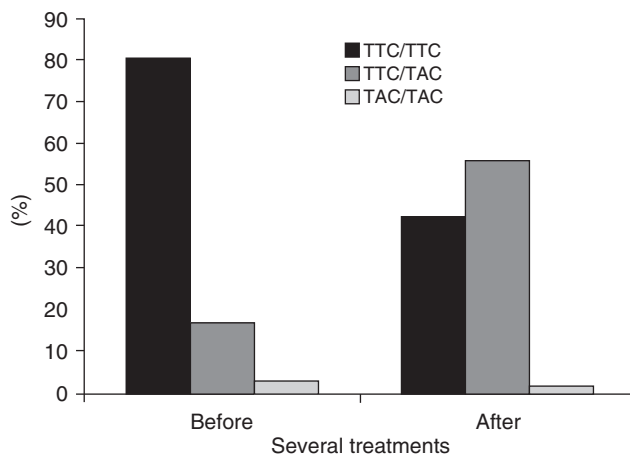


Figure 1.25 Shift of allele frequencies of the β -tubulin gene of small strongyles parasitic in horses after several treatments with benzimidazole. The replacement of phenylalanine with tyrosine in position 200 of the protein leads to drug resistance. Heterozygous genotypes increase in frequency under the pressure of the drug treatment. (According to data from G. Samson-Himmelstjerna.)

can be traced. Studies like this have confirmed that rapid adaptation to a new drug/new pathogen can occur within a few generations through changes in allele frequencies.

For example, the shift of allele frequencies in populations of parasites under evolutionary pressure is well illustrated by the resistance of gastrointestinal nematodes to the drug class of benzimidazoles (Figure 1.25). Their active agents create a long-lasting bond with the β -tubulin of the parasite; the bond prevents the formation of microtubules, ultimately leading to the death of the worms. The amino acid 200 of the β -tubulin, a phenylalanine, is crucially important for the bonding process. In a population of small strongyles parasitic in horses that has never been treated with benzimidazole, there is always a high percentage of worms in which the β -tubulin gene has a phenylalanine (TTC/TTC) in both alleles at position 200. A much smaller percentage of nematodes is heterozygous, where one allele codes for phenylalanine and the other for tyrosine (TTC/TAC), while very few individuals are homozygous for tyrosine in position 200 (TAC/TAC). Under the pressure of drug treatment, this balance changes rapidly. After only a few generations, the number of homozygous TTC/TTC parasites fell drastically, the frequency of the heterozygous TTC/TAC worms increased sharply and the homozygote TAC/TAC type remained almost constant. Therefore, it is clear that when under the pressure of the drug treatment, the β -tubulin allele with tyrosine at position 200 provides a distinct advantage to the heterozygous forms – and worms with this combination of genes can therefore prevail. A low-frequency allele in the parasite population is therefore “brought forward” – and because it provides a selective advantage in the presence of the drug, it can quickly spread through sexual recombination.

1.4.3

Rareness Is an Advantage

Individuals in a population have different alleles, as the above example with the β -tubulin allele shows. Frequently occurring alleles probably provide a selective advantage, while the rarity of other alleles suggests that they currently provide no advantage. So why do a population's rarely occurring alleles not simply dwindle away? The maintenance of inferior alleles in the population for an event that might occur later is not compatible with the selective pressure under which all organisms exist. Understanding this question provides a basic cornerstone for understanding coevolution itself.

A closer look reveals that the rare, unconventional alleles of a host can also provide selective advantages in its current situation, simply because they do not fit into the typical host genetic landscape to which parasites have adapted. Here we assume that parasites must overcome two major obstacles in order to reproduce

- infection success, persistence, and reproduction in the host;
- transmission of the offspring to a new host.

For most parasites, the probability of the offspring finding a suitable new host is very small. This chance is increased, however, when the genotype of the parasite enables the infection of a frequent host type – and the result of this is that pathogens which are compatible with a frequent host genotype and which specialize in that host genotype will prevail. Rare or aberrant genotypes of hosts therefore enjoy relative protection from pathogens. The selection pressure exerted by pathogens on the “normal type” provides a selective advantage to aberrant hosts in intraspecific competition. These conditions can follow a dynamic pattern, as captured by the “*Red Queen*” hypothesis. A negative frequency-dependent selection causes a cyclic change of genotypes in the populations of host and parasite, as schematically shown by Schmid-Hempel in the “coevolution wheel” (Figure 1.26).

Under certain circumstances, pathogens can decimate one of a host population's frequently occurring genotypes in which they have specialized – and to such an extent that the genotype can even become rare. In a case like this, previously aberrant host genotypes would now be expected to come to the fore and proliferate, subsequently forming a large proportion of the population. Parasites that are still specialized for the rarefied host genotype now have less chance of finding a suitable host and must adapt to specialize for the host type which now prevails under the current conditions. The parasites change their target, so to speak. After a reversal like this, the previously predominant host genotype (now in the minority) is relieved of the pressure of parasite infection and again enjoys a selective advantage.

This rarity advantage also benefits the parasite – the defenses of the host have to focus on the prevailing parasite genotype, so rare parasitic genotypes consequently enjoy a selective advantage. The dynamics of this coevolutionary cycle can be compared with a predator–prey relationship, in which predators that specialize

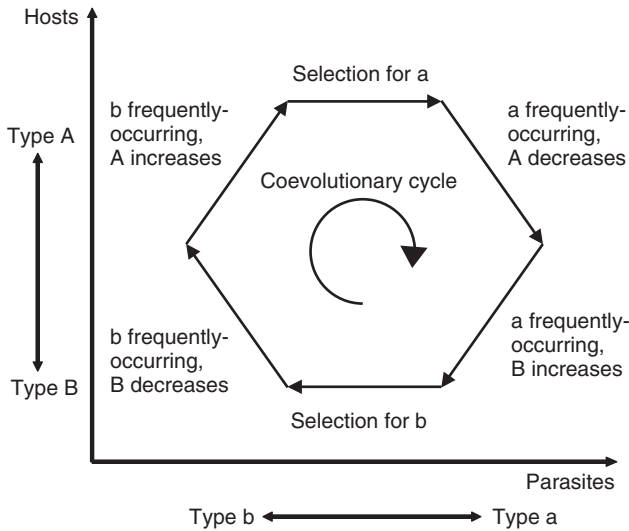


Figure 1.26 In the simplest case assumed here, with two types of hosts (A, B) and parasites (a, b), type a parasites can infect the hosts of type A and correspondingly, type b parasites can infect the hosts of type B. Infection leads to a decrease in the frequency of the corresponding type in the host population (fitness loss) and to an increase in the corresponding type in the parasite population (fitness gain). If, for example, there were currently many hosts of type B, but few parasites of type b, parasites of this type would have a high selective

advantage. Selection of the type b now occurs causing — with a time delay — an increase in type b's frequency in the population. The various frequencies of host and parasite types alternate accordingly during the course of a cycle. In the longer term, however, none of the types disappear from the population, as each type is "protected" against elimination by negative frequency-dependent selection. From Schmid-Hempel, P. in *Allgemeine Parasitologie* (2006). Eds. Hiepe, Lucius, Gottstein, Peyer in *MVS Medizinverlage Stuttgart*.

in one specific, very common prey animal first decimate its population, and then switch to a different species of prey. This allows the decimated prey species to recover. In the case of the host–parasite relationship, however, evolutionary pressure is reciprocal, so allele frequencies of both parasite **and** host are subject to changes.

1.4.4

Malaria as an Example of Coevolution

There is hardly a disease which more clearly illustrates the sequence and the consequences of host–parasite coevolution than malaria. All four human pathogenic *Plasmodium* species (*P. vivax*, *P. ovale*, *P. malariae*, and *P. falciparum* see Section 2.6.3) are human-specific; their evolution is therefore tied exclusively to humans. In the past, only the natural defense mechanisms of humans held the parasites at bay – but now our defense arsenal has been expanded by mosquito repellents,

insecticides, and, especially, drugs against which the parasites are evolving evasion mechanisms. The development of drug resistance is a very good example of how parasites evade the selection pressure exerted by the host.

The history of *Plasmodium*'s drug resistance begins with the use of chloroquine. It was first synthesized in 1934 by the German chemist Andersag and accumulates in the parasitophorous vacuole, preventing the neutralization of toxic heme formed as a by-product of the parasite's breakdown of hemoglobin. Heme is normally aggregated into polymers and then stored in the food vacuole as an insoluble complex with proteins. Chloroquine inhibits the aggregation; the free heme is then toxic to the parasite. Resistance to chloroquine is caused by a mutation in the gene of the transporter protein *cg2* (=crt). This gene enhances the discharge of the active ingredient, detoxifying the parasite. According to current opinion, the known mechanisms of chloroquine resistance are derived from two independent mutations, which arose in 1957 in Asia and 1959 in South America. They have since spread around the world (Figure 1.27). Since the parasites develop resistance to avoid the effects of such specific drugs, the use of combination preparations (mixtures of two or more drugs with different active mechanisms) is now preferred. However, multiple mutations can also evolve and confer resistance, even against drug combinations.

Just as drug-resistant genotypes prevail under selective pressure in the plasmodia population, rare mutations also spread throughout human populations in malaria-endemic regions – if these mutations provide resistance to *Plasmodium*. The *P. falciparum* infection exerts a particularly strong selective pressure due to its high mortality rate. This infection is responsible for 40% of child deaths in some parts of Africa. In such regions, malaria – as a selective factor – has affected

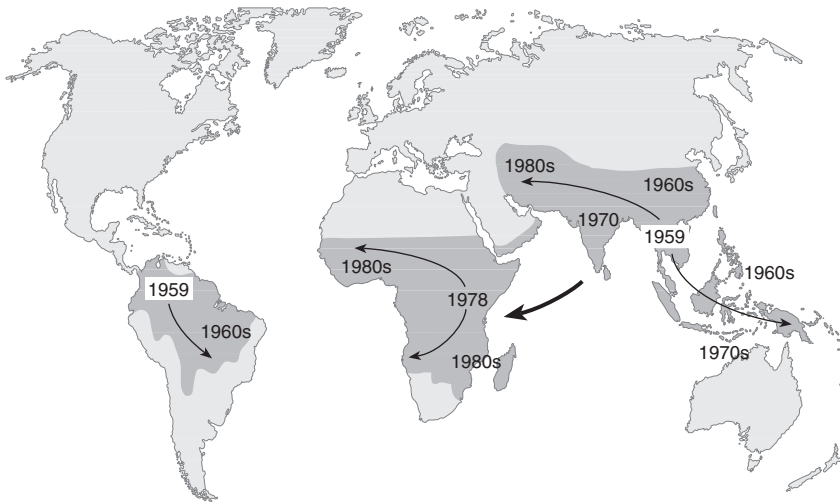


Figure 1.27 Chronological sequence of the worldwide spread of chloroquine resistance in *Plasmodium falciparum*. (Data from X. Su *et al.* (1997) *Cell* 91, 593–603.)

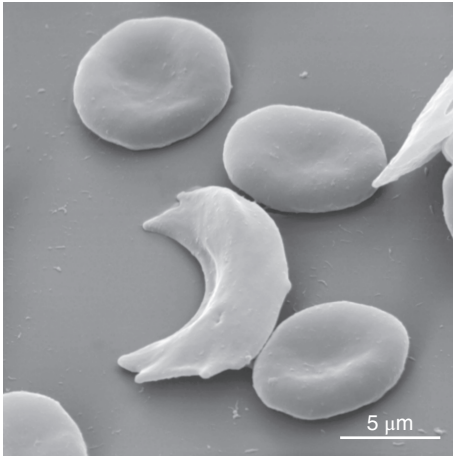


Figure 1.28 Sickle cell erythrocyte. (EM image: Courtesy of Eye of Science.)

humans as much as tuberculosis has affected the genome of the inhabitants of temperate climates.

One impressive example of the change of allele frequencies in humans as an adaptation to malaria is **sickle cell anemia**. This hereditary disease is caused by the amino acid valine replacing the glutamine at position 6 of the hemoglobin's β chain. With reduced oxygen tension, the peptide chains of the sickle cell hemoglobin form elongated polymers, causing deformation of the erythrocytes, which then take on a crescent shape (Figure 1.28). The red blood cells of sickle cell anemia sufferers also exhibit membrane changes and are relatively rigid. Since they are more rigid than normal erythrocytes, they get stuck in capillaries. Plasmodia cannot multiply as efficiently in these abnormal red blood cells as they would in normal erythrocytes, and therefore grow more slowly.

People who are homozygous for the sickle cell gene (HbSS) suffer from chronic hemolytic anemia, closure of capillaries, localized necrosis, and greatly increased susceptibility to bacterial infections. These symptoms are so severe that only 20% of HbSS patients reached adulthood before specialized medical centers were established in Africa. By contrast, there is hardly any clinical difference between heterozygous (HbAS) persons and those with normal hemoglobin (HbAA). However, heterozygous individuals possess 60–90% protection against severe malaria. They also have fewer parasites in their blood and the prevalence of parasitemia is lower. The heterozygous genetic trait probably exerts its main effect in early childhood: it appears that the poorer growth of the parasites allows the development of a more efficient immunity in infants aged up to 16 months.

The geographical frequency of the sickle cell disease correlates with the spread of tropical malaria (Figure 1.29). In some endemic areas, up to 40% of the population is heterozygous and manifests the HbS trait. The prevalence of the HbS trait in malaria-free areas, however, is negligibly low. So why is the frequency of

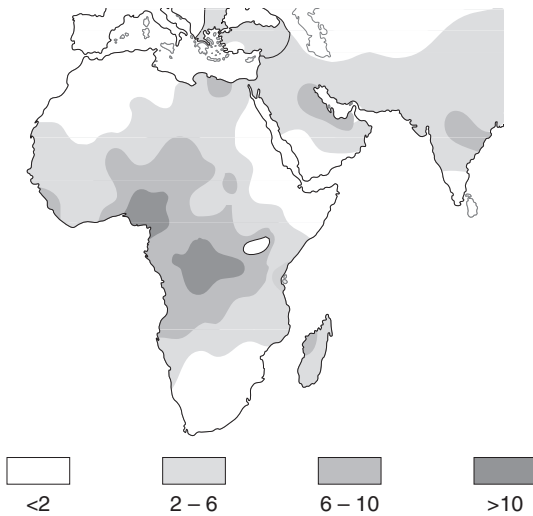


Figure 1.29 Frequency of HbS alleles (in %). The distribution of sickle cell anemia correlates with the spread of *Plasmodium falciparum*. (Compiled from various sources.)

the sickle cell gene not much higher in endemic areas? Models have ascertained that a balanced polymorphism is involved here – in malarial regions and under certain conditions, heterozygous carriers of the gene benefit from its protection against malaria and have a selective advantage, so their fitness is relatively high. This is why the frequency of the gene increases.

However, as the proportion of HbAS individuals increases, so does the probability that they will produce homozygous HbSS-type offspring that cannot survive. This reduces the genetic fitness of HbAS individuals; and under these conditions, it is comparatively advantageous to possess the HbAA genotype, although it does involve susceptibility to malaria. This trade-off results in a balance in which the proportion of persons with sickle cell disease correlates with the selective pressure induced by *P. falciparum*.

Other mutations that affect red blood cells have a similar effect: Abnormalities in the hemoglobin (e.g., hemoglobin C, various forms of thalassemia), enzyme defects (glucose-6-phosphate-dehydrogenase deficiency), or changes in transport proteins (in the case of Melanesian ovalocytosis) lead to severe handicaps or death in homozygotes, while heterozygous genotypes – in contrast to unchanged genotypes – have the advantage of immunity to malaria (Table 1.3). Alleles like this spread throughout endemic areas (even remaining prevalent in the human populations of former distribution areas some time after the disease has disappeared from the population) before ultimately subsiding. This is why the α^+ **Thalassemia** (from the Greek *thálassa* = the [Mediterranean] sea), the most common single-locus hereditary disease of the inhabitants of the former distribution areas of malaria, is widespread in the Mediterranean region.

Table 1.3 Some gene polymorphisms which cause resistance to *Plasmodium* infections in humans.

Protein	Disease	Mutation	Protection
Hemoglobin	Sickle cell anemia	Repl. in β chain at position 6 (valine)	Heterozygote: 60–90%
Hemoglobin	Hemolytic anemia	Repl. in β chain at position 6 (lysine)	Heterozygote: up to 74% Homozygote: up to 86%
Hemoglobin	α -Thalassemia	Deletion, limited production of α chain	Heterozygote: up to 34% Homozygote: up to 60%
Glucose-6-phosphate dehydrogenase	Favism (conditional hemolytic anemia)	Various mutations in the G-6-PD gene	Heterozygote: up to 46% Hemizygote: up to 58%
Band 3 protein	Melanesian ovalocytosis	N-terminal extended CD233 (bicarbonate transporter)	Protection against severe malaria

Susceptibility to malaria is determined by not only polymorphisms of hemoglobin but also immune responses. This is reflected in **polymorphisms of cytokine genes**, for example, mutations in the promoter region of the cytokines TNF- α and IL-10 or the inducible nitric oxide synthase. In addition, malaria has a strong influence on the **MHC make-up** of people living in endemic areas. In high-transmission areas, alleles that permit an efficient presentation of plasmodia peptides occur frequently – for example, the allele HLA B53 binds extremely efficiently to a peptide of the antigen LSA1 of *P. falciparum*, which is formed by liver cell stages. This is believed to permit the sensitization of cytotoxic T cells that can kill infected liver cells. Rare in Europe, this MHC genotype is associated with protection against the symptoms of severe malaria.

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Test Questions

1. How do parasites exert selective pressure on their hosts?
2. How do hosts exert selective pressure on parasites?
3. Why is intraspecific competition often the strongest form of competition?
4. Why are parasites much more dependent on their host than the other way around?
5. What circumstances cause parasites to adapt to their hosts and not vice versa?
6. What does the “Red Queen” hypothesis imply?
7. Give an example of a host switch.
8. What mechanism ensures the rapid spread of resistance in host or parasite populations?
9. Why do a host population’s rarely occurring alleles not simply dwindle away?
10. Which genetic diseases cause resistance to malaria?

1.5

Influence of Parasites on Mate Choice

The previous chapters have demonstrated that parasites diminish the condition of their hosts and their genetic fitness. Therefore, hosts would benefit if they could recognize and avoid infected conspecifics to avoid infection by directly transmitted parasites. Infected animals are also less suitable as sexual partners than healthy ones, as they could be less efficient in rearing the offspring and their offspring might inherit their susceptibility for parasites. What signals could allow an animal to discern whether a potential sexual partner is infected or not, and whether it carries suitable or less suitable genes? This is where **sexual selection** comes into play, a selection mechanism that relies among other things on conspicuous signals. Darwin rightly indicated that many animal species express conspicuous traits that are apparently disadvantageous and should therefore theoretically be counterselected. The expression of such **ornaments**, for example, the antlers of deer or the peacock’s tail (Figure 1.30), costs much energy and in many cases renders the animal much more visible or vulnerable to predators. Heavy and bulky ornaments would also exhaust their carrier, reducing its fitness at first sight. In spite of this, elaborate ornaments prevail in the males of many animal species, as they provide distinctive advantages in the context of the choice of sexual partners.

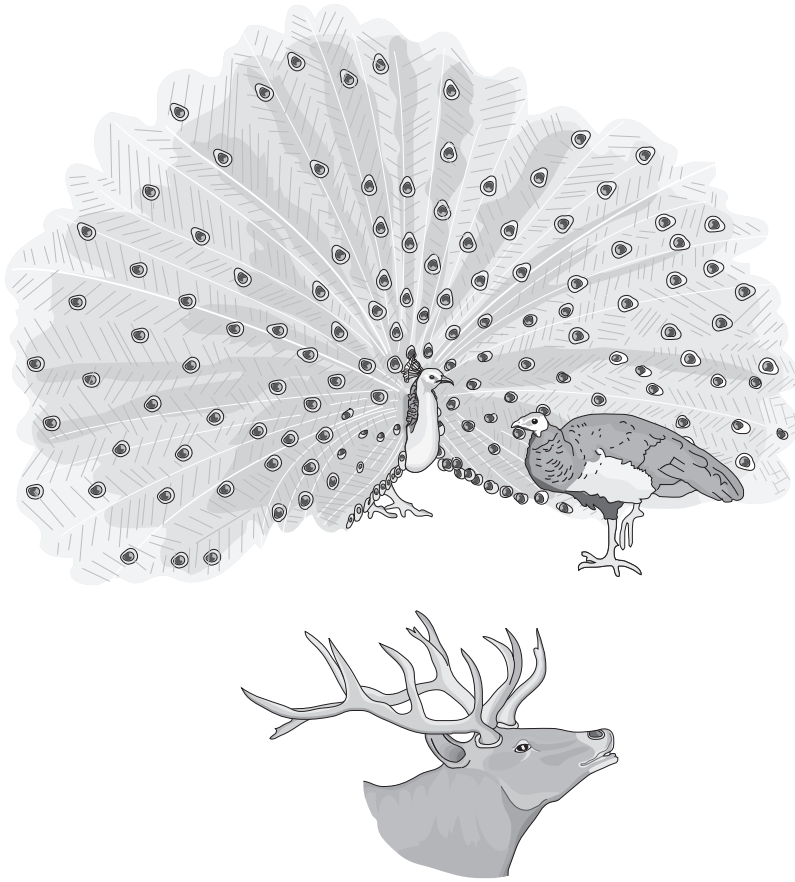


Figure 1.30 Ornaments such as the peacock's tail or deer antlers signal the genetic quality, including resistance against infections, of males to females.

According to a widely accepted hypothesis, costly ornaments are expressed by males as an indicator that these males can survive in spite of the handicap due to a good genetic constitution (**handicap principle**). In some animal groups, it is conspicuous decorative feathers, bright colors or the energetic songs and displays of males that determine which animals are finally chosen by females (**female choice**). In other animal species, for example, ungulates or seals, the selection is mainly driven by fights between competitors, the winner of which copulates with the most females (**male – male competition**). Both strategies are neither mutually exclusive nor can be strictly separated, since, for example, the dance of attractively plumed gallinaceous birds does also feature aggression among males, and vice versa the fights of deer also have an element of display, through which the males present themselves to the females. However, in both cases, a good physical condition is a prerequisite to win the favor of the females. Males with a poor physical condition, for example, due to malnutrition or infection, are disadvantaged and their genes

will not prevail. Therefore, ornaments are “**honest signals**,” which allow females to choose specifically between potential sexual partners. A parasite infection usually reduces the physical condition of males, and may also reduce the expression of ornaments. The preference of females for attractive partners therefore leads to the success of males that are resistant to infections, allowing them to pass on this genetic capacity to their offspring.

Before we address the mechanisms of mate choice more closely, we must discuss why in many cases females play the decisive role in the choice of the sexual partner. Irrespective of its gender, each individual strives to pass on to the next generation as many copies of its genome as possible. However, there is a significant gender-specific difference: Females usually invest relatively much energy in each single descendent, since they produce relatively few but large egg cells, eggs, or live offspring in comparison to the many small sperms produced by the males. Consequently, females are dependent on choosing the father of their offspring very carefully, to assure that their relatively few descendents have good chances of survival and reproduction. With this selection, females optimize their genetic fitness. Conversely, males should be less choosy regarding which females get their sperm, and seek to fertilize several females to produce many descendents. In simple terms, one could say that, regarding their choice of sexual partners, females focus on quality, whereas males go for quantity. In this context, it is necessary for females to check the health status of the male similar to an army doctor during physical examination of recruits.

Various explanations can account for the choices made by females:

- Avoidance of infection of the female and the offspring (transmission avoidance model).
- Provision of safety for the family and efficient acquisition of food by a healthy father (resource provisioning model).
- Optimization of genetic quality (good-genes model).

The good-genes model is nowadays the most widely invoked to explain mate choice, but the importance of the other factors is also accepted. It is assumed that females check the quality of males based on a variety of signals, and choose a partner with the condition and disposition to produce many high-quality offspring. In this context, resistance against parasites is an important factor. Information on the quality of the male is, among other routes, transmitted by visual and acoustical signals, and also through odors. Importantly, such key triggers do not only allow an assessment of the actual health status of the male, but also of the genetic quality of a candidate. Therefore, a female can check the qualities of a male in the sense of the good-genes model to find an optimal partner that matches its genotype and allows production of offspring that are resistant to parasites.

How does a female achieve **direct discrimination** between infected and non-infected conspecifics? Experiments with mice revealed that females decide based on information from the odor of urine whether a male mouse is infected with the nematode *Heligmosomoides polygyrus* or not. The same has been shown for infections with the apicomplexan parasite *Eimeria vermiformis* and other pathogens.

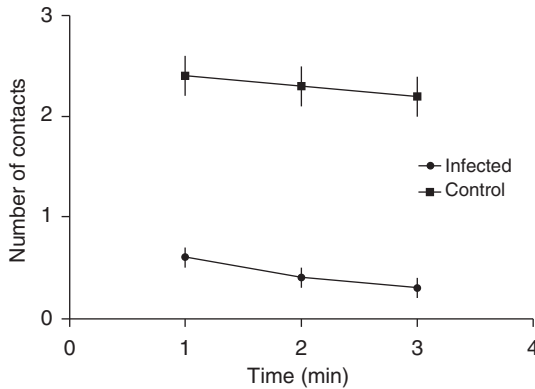


Figure 1.31 Lower attractiveness of infected males: female mice sniff at the urine of healthy male mice significantly longer than at the urine of males infected with *Eimeria vermiformis*. (According to Kavaliers and Colwell (1995) Proc. Roy. Soc. B. 261, 31–35.)

This is not surprising in itself as mice extract many chemical signals from the urine of their conspecifics. The experiments revealed that healthy females had an aversion to the urine of infected males (Figure 1.31). They avoid these males and prefer uninfected animals for mating. Males, too, discern between infected and healthy females by the odor of their urine and prefer uninfected female partners. Because females play a more important role in mate choice, their behavior is more decisive for mating and reproduction. Many similar studies suggest that the health status plays a key role in partner choice in other animals as well.

Studies with knock out mutants allowed to identify a key gene involved in the analysis of male infection status by female mice. Females with an inactivated oxytocin gene could not discern *H. polygyrus*-infected males from healthy ones. Oxytocin is a neurohormone that, among other things, is effective in creating a bond between sexual partners, or between parents and their offspring. Therefore, it seems as if the uptake of odor is followed by a rating that is mediated by oxytocin, and which decides between attraction or aversion. Oxytocin-deficient female mice cannot efficiently rate the quality of a potential male partner by its odor, and therefore instead copy the choices of other females regarding the selection of males, as revealed by mate choice experiments.

Indirect discrimination between male candidates based on their ornaments has also been very well demonstrated experimentally. As the genetic traits for the expression of ornaments seem to be linked to resistance genes, ornaments inform about not only the actual state of health but also the genetic quality of an animal. A female that chooses an attractive male therefore also chooses at the same time a partner that is likely to pass on resistance to parasites to their offspring. This **parasite-mediated sexual selection** is considered one of the driving forces in the coevolution of parasites and their hosts (Figure 1.32). Parasite-mediated sexual selection was first convincingly described in 1982 by Hamilton and Zuk. Analysis of data regarding parasite infection of American song birds revealed that males of

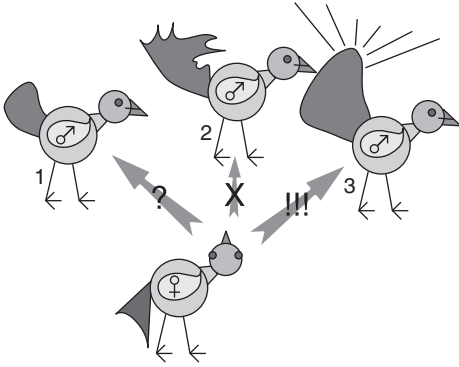


Figure 1.32 Parasite-mediated sexual selection. A female is rejecting male 1, since its poorly developed tail does not allow a statement on its parasite burden. The female rejects male 2, since its ruffled tail signals

a bad health status. Male 3 is accepted due to its healthy looking attractive tail. (According to Clayton, D.H. (1991) *Parasitol. Today*, 7, 329–334, by courtesy of the publisher.)

those species that are heavily parasitized by *Plasmodium* and related Hematozoa, as well as filarial nematodes, show the most conspicuous plumage colors. Since then, numerous experimental studies have corroborated the connection between expression of ornaments and resistance to parasites.

Some of the most convincing studies on parasite-mediated sexual selection were performed by Milinski and his group on the three-spined stickleback, a small freshwater fish. The experiments revealed that in this species, decorative colors are of great importance for the choice of a male by a female. In three-spined sticklebacks, the male builds a nest composed of plant materials and foam into which it lures the female to lay her eggs. In order to achieve this goal, it performs a dance consisting of a fixed sequence of behavioral elements: in the presence of a female ready to produce eggs, the male swims steeply upward and then falls back toward the nest with faltering movements. At the same time, it displays its bright red flanks to the females. With this mating dance (if successful), the female is lured closer to the nest, in which it deposits its eggs, which are then fertilized by the males (Figure 1.33). If the female is not interested in the male, it will swim away after a short time.

In a laboratory setting, the attractiveness of a male for a female has been shown to correlate with the length of time during which the female shows interest in the male's dance, from which it was separated by a glass pane. Males with extensive red color attracted the attention of female fish for significantly longer than the weakly colored males. The bright red color indicates the health state of the fish. The intensity of color declines in male sticklebacks that are infected with the ciliate parasite *Ichthyophthirius* (see Section 2.6.5.2). The key experiment consisted in comparatively determining the reaction of stickleback females to males before and after an infection with *I. multifiliis*. Male fish were significantly less attractive after they had undergone an infection and therefore showed diminished



Figure 1.33 Stickleback dance: The stickleback male tries to impress a female that is ready to lay eggs (noticeable by her bulging belly) through its red underbelly and lures the female into the nest. (According to J. Münzing in Grzimeks Tierleben (1970) Verlag Kindler Zürich.)

coloration (Figure 1.34). Consequently, male fish resistant to *I. multifiliis* have an advantage over their infected rivals, and their genotypes have a better chance to spread in the stickleback population.

The ornamental red coloration of male sticklebacks is produced by high concentrations of carotenoids in their skin. As the production of these pigments is relatively energy-intensive, red color is predominantly expressed by healthy animals. As the coloration indicates the actual state of health, it is known as a “**honest signal**” that allows females to choose healthy sexual partners. However, in the stickleback case, a rating based on coloration only allows a female to detect an actual infection, but not necessarily the genetic quality of a male. If coloration were the only criterion for choice, females might choose males that actually do not harbor a current infection, but are intrinsically highly susceptible due to their genetic disposition.

Further experiments have revealed that female sticklebacks not only rely on the coloration of male fish, but also check their genetic quality based on olfactory signals, as shown in choice tests. Male sticklebacks were kept in separate aquaria and only the “conditioned” water, containing soluble molecules released by the fish, was offered to females. It was shown that females exhibit individual preferences for water in which particular males had been maintained, probably due to olfactory signals of the males as key factors. Analysis of MHC genes showed that females preferred males whose MHC genes complemented their own genotype optimally, such that the probability of producing offspring with resistance to parasites was high. Such mate choice based on odors is not restricted to fish, but was also shown for mammals and even for humans. In the latter, too, odors convey information

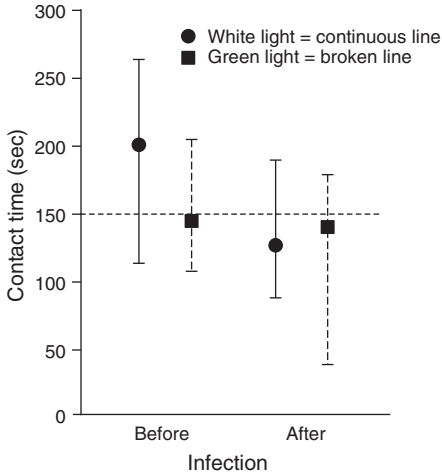


Figure 1.34 Time spent by female sticklebacks with male before and after infection with *I. multifiliis*. Before infection, males seen in white light (continuous line) are more attractive than in green light (broken line), because green light extinguishes the bright

red color of males. Infection reduces the red color, such that males are less attractive, and attraction is similar in white and green lights. (Created from data of Milinski, M. and Bakker, T.C.M. (1990) *Nature*, **344**, 330–333.)

on the MHC type of a potential partner. In choice experiments, women preferred odors of men whose MHC genes optimally matched their own genotype, such that their potential offspring would have good genes allowing efficient defense against pathogens.

The ranking of mates based on criteria that provide information on infection with parasites and/or the quality of the genotype allows the production of resistant offspring with a much higher efficiency than random mate choice. Apart from the aforementioned odors and ornaments, many other signals can contribute to the optimal choice of sexual partners. However, it should be remembered that parasites may also subvert such signals to increase their chances of being transmitted. Taken together, the existence of highly sensible communication systems suitable for the choice of partners resistant to parasites demonstrates the key importance of these pathogens in evolution.

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Test Questions

1. Which functions do ornaments have?
2. What is the handicap principle?
3. What are the potential disadvantages for a female and her offspring of mating with males showing weak ornaments?
4. Why is the male stickleback so colorful?
5. How do animals estimate the best fit of a partner's MHC genes with their own?

1.6

Immunobiology of Parasites

All parasites induce a variety of innate and adaptive immune responses – but they are not necessarily eliminated by these defensive reactions of the hosts. Parasites are in fact gifted immunologists that have developed successful strategies during the course of evolution – and these strategies help them evade host immune defenses and manipulate their hosts' immune systems. The ineffectiveness of some defense reactions previously led to the misconception that hosts do not develop immunity to parasites. Currently, it is known that many **effector mechanisms** of hosts kill parasites efficiently or at least limit their spreading. However, “successful” parasites that are well adapted to their hosts have efficient **evasion mechanisms**, which they use to thwart immune responses – a situation that often results in a stalemate. If malfunctions in the immune system disrupt this balance, some pathogens that are normally harmless can multiply unhindered, causing severe disease or even death (“opportunistic infections”).

In order to understand the immunobiology of parasite infections, we must consider the fact that individual genetic differences always occur within populations. As far as the host is concerned, immune effector mechanisms vary, giving them the ability to ward off parasites. Within a parasite population, the ability to evade effector mechanisms probably differs between individuals. Therefore, the course of the infection in many parasitoses varies greatly on an individual basis according to the different genotypes of host and parasite. In addition, there exist typical patterns for many parasite infections. In some host–parasite associations, clinically apparent infections occur only rarely, while the majority of the host population limits the infection to a subclinical level (e.g., in infections with *Leishmania donovani*). By contrast, the majority of the host population in highly endemic areas is infected with the filarial nematode *Onchocerca volvulus* and nearly all individuals will have clinically relevant infections, but with significantly varying degrees of severity – while most individuals will have relatively low worm burdens, a few

will be “worm-ridden.” These examples show that parasites always encounter a range of hosts with different degrees of susceptibility. Conversely, hosts are faced with a range of parasite genotypes with different degrees of virulence.

Depending on these differences, the symptoms of parasitoses can vary widely indeed. In particular, marked individual differences occur when the clinical outcome of a parasite infection is determined by immunopathology, that is, when immune responses significantly influence the symptoms.

Parasites are not only at the mercy of the immune system – in many cases, they use it for their own purposes, like the regulation of their population density. In a particular type of immunity – **premunition** – or “concomitant immunity,” protection against superinfection with the same parasite exists in the presence of infection (Figure 1.35). In many helminth infections, established worms evade the host immune responses – but infective stages do not have this ability and are eliminated. Also, in protozoan infections, for example, in the case of *Toxoplasma gondii* infections, immune responses induced by tissue cysts protect against new infections, with the result that competing conspecifics cannot colonize the host and the parasite burden remains limited. The term premunition has now been largely superseded by *concomitant immunity*, a term that originated in tumor research. In the case of intense infections with worms, yet another mechanism of population regulation (the *crowding effect*) results in the individual parasites remaining, on average, small and producing few offspring – the host suffers no undue stress and this consequently benefits the parasite in the longer term. Immune responses can also be exploited by parasites to transport their offspring to the outside world (see *Schistosoma mansoni*, section 3.1.1.5) and in some parasitoses it has been shown that host cytokines act as growth factors for the parasites, so well-adapted pathogens parasitize not only the host but also the host’s immune system.

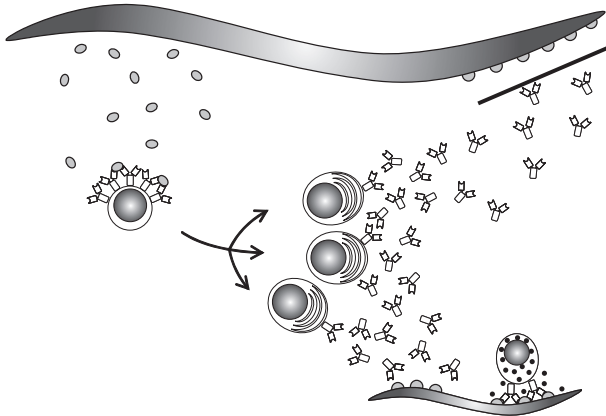


Figure 1.35 Schematic representation of premunition. The antigens of worms (gray ovals) induce immune responses that eliminate infective larvae; but established worms block these responses with immune evasion

mechanisms (represented by a bar). (By R. Lucius (1996) in *Allgemeine Parasitologie* (2006). Eds. Hiepe, Lucius, Gottstein, Pary in MVS Medizinverlage Stuttgart.)

This portrayal of the interaction between parasite and host at the level of the immune system will be limited here to parasites of vertebrates, although similar processes occur in invertebrate hosts. Typical patterns will be illustrated through examples of infections which have been intensively studied due to their medical and economic relevance. Since a comprehensive description of the functioning of the immune system is beyond the scope of this chapter, a textbook of immunology should be consulted where necessary.

1.6.1

Defense Mechanisms of Hosts

Hosts mount very different innate and adaptive immune responses against different parasites, depending on the different stimuli of the pathogen, the cells or organs affected, the duration of infection, and other factors. Even when infected with a single species of parasite, different immune responses can be induced, since each development stage may trigger specific reactions or can colonize immunologically distinct compartments within the host. For example, the liver stages of the malaria parasite *Plasmodium falciparum*, see Section 2.6.3.5) can be eliminated by cytotoxic T cells, while the blood stages of the same parasites are being attacked by antibodies. Therefore, the overall result of a parasite infection is usually a very complex suite of immunobiological processes.

1.6.1.1 Innate Immune Responses (Innate Immunity)

The infective stages of pathogens first trigger innate immune responses in a host. Here, molecular structures are detected as foreign to the host, but typical of pathogens, such as bacterial cell wall components or characteristic DNA sequences, or double-stranded viral RNA. The general term used for these structures is ***pathogen-associated molecular patterns*** (PAMPs). PAMPs are recognized by host receptors located on the cell surface or inside the cells. These receptors are referred to as ***pattern-recognition receptors*** (PRRs), such as Toll-like receptors (TLR) and Nod receptors. The binding of PAMPs to PRRs triggers specific signal chains, resulting in the activation of the cells and leading to the activation of effector reactions and the attraction of inflammatory cells. Pathogen molecules can also be detected by the complement system, which can cause the attraction of inflammatory cells and the destruction of foreign cells by soluble factors. Innate immune reactions like these often kill a large proportion of the parasite. For example, as many as 80% of the infective larvae are killed in some helminth infections. At the same time, these early-occurring, nonspecific immune responses also set the course for the imprinting of the later-occurring adaptive immune response.

One typical configuration of innate immunity against parasites is the activation of dendritic host cells, which in turn sets off a chain of reactions (Figure 1.36). PAMPs activate the dendritic cells and the latter produce cytokines (IL-12, IL-18, TNF- α , and possibly also IL-4), chemokines, and other factors that attract other cells chemotactically. The cytokines produced by dendritic cells often activate

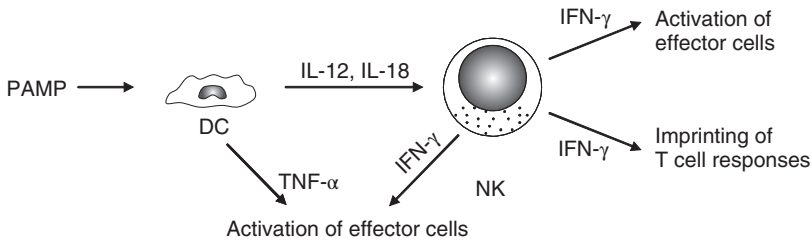


Figure 1.36 Example of the triggering of innate immunity. In dendritic cells (DC), parasite molecules (PAMPs) initiate an activation process, which leads to the formation of IL-12 and IL-18. In natural killer cells (NK), this leads to the production of IFN- γ , which affect other cells. For details, see text. (By R. Lucius In *Allgemeine Parasitologie* (2006) Eds. Hiepe, Lucius, Gottstein, Pary in MVS Medizinverlage Stuttgart.)

natural killer (NK) cells. These cells secrete IFN- γ , which, in turn, activates other cells. Relatively few PAMPs of parasites have been discovered to date. In the case of trypanosomes, plasmodia and *Toxoplasma*, glycolipid anchors of proteins have been identified as triggers that lead to the production of IL-12, IL-18, and TNF- α through binding to TLRs, with subsequent induction of IFN- γ . When amplified by TNF- α , this cytokine can trigger parasite-infected cells to kill their intracellular pathogens. Simultaneously, the nascent adaptive immune responses are instructed towards a proinflammatory Th1 direction (see below). However, some PAMPs (such as certain lipids from schistosomes) result in the production of IL-4 by dendritic cells and this promotes the less inflammatory Th2-type immune responses.

The activation of the effector cells by IFN- γ and other cytokines varies depending on the cell type. In the case of macrophages, activation causes (among others) the upregulation of phagocytosis and the production of reactive oxygen products (*oxidative burst*). Neutrophils and eosinophils release cytotoxic molecules stored within granules. The granules' cytotoxic molecules attack the pathogens, but also damage the host's own tissues. Even in the case of epithelial cells or fibroblasts, the activation by cytokines may result in changes in cell metabolism, resulting in the killing of parasites. Intracellular parasites can, for example, be defeated by changes in the tryptophan or iron metabolism. Just a single cytokine can trigger an extensive defense program, for example, the action of IFN- γ regulates more than 1000 genes of host cells.

The importance of a recently defined group of innate leukocytes, innate lymphoid cells (ILCs), has been confirmed in parasitic infections. These cells are highly potent cytokine-producing cells and comprise at least three major subsets. NK cells are also members of this group and the different populations are believed to work in concert with cells of the adaptive immune system in promoting different types of immune responses. They often play very important roles in the initiation of immune responses at barrier surfaces, for example, the skin and gut, where they expand in numbers in response to growth factors released by cells found at these sites (e.g., epithelial cells) following infection and damage.

The traditional roles of many innate cells are also increasingly recognized following the use of sophisticated techniques for analyzing cell function such as flow cytometry and gene expression. Macrophages adopt different functional capabilities depending on whether they are activated by particular cytokines, for example, M1 macrophages activated by IFN- γ and M2 macrophages by IL-4.

Furthermore, granulocytes such as eosinophils, neutrophils, basophils, and mast cells have been identified as regulatory cells that can modify their environment and the immune response through the secretion of cytokines such as IL-4, IL-13, TNF- α , and others.

1.6.1.2 Acquired Immune Responses (Adaptive Immunity)

The nature and intensity of initial innate immune responses have a major impact on the direction of the acquired immune response, which develops in the days following infection. The early cytokine response also influences the reaction of T cells, which are sensitized in lymph nodes near the infection site. Here, T helper cells play a dominant role through their function in orchestrating the qualitative and quantitative aspects of immune responses. Cytotoxic T cells play a more specialized role in targeting host cells with intracellular infection. The T helper cells are sensitized by presentation of parasite-derived peptides in the context of MHC II by dendritic cells and other antigen-presenting cells. The presentation of such peptides to the T cell receptor – in conjunction with costimulation by other molecules – activates the T cells to divide and produce cytokines. Depending on how a dendritic cell was triggered in the early phase of infection by PAMPs, the cell steers the differentiation of T cells in different directions (see below) and the dividing T helper cells (Th) take on a different phenotype (Figure 1.37).

- Th1 cells are characterized by the production of IFN- γ and other cytokines. They activate macrophages and other cells to kill intracellular pathogens; in humans, this leads to the formation of IgG2 and IgG3 antibody classes (IgG2a and IgG2b in mice), which are in turn efficiently detected by many effector cells. Strong overall inflammatory responses are the result, and these often damage the host tissue (“immunopathology”).
- Among other messenger substances, Th2 cells produce IL-4 as a typical cytokine. This mainly triggers B cells to grow, and as a result greatly stimulates the production of antibodies, particularly of the classes IgG1, IgG4, IgA, and IgE in humans (IgG1, IgE, and IgA in mice). Mast cells and eosinophils are also stimulated to divide and are subsequently activated. Th2 responses thus move the immune response in a direction that is particularly suited to the destruction of worms, by IgE and eosinophils, for instance. This too can result in damaged host tissues (“Th2 inflammation”). These inflammatory responses, however, tend to be weaker than Th1 responses.
- Th17 cells produce IL-17 and IL-22, which induce recruitment of neutrophils and stimulate epithelial cells to produce antimicrobial effector molecules. They are involved in epithelial and mucosal immunity, but also in many autoimmune diseases.

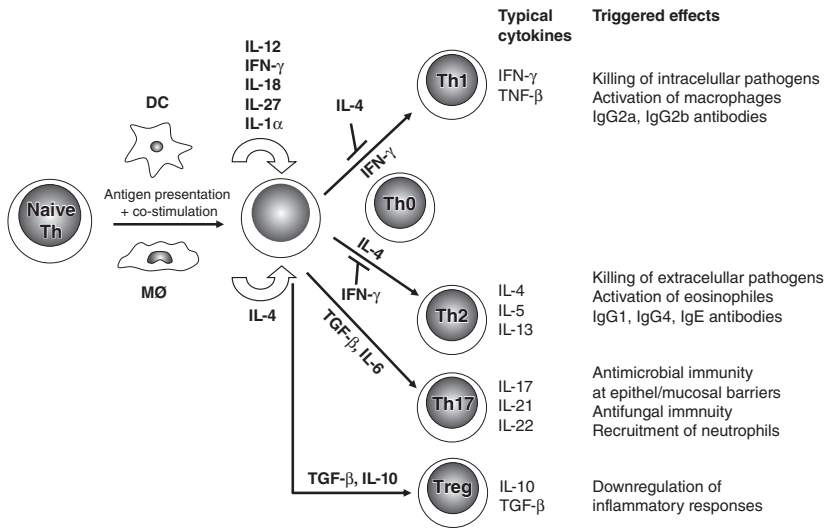


Figure 1.37 Differentiation of T cell subpopulations in the mouse. The differentiation is significantly influenced by the context of antigen presentation, in particular by the cytokine signals of antigen-presenting cells during the sensitization of T cells. In the presence of IL-4, there is a tendency to imprint Th2 cells (typical for

helminth infections), producing a specific pattern of cytokines. Similarly, the presence of other cytokines results in Th1, Th17, or Treg responses. For details, see text. From Lucius, R. In *Allgemeine Parasitologie* (2006) Eds. Hiepe, Lucius, Gottstein, Pary in MVS Medizinverlage Stuttgart.

- Regulatory T cells produce anti-inflammatory cytokines such as IL-10 and TGF- β . Their main task is the specific downregulation of excessive immune responses.

In a number of well-studied infections, Th1 responses develop in the early stages of a parasite infection. These responses limit the spread of the parasite, but switch to Th2-type responses during the course of a chronic infection. Often a crucial factor during the course of an infection is the correct sequence of immune responses. If switching to less inflammatory Th2 responses is insufficient during the chronic phase of infection, for example, the host may suffer from severe immunopathology.

1.6.1.3 Scenarios of Defense Reactions Against Parasites

Just which effector mechanisms attack and eliminate parasites depends greatly on the size and location of pathogens and is also determined by the compartment (e.g., skin, intestine, and blood) in which they live. Intracellular protozoa are thus targeted by different immune responses than large extracellular parasites such as helminths. In most cases, there is not merely a single suitable effector mechanism – several or many components of the immune system work together. The effectiveness of immune responses is also decisively determined by the immune evasion mechanisms of the parasites (see below):

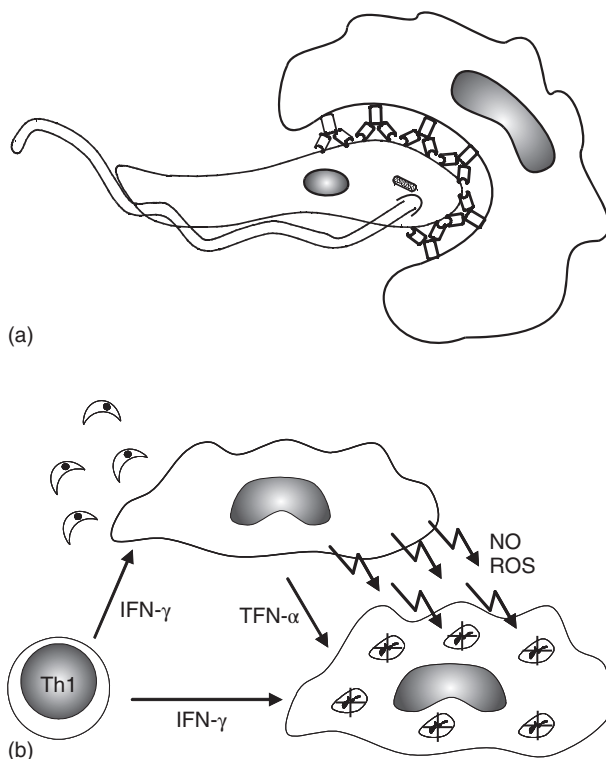


Figure 1.38 (a) Immune attack on extracellular protozoan parasites. Surface-bound antibodies make the parasite detectable for effector cells, resulting in phagocytosis. This process can be amplified by complement activation. (b) Killing of intracellular parasites. Th1 cells stimulate the host cell with IFN- γ to kill their intracellular parasites. IFN- γ can also result in the activation of macrophages that use their effector molecules to kill intracellular parasites in neighboring cells. From Lucius, R. in *Allgemeine Parasitologie* (2006). Eds. Hiepe, Lucius, Gottstein, Pary in *MVS Medizinverlage Stuttgart*.

- Small extracellular parasites can often be controlled by humoral immune responses alone (Figure 1.38a) – so probably the great majority of *Leishmania* from an early infection are repelled by activation of complement on the alternative pathway. Antibodies can prevent the adhesion of pathogens to host cells, agglutinate parasites, or make them detectable for phagocytes, mechanisms which, for example, eliminate many merozoites of plasmodia. Antibodies which activate complement are very efficient – the activation results, for example, in the elimination of *T. brucei* trypomastigotes in the blood by phagocytes.
- Intracellular parasites are of course shielded from antibodies and complement, but they can still be reached by several effector mechanisms. If presentation of parasite epitopes in the MHC I context occurs on the surface of the host cell, the cell can be killed by cytotoxic T cells – liver stages of *Plasmodium* can be eliminated in this way, for instance. Under certain circumstances, infected

host cells may kill their intracellular pathogens themselves by either producing cytotoxic molecules (e.g., reactive oxygen products or NO) or, if they have been activated by exogenous factors such as IFN- γ or TNF- α , by changing metabolic pathways (Figure 1.38b). A “kill” from the outside can also take place when nearby effector cells secrete cytotoxic molecules that diffuse into the infected cells, killing intracellular parasites.

- In order to defend against the relatively large helminths, however, the joint effort of several components of the immune response is usually necessary. The classic defense against worms is *antibody-dependent cellular cytotoxicity* (ADCC) – here, antibodies, possibly reinforced by complement activation through the classical pathway, make the surface of the parasites detectable for effector cells, which can then attack. In this way, eosinophils, neutrophils, or macrophages bind to the worms and release their effector molecules on to the surface of the parasite, harming it (Figures 1.39 and 1.40).
- The IgE-dependent degranulation of mast cells plays an important role in the defense against helminths in the intestines. Products of mast cell granules (primarily histamine) make the capillaries and epithelia permeable, attracting eosinophils, which in turn attack the worms. The release of certain peptides can activate peristalsis and initiate massive mucus production, expelling parasitic worms from the gut with a mechanism (*rapid expulsion*) that exhibits similarities to allergic reactions (Figure 1.41). Antibodies which gain access to the intestines can also lead to ADCC reactions.

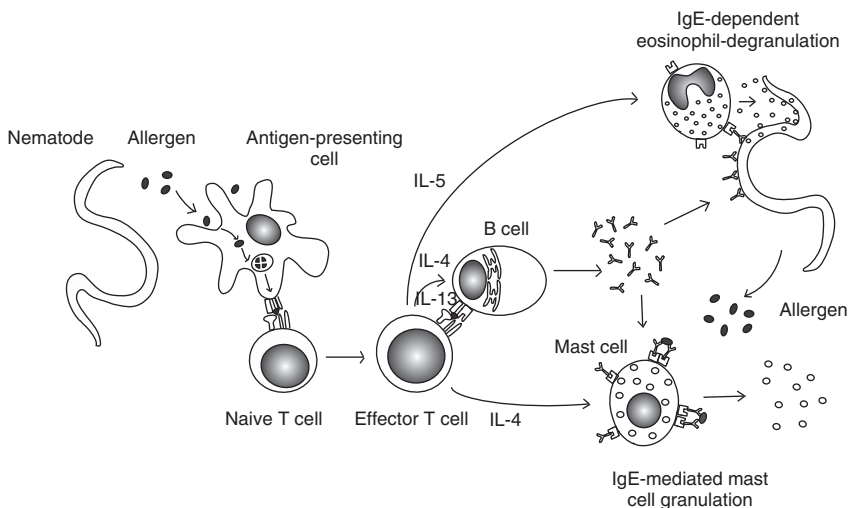


Figure 1.39 Immune attack on worms. The allergens secreted by worms induce IgE antibodies, which make the worms detectable for attacking eosinophils. The IgE-dependent

degranulation of mast cells facilitates the recruitment of eosinophils. For details, please see the text.

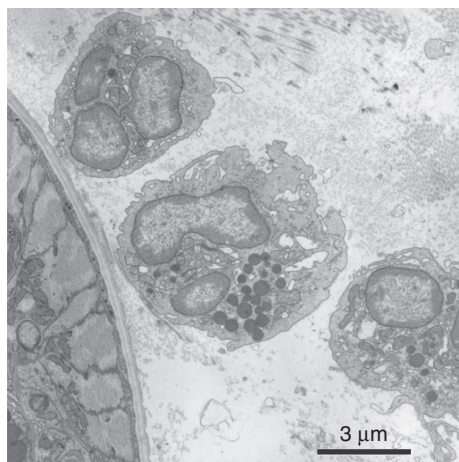


Figure 1.40 Eosinophils attack a third-stage larva of the filarial nematode *Acanthocheilonema viteae* in the tissue of a gerbil. (EM image: Department of Molecular Parasitology, Humboldt Universität.)

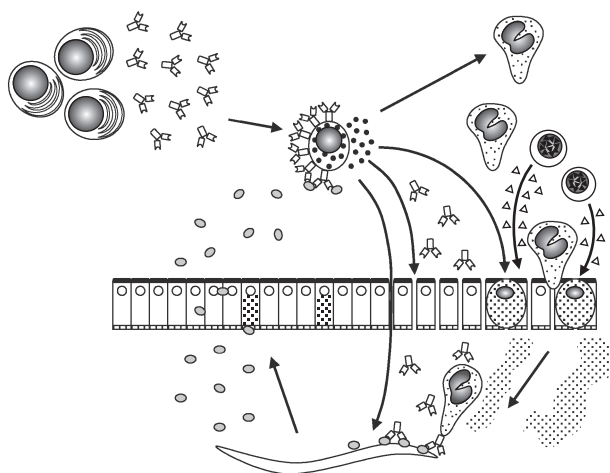


Figure 1.41 Immune attack on nematodes in the intestine. Worm antigens (*gray ovals*) passing into the sensitized tissues of the host that have already formed IgE antibodies, result in the degranulation of mast cells. The released mast cell products attract granulocytes and myeloid cells that release cytokines (black triangles), stimulate epithelial turnover and goblet cells to produce mucus. These factors loosen the association of epithelial

cells, creating permeability for antibodies, eosinophils, and the effector molecules of mast cells. Some mast cell products also act directly on worms. The combination of these effects results in the rapid expulsion of nematodes. For details, see text. (From Lucius, R. in *Allgemeine Parasitologie* (2006). Eds. Hiepe, Lucius, Gottstein, Pary in MVS Medizinverlage Stuttgart.)

- The saliva of hematophagous arthropods contains various compounds, which can trigger allergic reactions of both rapid and delayed types. This can prevent the parasites from taking blood.

1.6.1.4 Immunopathology

The symptoms of many parasitoses are characterized by pathological reactions caused by immune responses. Since the immunoreactivity of individuals is very varied depending on individual genetic predisposition and environmental influences, immunopathology is also varied – as is the clinical picture of the infection as a result. In host–parasite associations that have a long evolutionary history, the reactions are often limited, so serious diseases tend to be rare.

A common cause of immunopathology is **excessive inflammatory reactions**, where cytotoxic effector molecules are released. These not only damage the parasites, but also harm the surrounding host tissue (collateral damage). The constant stimulation by PAMPs (which are derived from persistent parasites) can thus cause chronic inflammatory responses that lead to the damage of host tissue. One example of this is the chronic infection of heart muscle cells (cardiomyocytes) by *Trypanosoma cruzi*, see Section 2.5.8). This leads to permanent myocarditis (Figure 1.42). This, in turn, causes the long-term degeneration of areas of the heart muscle, which may lead to muscle fatigue and rupture.

Diseases caused by immune complexes are another frequently occurring element of immunopathology: antibodies bind to parasite antigens, when they are released in great numbers in malaria infections, for instance. These immune complexes circulate in the blood, and are preferentially deposited in narrow vessels with high pressure and flow speed. They then activate complement, initiating the attraction of inflammatory cells and causing tissue damage. In the glomeruli of the kidney, this process can cause immune complex glomerulonephritis with chronic kidney problems, such as those that frequently occur in malarial or filarial

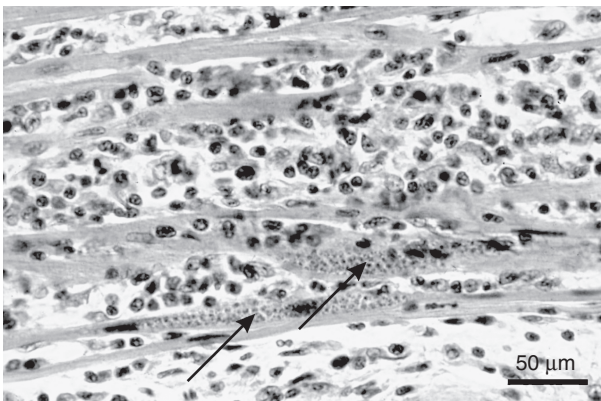


Figure 1.42 Myocarditis in Chagas disease. The muscle fibers have been infiltrated by inflammatory cells. Arrows: amastigote stages of *Trypanosoma cruzi* in muscle cells. (Image: Archive of the Department of Molecular Parasitology, Humboldt University, Berlin.)

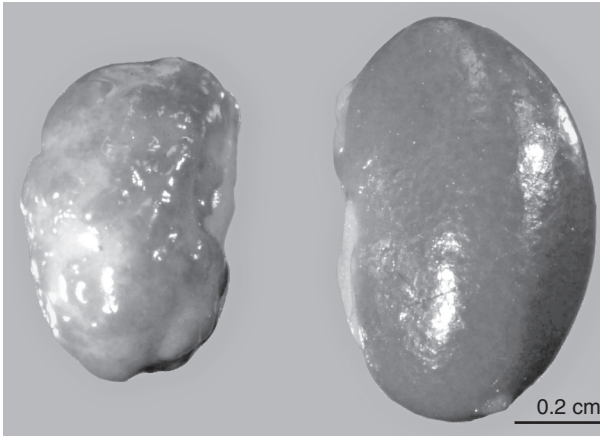


Figure 1.43 Kidney damage due to immune complex-mediated inflammation in gerbils infected with the filarial nematode *Acanthocheilonema viteae*. Left, damaged kidney; right, healthy kidney. (Image: Richard Lucius.)

infections (Figure 1.43). Small immune complexes can also escape from capillaries and activate complement in tissue, resulting in perivascular inflammations. In the case of *T. brucei* infections, perivascular inflammations are assumed to be a major factor in the development of sleeping sickness.

In many parasitoses, **immunosuppression** is the result of defects in the formation or function of leucocytes caused by parasite-related immunomodulation or exhaustion of particular immune responses. This can lead to increased susceptibility to other infections. In the case of *Leishmania donovani* infections, for example, a general depression of cell-mediated immune responses is observed. Together with other factors such as malnutrition, this depression is considered to underlie secondary infections (measles, pneumonia, tuberculosis, and others), which are a common cause of death. In the case of infections with trypanosomes and *Leishmania*, macrophages emerge with strong immunosuppressive properties. They produce prostaglandin E₂, for instance – and this strongly impairs the ability of the lymphocytes of infected individuals to proliferate. Another type of immunosuppression takes place after massive stimulation of B cells by B cell mitogens of *Trypanosoma cruzi*. Here, the simultaneous stimulation of all the B cells impedes specific antibody responses from developing. In addition, the constant stimulation of T or B cells by parasite antigens can lead to clonal exhaustion – a mechanism that has been held responsible for immunosuppression in malaria patients.

1.6.2

Immune Evasion

Parasites can only colonize an immunocompetent host if they avoid, thwart or alter its immune responses. This capacity is known as **immune evasion**. In most

parasite–host systems with a long coevolutionary history, every host effector mechanism has its counterpart in a parasite evasion mechanism, so effector and evasion mechanisms cancel each other out to some extent. This balance prevents the host from controlling parasite infections completely, as it must limit its effort because of trade-offs with other functions. Excessive investments in immune defense would not necessarily result in improved net fitness for the individual. A host that perfects its defenses at the cost of reproduction probably has a lower level of fitness than a conspecific which takes a residual risk of infection into account. On the contrary, investment in evasion mechanisms is of ultimate importance for a parasite, as their failure would be lethal (see also life/dinner principle, 1. 4. 1). The existence of very efficient immune evasion mechanisms also explains why it is difficult to develop antiparasite vaccines.

The spectrum of evasion mechanisms ranges from simple immune response-avoiding tactics and the circumvention of effector mechanisms to interfering with the control of the immune system (Table 1.4). The establishment of parasites in cells, tissues, or organs characterized by low immune responses is considered an

Table 1.4 Examples of effector mechanisms of hosts and corresponding immune evasion mechanisms of parasites.

Effector mechanisms	Evasion mechanisms	Pathogens
Activation of complement	Complement inhibitors in the surface membrane	<i>Trypanosoma cruzi</i> , <i>Schistosoma mansoni</i>
Oxidative burst of macrophages	Inhibition of macrophage activation and detoxification of reactive products through LPG	<i>Leishmania</i>
Antibodies	Intracellular lifestyle	<i>Trypanosoma cruzi</i> , <i>Leishmania</i> , Apicomplexa, <i>Trichinella</i>
Antibodies	Cutting of the FC ends by specific proteases	<i>Schistosoma mansoni</i>
Antibody-dependent complement-mediated cytotoxicity through Kupffer stellate cells	Antigenic variation	<i>Trypanosoma brucei</i>
Antibody-dependent cellular cytotoxicity by eosinophils	Induction of connective tissue nodule, permanent migration through the tissue	<i>Onchocerca volvulus</i> , <i>Loa loa</i>
Cytotoxic T cell responses	Survival in cells without or with little MHC I on the surface, Reduction of MHC I	<i>Plasmodium</i> (erythrocytes), <i>Toxoplasma</i> (neurons)
Inflammation caused by Th1 responses	Polarization of the T cell response to Th2	<i>Schistosoma mansoni</i> , filarial nematodes
Inflammation caused by Th2 responses	Inhibition of cell activation through IL-10 produced by various immune cells	Filarial nematodes

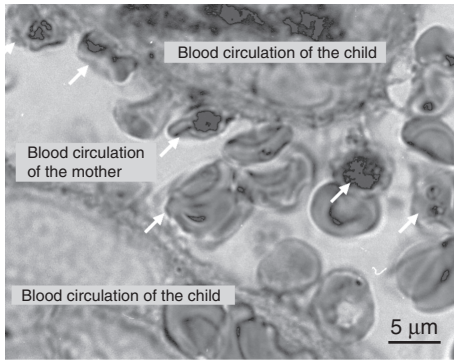


Figure 1.44 Cytoadherence. *Plasmodium falciparum*-infected erythrocytes (arrows) in a maternal blood vessel of the placenta. (Image: Courtesy of Mats Wahlgren.)

avoidance strategy. For instance, erythrocytes infected with *Plasmodium falciparum* prefer to adhere to the placenta's capillary walls. This is attributed to the fact that this environment is “immunoprivileged” (Figure 1.44) owing to immunosuppressive mechanisms active in this organ to prevent rejection of the fetus. The preference of some parasites for the central nervous system (e.g., tissue cysts of *Toxoplasma gondii*, see Section 2.6.2.6) is also attributed to less efficient immune responses in that environment. An intracellular localization can protect parasites from immune responses to a certain extent, as the spatial partitioning exempts them from being recognized by antibodies. Inflammatory cells can also be kept at bay to some extent through tissue barriers, a strategy that is pursued by some parasitic worms. The filarial nematode *Onchocerca volvulus*, see Section 3.3.4.14), for example, induces the formation of coarse connective tissue nodules, in which the convoluted female worms (up to 50 cm long) are ingrown, while the males are mobile. Very few inflammatory cells usually exist in these nodules, suggesting that the dense nodule tissue together with other mechanisms prevents effector cells from accessing them (Figure 1.45).

Parasites can also avoid effector mechanisms if they constantly keep on the move, preventing the effector cells from attacking effectively. It is quite conceivable that skin-dwelling microfilariae of the filarial nematodes *O. volvulus* and *Mansonella streptocerca* actually cast off effector cells during their constant migration through the connective tissue – and the same probably applies to the adult stages of the filarial nematode *Loa loa* that migrates through subcutaneous tissue.

Parasites can also incorporate host molecules into their surface, thereby escaping detection by the immune system. The best known example of this *antigen disguise* is displayed by adult *Schistosoma mansoni*: These worms incorporate among others MHC molecules, blood group antigens, and complement protein into their outer surface layer.

Some small parasites, which are genetically flexible due to rapid division rates, can evade the antibody responses of the hosts by varying their surface antigens

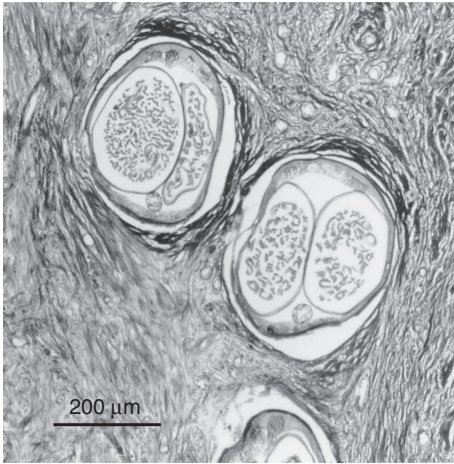


Figure 1.45 Sections of *Onchocerca volvulus* females in skin nodules. Note the absence of inflammatory cells in the connective tissue. (Image: Department of Molecular Parasitology, Humboldt University, Berlin.)

(trypanosomes, plasmodia, *Giardia*). The best example of antigenic variation is illustrated by *Trypanosoma brucei*. It has a large family of genes, which encode variable surface glycoproteins, and different variants of these antigens are expressed approximately every 10 days – so any specific antibody response will quickly become obsolete and prove futile, with the parasites managing to remain one step ahead of the immune response. The specific aspects of antigenic variation in individual parasites will be discussed later in this book.

One key strategy of immune evasion is the inactivation of effector molecules. The inhibition of complement activation is vital for many single-cell organisms and worms – three different complement inhibitors have been found in *Trypanosoma cruzi* alone. Antibodies can be rendered ineffective by highly specific proteases secreted by parasites, and cytotoxic effector molecules of immune cells, such as reactive oxygen and nitrogen products, are counteracted by increased production of detoxifying parasite enzymes (glutathione-S-transferase, glutathione peroxidase, catalase, etc.).

By secreting specifically-acting products, parasites can also interfere with the cytokine network, enabling them to modulate local or systemic host immune responses. Some parasites manage to suppress proinflammatory Th1 immune responses (which are potentially dangerous to the pathogens) in favor of less aggressive Th2 immune responses (see *Taenia crassiceps*, Section 1.7.2). In filarial infections, studies have identified several secreted parasite products that alter the activation and cytokine production of immune cells, downregulating inflammatory responses. It is therefore assumed that helminths and other parasites interfere with the central switching points of the immune system, altering the host's “immunological phenotype” to suit their purposes.

1.6.3

Parasites as Opportunistic Pathogens

Individuals with an intact immune system (“immunocompetent”) can repel or limit many potentially pathogenic organisms. By contrast, if important components of the immune system fail, some protozoa, helminths, and arthropods can establish themselves, causing diseases that either do not occur in immunocompetent individuals or are limited or controlled by their immune system. Pathogens that occur exclusively or predominantly in immunocompromised hosts are termed **opportunistic pathogens**. This category includes many important parasites of humans and animals.

Since the spread of HIV/AIDS in the 1980s, the importance of opportunistic pathogens has increased dramatically, because AIDS patients usually die from infections that would normally pose no threat to immunocompetent individuals. In the case of AIDS, the decrease in the number of T helper cells colonized and destroyed by the virus is the main cause of immunosuppression in HIV-infected individuals. There is a clear correlation here between the number of CD4⁺ cells and susceptibility to different pathogens (Figure 1.46).

Similarly, immunosuppression through other causes can also increase susceptibility to pathogens. Transplant recipients are threatened, for example, since they are chemically immunosuppressed to reduce rejection reactions. The chemotherapy or radiation therapy of tumors may also be associated with immunosuppression, increasing the risk of infection. The unborn and the old are also more susceptible to certain infections, since the immune system of the fetus is not yet developed and the immune system’s efficiency decreases with age. Malnutrition (and particularly the protein deficiency usually associated with it) is also a widespread cause of immune deficiency – and this is why many infectious diseases in tropical developing countries are more frequent and severe.

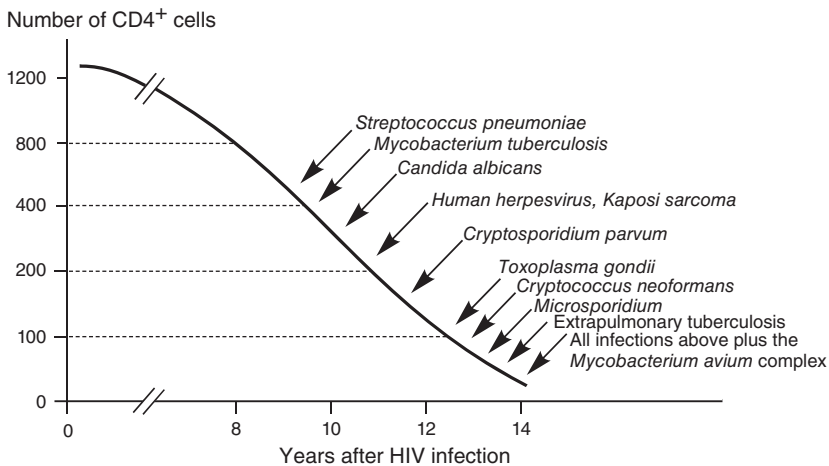


Figure 1.46 Occurrence of opportunistic infections depends on the density of CD4⁺ T cell per μl of blood. (Composed from various sources by W. Presber.)

As opportunistic pathogens, *Leishmania* (see Section 2.5.9) have become very important in relation to the AIDS pandemic. Many clinically healthy persons are probably latently infected in endemic areas, but the parasites cannot spread under the pressure of the immune response. It is believed that such silent infections are clinically relevant in persons suffering from immunosuppression, due to AIDS, for instance. The probability of developing a visceral leishmaniasis is therefore 100–2300 times higher in AIDS patients than in immunocompetent people infected with *Leishmania* – and the fact that around 70% of all reported cases of leishmaniasis in Spain and Portugal involve HIV patients is explained by the reactivation of latent infections.

Among Apicomplexans, one important pathogen-causing opportunistic infection is *Cryptosporidium parvum*, see Section 2.6.2.1). This parasite can cause severe bouts of diarrhea in AIDS patients – and such bouts can be the direct cause of death. Unfortunately, there is no specific treatment for cryptosporidiosis, as drugs acting against other Apicomplexans are not effective against *C. parvum*. *Cyclospora cayetanensis*, an *Isospora*-like parasite of tropical climes, may also cause severe diarrhea in immunocompromised people. In healthy persons, infections with *Toxoplasma gondii*, see Section 2.6.2.6) mostly run subclinical courses with flu-like symptoms that heal after several weeks: under the pressure of the immune response, tissue cysts form preferentially in the brain. These cysts contain long-term resting stages, the bradyzoites. If the level of immune responses decreases (e.g., as a result of HIV infection), the dormant stages can be activated and tachyzoites then differentiate, spreading locally into the surrounding tissue. Inflammation and tissue damage in the brain can cause large and potentially lethal lesions (Figure 1.47). *Toxoplasma* infections passed from mother to fetus can also

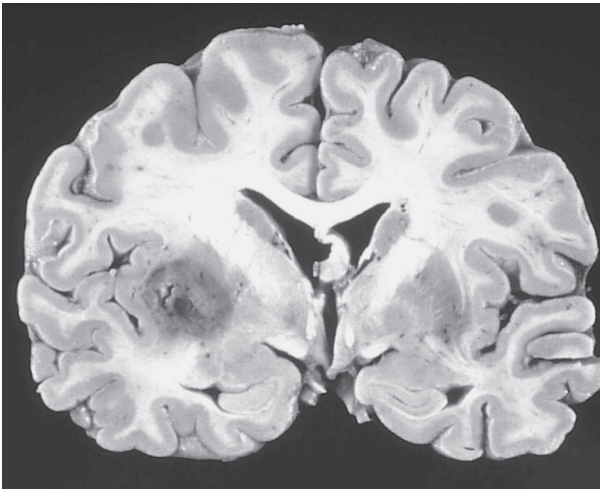


Figure 1.47 Reactivated toxoplasmosis in the brain of an AIDS patient. Note the necrotic area in the left hemisphere. (Image: Courtesy of Julio Martinez.)

cause varying degrees of fetus damage. In the first trimester of pregnancy, a *Toxoplasma* infection usually results in the death of the embryo or an abortion, while later infections can cause severe defects.

In immunocompromised individuals, infections with *Balantidium coli* (see Section 2.6.5.1) and *Entamoeba histolytica* can cause severe bouts of diarrhea – and in the case of amoebic infections, extraintestinal infections in HIV-infected patients may occur more frequently than in immunologically healthy individuals. *Acanthamoeba*, the pathogen that causes granulomatous meningoencephalitis, is also more common in immunocompromised individuals.

Certain helminths and arthropods can also be opportunistic pathogens. The nematode (*Strongyloides stercoralis*, see Section 3.3.4.1) can cause severe infections in immunocompromised people. One peculiarity in this parasite's life cycle is noteworthy: *S. stercoralis* is capable of autoinfection, which is unusual for helminths (see Section 1.2.3). Great numbers of larvae occur in immunosuppressed hosts. During their migrations through the host's body, the larvae can cause life-threatening inflammations and various changes in organs like the lungs and brain.

Eyelash mites, *Demodex folliculorum* and *Demodex brevis* (see section 4.2.4.1), can also play an opportunist role. These mites, living inconspicuously in hair follicles and the sebaceous glands of the hair follicles can cause skin diseases in immunocompromised individuals. The itch mite *Sarcoptes scabiei* causes a higher-grade disease in immunocompromised patients. Large areas of the body can be affected and the disease can develop into the severe form known as Norwegian scabies.

1.6.4

Hygiene Hypothesis: Do Parasites Have a Good Side?

The last half of the twentieth century has seen a steady increase in allergic and inflammatory diseases in developed countries, but not, however, in less developed countries. According to many scientists, this is due to the decline of infections in countries with highly developed hygiene (the “hygiene hypothesis”). It has been suggested that the relatively rare occurrence of childhood infections in industrialized countries together with other factors would leave regulatory circuits of the immune system untrained. As a consequence, overshooting inflammatory responses in adults would become more frequent. This hygiene hypothesis has an additional aspect, as infections with pathogens may also downregulate inflammatory responses. In particular, helminth infections have a significant impact on allergic and inflammatory reactions, as recently revealed by epidemiological data, animal experiments, and clinical trials.

For instance, in Africa and South America, children infected with *Schistosoma mansoni* or with the hookworm *Necator americanus*, respectively, were dewormed in carefully controlled studies and checked for allergic skin reactions. Dewormed children had significantly more allergic skin reactions to house dust mite allergen – thus infestation with parasitic worms clearly protects against this

type of allergy. However, only chronic worm infections have this effect – weaker, temporary worm infections can even increase susceptibility to allergies – so it is obvious that long-term helminth infections can alter the regulation of the immune system in such a way that the tendency to allergies (and other inflammatory reactions) is reduced.

This alleviation of allergic diseases is seen today as a positive side effect of the evasion mechanisms through which parasitic worms block IgE-mediated immune attacks of the host. IgE-mediated mast cell degranulation and IgE-mediated binding and degranulation of eosinophils are classical defense reactions against worms. In allergic infections, these same reactions – elevated levels of IgE, eosinophilia, and activation of mast cells – are triggered by environmental allergens such as pollen, molecules in cat hair, or dust mites. In a sensitized individual, when allergens like these are detected by IgE antibodies bound to the surface of basophils or mast cells via specific Fc receptors, an immediate reaction takes place, in which the cells release histamine, chemotactic substances, and cytokines. The subsequent reactions lead to swelling, redness, and itching. Later stages of the allergy are characterized by the accumulation of cells, which are mainly eosinophil granulocytes that cause tissue destruction through the release of their granules. These allergic symptoms can affect the skin, the mucous membranes of the eyes and nose, for example, or the lungs in the form of allergic asthma.

So, which evasion mechanism of parasitic worms could prevent the onset of these allergic symptoms? Four main causes have so far been discussed:

- Inefficient degranulation of basophils and mast cells due to changes in antibody responses. Helminth infections usually stimulate the production of nonspecific IgE. This results in the “dilution” of allergen-specific IgE on the surface of effector cells. At the same time, IgG4 production can be strongly stimulated and compete for epitopes, intercepting antigens before they come in contact with IgE-sensitized basophils and mast cells.
- The secreted products of parasites could prevent the attraction and activation of effector cells, for example, by cleaving eotaxin, an attractant and activator of eosinophils.
- The induction of regulatory T cells, which downregulate inflammatory responses with the IL-10 and TGF- β cytokines they produce.
- The induction of regulatory macrophages, which inhibit downstream activation of immune cells and effector mechanisms.

Can the anti-inflammation effects caused by helminth infections be used to influence undesirable immune reactions such as allergies and inflammations? Various animal models have shown that colon inflammation, autoimmune diabetes, asthma, gastritis, and experimentally induced brain inflammation may indeed be reduced by nematode infection or nematode products. Positive effects like this could be harnessed if it were possible to decouple them from the harmful effects of a parasite infection.

The following example shows that this is indeed possible: on the basis of data from studies in animal models, clinical studies have been conducted with patients

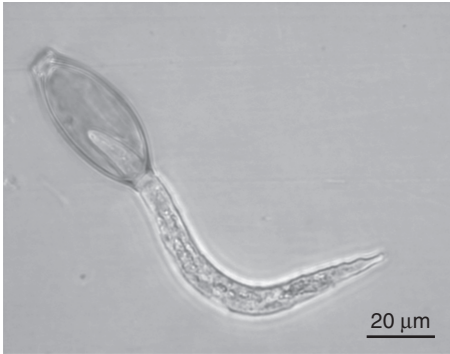


Figure 1.48 Hatching larva of *Trichuris suis*. (Image: Courtesy of Ovamed.)

suffering from the chronic inflammatory bowel diseases known as ulcerative colitis and Crohn's disease. Eggs of the pig whipworm *Trichuris suis* (Figure 1.48 see also Section 3.3.3.2) were administered to the subjects at regular intervals. The larvae of *Trichuris suis* hatch in the human intestine and die there, since they do not reach sexual maturity in what for them is an unsuitable host. During the course of their brief development, they reduce inflammatory responses, with the result that a marked improvement of the disease was observed in a significant proportion of patients.

These patients do not suffer ill effects from the parasite, since the larvae die at an early stage. The spreading of the parasites is also excluded, because the worms do not produce eggs. It is thus possible to take advantage of the positive effect of a parasitosis – without suffering any negative impact. Further studies must show whether or not a similar treatment can also affect allergies and other inflammatory diseases. As parasite molecules involved in downregulation of immune responses have been characterized, treatments based on defined molecules might become available in the future.

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Test Questions

1. How are pathogens recognized by innate immune responses?
2. How can intracellular parasites be killed by their host cells?
3. By which mechanisms can intestinal helminths be expelled very rapidly?
4. Which type of immune response is induced by insect saliva?
5. Give an example of inflammatory disease caused by persisting parasites.
6. Which organ is frequently damaged by immune complex diseases?
7. How can nematodes isolate themselves spatially from immunoreactive compartments of the body?
8. Give an example of disguise with host antigens and examples of antigen variation.
9. What is the danger of latent toxoplasmosis in immunocompromised individuals?
10. What is the relationship between allergy and helminth infections?

1.7

How Parasites Alter Their Hosts

With their relatively long generation times, eukaryotic parasites tend to exploit their hosts for long periods. In order to create an optimal niche, they modify the morphology, metabolism, immune reactions, and/or behavior of their hosts. Using highly specific mechanisms, the pathogens alter properties of their host – or in other words, they modify its phenotype. Therefore, parasite genomes do not stop at encoding their own phenotype; parasite genes are also expressed through modifications of the host phenotype. Evolutionary biologist Richard Dawkins compared this capability of parasites with the ability of beavers to change a landscape to their advantage by building dams and coined the term “**extended**

phenotype.” Many spectacular changes such as parasitic castration or bizarre behavioral alterations of the host provide examples of the importance of this concept. More subtle modifications are found in almost all parasite infections, so we can generally assume that well adapted parasites manipulate their hosts to optimize their own survival, reproduction, and transmission. The following chapter presents examples of this phenomenon. Modifications of host-defensive reactions have already been discussed in Section 1.6.

1.7.1

Alterations of Host Cells

Many intracellular parasites alter their host cell in a spectacular way – and the mechanisms they use to do this remain mostly unknown. For example, the transformation of host cells by stages of cyst-forming coccidia can result in extreme enlargement – *Sarcocystis gigantea* produces tissue cysts of up to 15 mm in length within the pharynx muscle cells of sheep (Figure 1.49). The survival of these modified cells – which are almost completely filled by parasite stages – necessitates a substantial reprogramming of the host cell. In a less obvious way, *Toxoplasma gondii*, see Section 2.6.2.6, Fig. 2.57). modifies its host cell by attracting mitochondria and the endoplasmic reticulum toward the parasitophorous vacuole and by inducing the formation of a thin wall around tissue cysts. The molecular processes underlying such changes are studied by -omics techniques such as transcriptomics, proteomics, and metabolomics, but these studies are still restricted to model parasites. Such work indicates that intracellular parasites interfere with transcription regulation and signal transduction in a targeted manner. For instance, *T. gondii* releases specific phosphatases that activate particular transcription factors, which, in turn, regulate cytokine expression of the host cell. A far-reaching modification can also be achieved without influencing gene-regulatory networks, as shown by the example of *Plasmodium falciparum* modifying its red blood host cell, which is devoid of a nucleus. *P. falciparum* creates within the erythrocyte’s cytoplasm a network of membranes, through which proteins are transported to the surface of the host

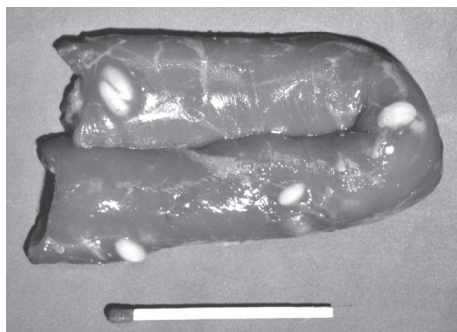


Figure 1.49 Muscle cyst of *Sarcocystis gigantea* on the pharynx of a sheep. (Image: Archive of the Department of Molecular Parasitology, Humboldt University, Berlin.)

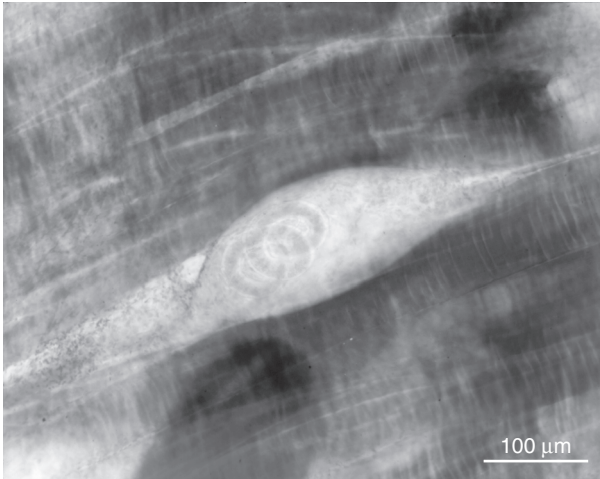


Figure 1.50 Nurse cell first-stage larva of *Trichinella spiralis* in the muscle tissue of an infected rat. (Image: Archive of the Department of Parasitology, University of Hohenheim.)

cell to allow adhesion of infected erythrocytes to blood vessel endothelia. These mechanisms are dealt with in more detail in other chapters.

The ability to alter host cells is not limited to single-celled organisms. The first larval stage of the nematode *Trichinella spiralis*, see Section 3.3.3.2) penetrates a muscle fiber and reorganizes the fiber in such a way that it grows to several times its original size (Figure 1.50). A collagen sheath is also formed and the resultant nurse cell is supplied with nutrients from newly formed blood vessels. In the case of *T. spiralis*, parasite proteins have been found in the nucleus of the host cell – thus, it is assumed that the intracellular nematode larva interacts with transcription regulation to alter the cell activity. A similar ability to reprogram the host cell has also been demonstrated in plant-parasitic nematodes. These examples show that parasites possess strong mechanisms to reprogram their host cell in very targeted ways.

1.7.2

Intrusion into the Hormonal System of the Host

Digenetic trematodes provide particularly compelling examples of the intrusion of parasites into the hormone metabolism of their hosts. Trematodes have inhabited their molluscan hosts since the Paleozoic era about 570 million years ago – and thanks to this prolonged coevolution, they have evolved the ability to exploit their hosts to a very great extent. This is impressively demonstrated in the study of infected snails: the largest organ in mollusks, the hepatopancreas, is normally brown, but in infected individuals of many species, it is very bright-colored. This is caused by the almost total replacement of the tissue by trematode stages (sporocysts, rediae, cercariae, Figure 1.51). The gonads of infected snails are often reduced or even missing altogether because the parasites have castrated

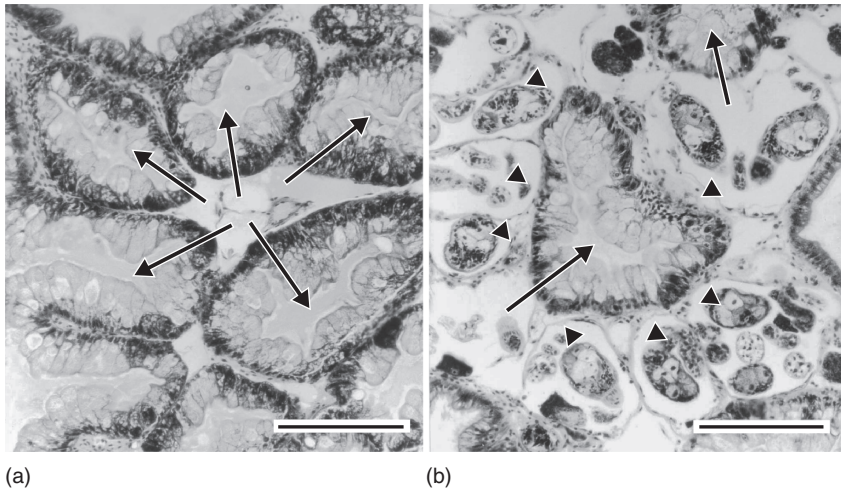


Figure 1.51 Cross section of the liver of a *Biomphalaria glabrata* snail infected with *Schistosoma mansoni* (b) and the liver of a control animal (a). Note the degree of displacement of liver tissue (arrows) by parasitic stages (arrow heads). (Scale = 150 μ m). (Image: Department of Molecular Parasitology, Humboldt University, Berlin.)

their hosts, either hormonally or mechanically. In trematodes with sporocyst stages, hormonal castration usually occurs, while species with rediae can actually eat the gonads. This “parasitic castration” diverts resources from the host snail’s own reproduction to the production of parasite stages. Egg laying by the snail is either limited or completely stopped in favor of cercariae production.

However, this is not the only consequence of castration. In the dwarf pond snail *Galba truncatula*, infection with *Fasciola hepatica*, see Section 3.1.1.8) larvae results in not only complete castration but also enhanced growth of the snail, with the result that parasitized snails achieve a significantly greater weight than uninfected control animals (“parasitic gigantism,” Figure 1.52). This seems paradoxical, since the rediae of *F. hepatica* actively consume host tissue. However, the loss of the gonads seems to allow diversion of resources normally allocated to reproduction and makes them available for somatic growth, allowing other host tissues, including the shell, to achieve greater than normal sizes. In addition, the loss of parts of the host is obviously offset by the biomass of the parasite.

Evidence of molecular mechanisms that cause hormonal castration is found in *Trichobilharzia ocellata* infections of *Lymnaea stagnalis*. This pond snail regulates its growth, metabolism, and reproduction activity by means of peptide hormones produced by specialized nerve cells in the brain. It has been found that infection causes a marked change in the snail’s hormone pattern. An obvious key element in these alterations is the defense peptide schistosomin, which is released into the hemolymph shortly after contact with the parasite occurs. Schistosomin suppresses the female gonadotropic neurohormone calfluxin. The decrease in hormone levels inhibits the rate of protein synthesis in the snail’s albuminous

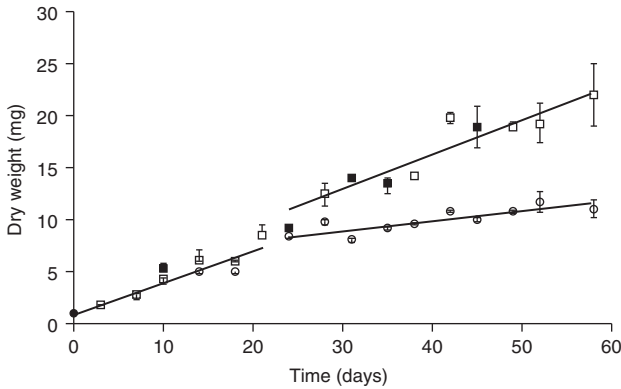


Figure 1.52 Growth of the snail *Galba truncatula* after infection with *Fasciola*, expressed by increase in dry weight. Uninfected snails (circles) begin to produce eggs after 20 days and grow only slightly. Infected snails (squares) are castrated, produce no eggs, and continue to grow. (From Wilson, R. A. and Denison, J. (1980) *Z. Parasitenkd.* 61, 109–119.)

gland, reducing it to <1% of the initial rate. Since the albuminous gland produces the highest proportion of egg protein, this intrusion leads to a drastic reduction in egg production.

Metacestodes also effectively regulate the hormonal system of mammalian hosts, as illustrated by a series of studies on *Taenia crassiceps* infection in mice (Figure 1.53). *T. crassiceps* is a cestode of foxes and dogs; its metacestodes develop in the abdominal cavity of rodents and multiply there asexually. Mice can thus be easily infected with metacestodes intraperitoneally – and the growth and the effects of metacestodes on the host can then be studied. In the early stages of the infection, *Taenia crassiceps* reproduces faster in female mice than in male mice.

In later stages of the infection, the male mice also provide good conditions for the parasites. This shift is due to the feminization of the males by the parasites. In the case of a prolonged infection, male mouse testosterone levels drop to 10% of their initial value, while the levels of estradiol increase up to 200 times their normal amount. Here the benefit for the parasite lies in the modulation of immune responses, which are partly controlled via the endocrine system. A female-oriented hormone system favors the development of the immune responses of the less aggressive Th2 type. This response allows better growth of the metacestodes than the Th1-oriented immune responses of uninfected males. Estradiol also acts as a growth factor by favoring the growth of the metacestodes.

Feminization by *T. crassiceps* involves the interaction of the immune and endocrine systems. A key event here is the production of IL-6 in cells of the testes, which, in turn, induces the expression of aromatase P-450. This enzyme causes testosterone to be converted to estradiol. IL-6 also boosts the production of the follicle-stimulating hormone (FSH), which in turn increases the expression of aromatase. The importance of IL-6 is underpinned by the fact that IL-6 *knock-out* mice are not feminized by the parasite.

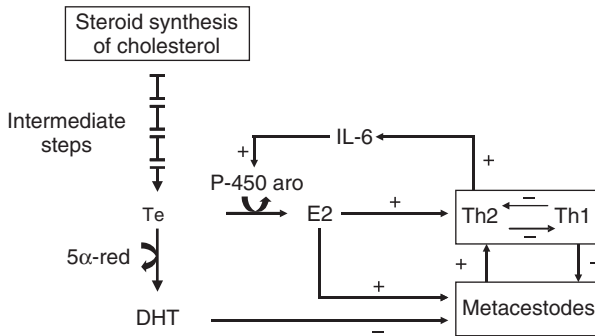


Figure 1.53 Suggested mechanism of the feminization of male mice by metacystodes of *Taenia crassiceps*. The metacystodes stimulate the immune system toward a Th2-oriented response, leading to the expression of IL-6 in cells of the testes. IL-6 stimulates the expression of the enzyme aromatase p-450 (P-450 aro), which converts testosterone

(Te) to estradiol (E2) rather than converting it into dihydroxytestosterone (DHT) by means of 5 α -reductase (5 α -red). Estradiol in turn acts as a growth factor for metacystodes and favors Th2 immune reactions. (From Morales-Montor, J. and Larralde, C. (2005) *Parasitology*, 131, 287–294.)

The consequences of infection with *T. crassiceps* metacystodes are serious for the male mouse, because its sexual activity ceases and its male dominance behavior changes completely. Feminization thus represents a hormonal castration, the purpose of which is to optimize asexual reproduction of metacystodes in the peritoneal cavity of mice. The metacystodes of other tapeworms are also dependent on the hormone levels of their hosts for their growth, as demonstrated by infections with metacystodes of the pig tapeworm *Taenia solium*. In boars, the prevalence and intensity of metacystode infection is significantly lower than in sows, but this ratio is balanced when boars are castrated. Even in the human population, women are more frequently seropositive and have higher titers of anti-*Taenia* antibodies, an indication of an increased prevalence of cysticercosis. However, it is not known whether tapeworms also interfere with the hormonal system of their human hosts.

1.7.3

Changing the Behavior of Hosts

Many parasite infections bring about changes in the behavior of hosts. It has often been documented that behavioral changes of infected intermediate hosts make it easier for final hosts to catch and/or ingest the intermediate hosts. In some cases, infected intermediate hosts have reduced escape responses and are probably simply exhausted – and this poorer condition increases chances of falling prey to the final host. Any time the behavioral changes of an infected host result in an increase in parasite fitness, natural selection will favor parasites capable of sophisticated manipulation of host behavior. The available evidence shows that in such cases, parasites often repurpose the reactions the host needs for its defense, healing or

recovery. In order to achieve this aim, pathogens often seem to affect the processing of stimuli, resulting in atypical reactions such as impaired movement, a reduction in reaction speed, or decreased photophobia. Parasites can even induce the appearance of completely new phenotypic traits (either behavioral or morphological) in their hosts, with positive consequences for parasite fitness. Examples of host manipulation extend to parasites with all types of transmission modes.

1.7.3.1 Increase in the Transmission of Parasites by Bloodsucking Vectors

Studies on insects that serve as vectors of *Plasmodium* and, *Leishmania*, have shown that the probability of transmission is greatly increased by changing the behavior of vectors. Due to the specific effects of parasites, infected insects bite victims more often, increasing the probability of transmission.

Leishmania (Section 2.5.9) develop into infective promastigote forms in the midgut of sandflies. While the fly is sucking in its meal of blood, they have to migrate through the sand fly's proboscis into the skin of the vertebrate host, against the incoming flow of blood. This difficult migration is enabled by manipulating the valve section (*Valva cardiaca*) which lies between the sandfly's midgut and the pharynx. This segment of the intestinal tract is part of the foregut and is lined with a chitinous membrane. The parasites secrete chitinases that damage the membrane, preventing the valve from closing properly, and allowing the parasites to migrate from the midgut into the pharynx, from where they reach the host tissues with the saliva. As the sand fly's bloodsucking process becomes inefficient due to the defect in the valve it interrupts its blood meal after only a short time and – still hungry for blood – flies off to land on a new host where it once more attempts to feed and spreads the parasites. In experiments with laboratory animals, nonparasitized flies only bit victims once or twice, while infected flies bit at least three times. The maximum number of bites observed was 26, of which 11 resulted in *Leishmania* infections of the animals.

Plasmodium-infected *Anopheles* mosquitoes also bite more often than uninfected control insects – and the number of bites increases in relation to the number of sporozoites in the salivary glands. Experiments have shown that the apyrase content in the saliva of infected mosquitoes is significantly reduced. Mosquitoes use this enzyme to feed from host blood vessels. It inhibits the aggregation of platelets, the first step in blood coagulation. Apyrase is therefore essential in the bloodsucking process. The reduction of the apyrase content is thought to reduce the success rate of bloodsucking attempts – but since sporozoites are transmitted with each injection of mosquito saliva, the transmission potential of mosquitoes is greatly enhanced by the parasite's actions.

1.7.3.2 Increase in Transmission Through the Food Chain

In many parasite life cycles, the infection of the definitive host occurs through the consumption of infected intermediate hosts that are the definitive hosts' natural prey. Closer analysis shows that many parasites do not passively wait for the capture of the intermediate host, but increase the likelihood of predation by changing the intermediate host's behavior.

One simple way to increase the chances that the intermediate host gets captured is to weaken it. A weak animal often detaches from its social group, reacts more slowly, and has less pronounced defense reactions, making it easy prey for predators. Metacystodes of the small fox tapeworm *Echinococcus multilocularis*, see Section 3.1.2.18) first grow in the liver, but develop later in other organs of the abdominal cavities of field mice, voles, and muskrats. Animals with advanced-stage infections show decreased mobility and less pronounced escape responses, greatly increasing the likelihood of being taken by the fox definitive host. Similarly, studies of *Echinococcus granulosus* have documented that the infection of moose with metacystodes of this tapeworm increases the probability of falling prey to wolves. This is particularly pronounced when hydatids are located in the lungs of the moose, preventing the animal from breathing properly during its headlong flight from the wolf pack.

In many cases, it is difficult to determine whether the weakening of an intermediate host is merely a by-product of parasite infection or adaptive manipulation by the parasite. However, the localization of the parasite stages and the severity of their pathological impacts often point to the action of natural selection, and suggest that the parasite have adapted to infect a particular tissue to induce a specific disability in the intermediate host. For example, the larvae of the nematode *Tetrameres americana* encyst in the muscles of grasshoppers. This restricts the insect's mobility, and the definitive bird host finds it easier to catch the slower, infected grasshoppers than the faster uninfected insects. Similarly, the metacercariae of the trematodes *Curtuteria australis* and *Acanthoparyphium* sp. encyst within the foot muscle of their bivalve intermediate hosts, impairing their ability to burrow into the sediment (Figure 1.54). This leaves the bivalves exposed to predation by oystercatchers, the parasite's definitive host. Field experiments have confirmed that heavily infected bivalves stranded on the sediment surface are several times more likely to be eaten by oystercatchers than bivalves that successfully burrow under the sediment. Impairment of the bivalve is essential to allow the parasites to reach the intestine of a bird, in which they leave their cyst (Figure 1.55) and complete their life cycle.

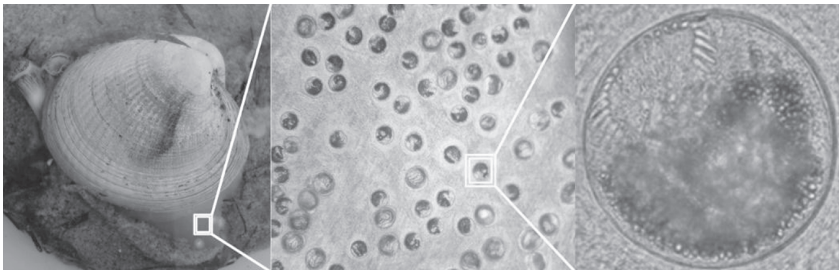


Figure 1.54 Metacercariae of *Curtuteria australis* and *Acanthoparyphium* sp. encysted in the foot tissue of the bivalve *Austrovenus stutchburyi*. (Image: Tommy Leung and Robert Poulin, University of Otago.)

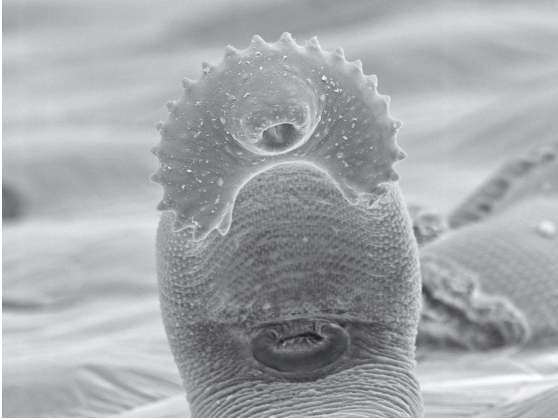


Figure 1.55 Scanning electron micrograph of a recently excysted metacercaria of *Acanthoparyphium* sp. (EM image: Haseeb Randhawa, Matthew Downes, and Robert Poulin, University of Otago.)

Not surprisingly, infection of the central nervous system can also lead to behavioral changes that facilitate transmission to the definitive host. The metacystode of the tapeworm *Taenia multiceps* settles in the brain or spinal canal of sheep, which can lead to behavioral changes. Infected sheep leave the herd and run around in circles with erratic movements, easily falling victim to the definitive hosts, which in this case are wolves or wild dogs. The metacystode consists of a cyst of a few centimeters in diameter, which contains multiple protoscolices (“coenurus”). The space occupied by this cyst in the host’s central nervous system leads to pressure atrophy and subsequent deficiency symptoms, which cause the atypical behavior.

An infection of the brain of intermediate hosts can also lead to very specific behavioral changes without the need for any massive space-occupying process. This is demonstrated by *Toxoplasma gondii* infections (see Section 2.6.2.6). Bradyzoites function as long-lived resting stages of *T. gondii*, typically residing in the brain in modified host cells (Figure 1.56). Compared with control animals in maze tests, infected mice learned how to find a food reward much more slowly, and they also had poorer memory. However, they are more active, more curious, and less sensitive to light than the control animals. Importantly, the smell of cat urine is attractive to infected mice and rats – in contrast to the pronounced aversion shown by infection-free animals for that odor (Figure 1.57). This change in odor preference is highly specific. It has been explained by the concentration of brain cysts in the amygdala, an area of the brain that is involved in the development of anxiety and emotional evaluation. The behavioral changes induced by *Toxoplasma* probably make it easier for cats to catch infected rodents. Other research has even suggested a link between *Toxoplasma* infection and personality changes in human beings. However, these changes appear very subtle, and it remains to be seen whether or not a causal link can be established by further investigation.

A change in behavior can also be achieved without directly affecting the brain of the host. For instance, consider the Acanthocephala (thorny-headed worms see



Figure 1.56 Bradyzoites of *Toxoplasma gondii* in a tissue cyst from the brain of a mouse. (Image: Archive of the Department of Molecular Parasitology, Humboldt University, Berlin.)

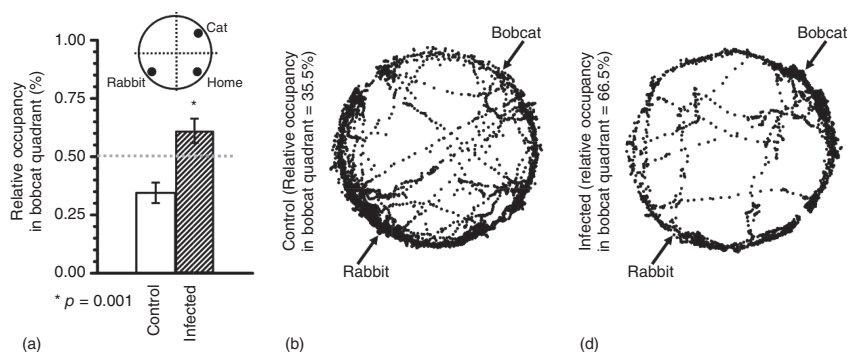


Figure 1.57 Behavioral alteration of rats infected with *Toxoplasma gondii*. Uninfected and infected rats were exposed to bobcat urine and rabbit urine in a circular arena. (a) Control animals visited the quadrant laced with bobcat urine significantly less often as compared with infected rats. (b, c) Representative scatter blots

showing the movements of a control rat (left) and infected rat (right) within the arena. (From Vyas, A., Kim, S.-K., Giacomini, M., Boothroydt, J.C., and Sapolsky, R.M. (2007) *Proc. Natl. Acad. Sci. U.S.A.*, **104**, 6442–6447, with kind permission of the publisher.)

Section 3.2). The adult worms live in the intestines of vertebrates, while the cystacanth larvae develop in the hemocoel of invertebrates, usually crustaceans.

These cystacanth stages can induce distinct behavioral changes in arthropods that facilitate transfer to the definitive host. In the case of infections with *Plagiorhynchus cylindraceus* (definitive host: birds, e.g., starlings; intermediate host: woodlice), infected intermediate hosts often leave their damp hiding places and look for bright areas with low humidity, where starlings can find and ingest them more easily than uninfected woodlice. In the case of the spiny-headed worm, *Moniliformis moniliformis*, infected cockroach intermediate hosts run

more slowly, but are more active for longer periods – and when light suddenly falls upon them, they move around more than uninfected cockroaches, making them easy targets for rats, their definitive hosts.

Such behavioral changes can be very precisely controlled by parasites, as illustrated by a comparative study of the behavioral changes induced by three acanthocephalan species that exploit dabbling ducks and/or diving ducks as definitive hosts. The intermediate host for all three acanthocephalans was the amphipod *Gammarus lacustris*. Cystacanth stages of the three spiny-headed worms each induced different behavioral changes in the same amphipod – and each of the behavioral change specifically facilitated transmission to the respective definitive host (Figure 1.58). Uninfected amphipods avoided light, burying themselves in the bottom mud layer when disturbed, while infected individuals lost their aversion to light, moving to upper water layers that were not so dark. Amphipods infected by *Polymorphus paradoxus* preferred to remain at the surface. When disturbed, they swam along the surface or clung to a plant with a rigid posture – they were then easily noted and caught by dabbling ducks or muskrats.

When equal amounts of infected and uninfected amphipods were put into a pool with ducks, the birds ingested 68% of the infected amphipods, and only 19% of uninfected individuals.

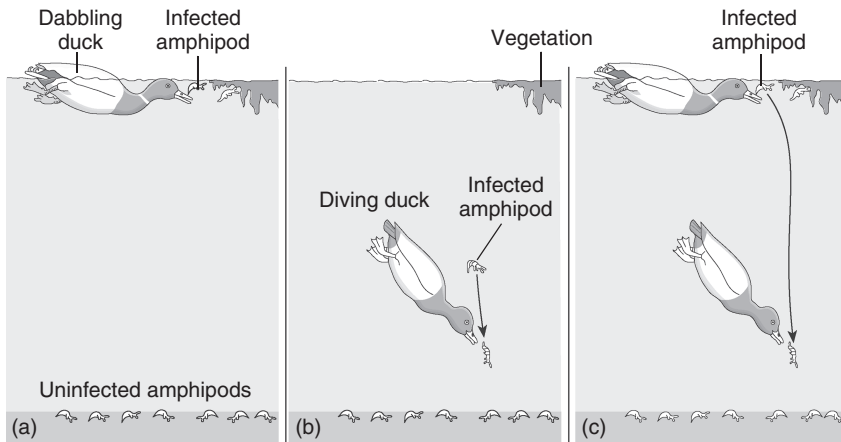


Figure 1.58 Behavioral changes in amphipods after infection with three different species of spiny-headed worms. Uninfected amphipods are primarily bottom dwellers, burying themselves in the mud when danger threatens. (a) Amphipods infected with *Polymorphus paradoxus* prefer the surface of the water, anchoring themselves rigidly in the aquatic vegetation when threatened, where they are taken by dabbling ducks (e.g., mallards). (b)

Amphipods infected with *P. marilis* prefer better-lit areas in zones of average depth, where they are taken by diving ducks. (c) Amphipods infected by *Corynosoma constrictum* float on the surface. When danger threatens, however, they swim down to deeper zones, where they are taken by both dabbling and diving ducks. (From Moore, J. (1984) *Sci. Am.*, 250, 2–89, by kind permission of the publisher.)

By contrast, amphipods infected with *Polymorphus marilis* remained at an average depth, swimming downward when disturbed. They did not, however, hide in the mud at the bottom and were thus easily taken by diving ducks, their definitive hosts. In the case of the third acanthocephalan species, *Corynosoma constrictum*, infected amphipods floated on the surface of the water. When disturbed, some of them swam downward and were taken by both dabbling and diving ducks, in the gut of which they attain sexual maturity. Each parasite species induced behavioral changes in the amphipod that matched very well with the foraging behavior of their target definitive host, indicating that the parasites' actions are extremely host-specific.

The mechanisms underlying this behavioral change were partially elucidated in the case of *P. paradoxus*. Injections of serotonin, a neurotransmitter, induced the same behavior in uninfected amphipods as seen in fleeing infected animals, while other neurotransmitters had no effect. A study of the neurons of the infected amphipods later found an increase of serotonin-containing vesicles at specific synapses. Acanthocephalans synthesize very little serotonin themselves, so this indicated increased serotonin synthesis in the host caused by parasite-secreted substances – and since serotonin levels rise in other invertebrates as a result of immune responses, it is generally believed that *P. paradoxus* exploits this reaction, reinforcing it to specifically manipulate the behavior of its intermediate host. Since that early study, several other researchers have identified alterations in neurotransmitter levels as a likely mechanism underlying behavioral changes in intermediate hosts ranging from crustaceans to fish.

Another example of the deliberate manipulation of intermediate hosts by acanthocephalans comes from *Pomphorhynchus laevis*, a spiny-headed worm that uses predatory fish as definitive hosts, and the amphipod *Gammarus pulex* as intermediate host. In experiments, infected intermediate hosts preferred the area of an aquarium occupied by a perch – but uninfected amphipods showed a strong aversion to the perch's presence. This preference was based on olfactory and not visual stimuli, suggesting a change in the perception of smell – and in nature, this should lead to more efficient transmission of cystacanth stages to the predator.

The list of such examples of manipulation of host behavior by parasites transmitted via predation is growing each year. These involve host and parasites from numerous taxa; indeed, among parasites, host manipulation is known to be used by a wide range of parasites using transmission through the food chain, including protozoans, trematodes, cestodes, nematodes, and acanthocephalans. The independent evolution of adaptive alteration of host behavior in many separate lineages of parasite suggests a case of convergent evolution – the problem of transmission by predation has been solved in similar ways by different parasites with similar life cycles.

1.7.3.3 Introduction into the Food Chain

Sometimes, a parasite must be transmitted by predation from an intermediate host to a definitive host, even if the two hosts do not belong to the same food chain. These situations can lead to astonishing evolutionary achievements, whereby a

parasite can induce such profound changes in its intermediate host's behavior or appearance that it fools the definitive host into ingesting an item not normally in its diet. An example of this truly manipulative behavior comes from trematodes of the family Dicrocoeliidae. *Dicrocoelium dendriticum* (see Section 3.1.1.11), the “lancet fluke,” which is widespread in Europe and North America, and *Dicrocoelium hospes*, a liver fluke which occurs in sub-Saharan Africa, both inhabit the bile ducts of ruminant herbivores. The first intermediate host is a land snail and ants act as the second intermediate hosts. Since ruminants ingest ants only accidentally at best, the transmission from the ant to the definitive host is only made possible by a radical change in the ants' behavior. Uninfected ants, if weather permits, roam outdoors during the day and return home to their nest at dusk – but infected ants show a very different behavior.

Ants of the genus *Formica* infected with *D. dendriticum* do not return to their nest with the onset of dusk – rather they climb grass stems and plants near the nest and bite into them with their mandibles (Figure 1.59). They cannot free themselves when disturbed, since spasms keep their mandibles firmly closed – this way, there is an increased likelihood that they will be accidentally ingested by herbivores feeding on grass in the early morning hours. The metacercariae encysted in the ant's abdomen then reach the small intestine of the definitive host, and exit their cyst to colonize the bile ducts of the liver. Infected ants can only open their mandibles when the temperature increases – they then mix with their nest mates and behave normally during the middle part of the day. Ants of the genus *Camponotus* infected with *Dicrocoelium hospes* also climb up plants – they do not

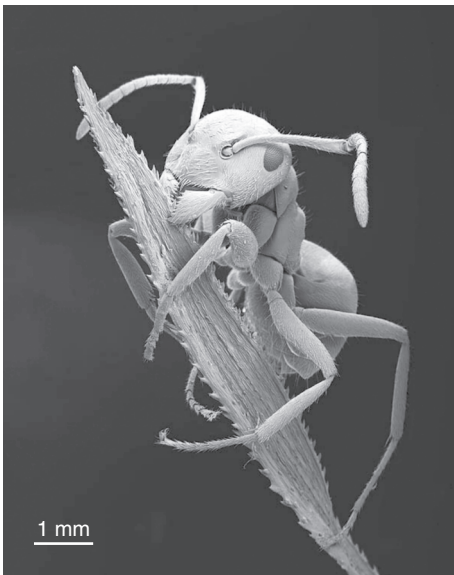


Figure 1.59 *Dicrocoelium dendriticum*-infected *Formica* with mandibles firmly clenched on a blade of grass. (EM image: Courtesy of Eye of Science.)

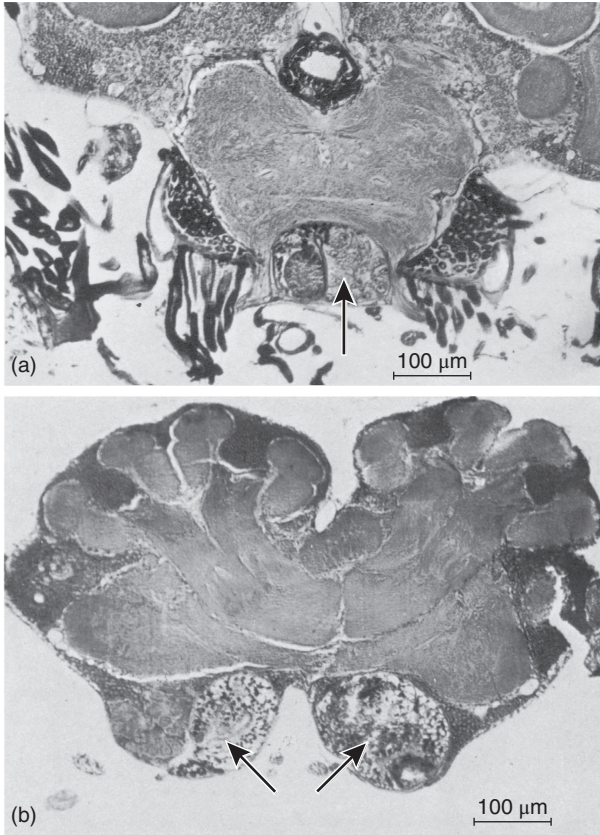


Figure 1.60 Specific localization of the brain worms of *Dicrocoelium dendriticum* and *Dicrocoelium hospes*. In *D. dendriticum* infection, a brain worm usually penetrates into the subesophageal ganglion (a).

In *D. hospes* infection, two brain worms are usually localized in the antennal lobes of the supraesophageal ganglion (b). Arrows: Brain worm. (Images: Courtesy of Thomas Romig.)

bite into them, however, but simply sit there day and night. They are fed by passing nestmates and only leave their post temporarily when severely disturbed. The probability of an infected ant being eaten by a definitive host is thus much higher than that of an uninfected individual, since it should be proportional to the time spent at the tip of grass blades or on leaves of plants.

It is cercariae that are responsible for this behavioral change. They penetrate specific areas of the ant brain, where they usually remain without a cyst wall. *D. hospes*-infected *Camponotus* ants usually harbor two “brain worms” in certain areas of the supraesophageal ganglion, the antennal lobe (Figure 1.60). By contrast, the single brain worm of *D. dendriticum* lies in the subesophageal ganglion of the *Formica* ant.

In the 1960s, Hohorst and his team studied the exact sequence of a *D. dendriticum* infection of *Formica pratensis* and found that cercariae ingested by the ant first drill through the wall of the stomach and close the resulting wound. All cercariae first migrate toward the head. When a larva has entered the brain of the ant, the others migrate back into the abdomen to encyst there. The change in behavior occurs around 30 days after infection, when the encysted metacercariae are infective to the final host. After being ingested by a suitable host, the brain worm itself probably not develop into a liver fluke, because it is not protected by a cyst wall when it is digested (Figure 1.60). However, other metacercariae can survive and grow into adult flukes.

This is not the only example of a parasite creating a new predator–prey association for the benefit of its own transmission. When infected with the Dicrocoeliid trematode *Brachylecithum mosquensis* (definitive host: redwing; first intermediate host: land snail; second intermediate host: *Camponotus* ant), the behavior of ants changes drastically. While uninfected ants strictly avoid light, infected intermediate hosts run around conspicuously in a circle on sunlit stones. They also have a strong abdominal distension, the bright connective tissue of which shimmers between the segment boundaries. For some reason, the infected ants are taken by redwings, which do not normally eat them. Studies on *B. mosquensis* have also shown that a metacercaria with a slightly different morphology lies either in or near the brain. A similar behavioral modification is caused when ants are infected by an insect pathogen, the fungus *Entomophthora* (Zygomycetes). It forces the ant to climb up plants in a similar manner. The ants do not, however, cling to the plant by their mandibles, but are permanently glued to the substrate by hyphae of the fungus. The exposure of infected ants facilitates the dissemination of fungal spores.

How does such a complex behavioral change in dicrocoeliids develop? It is particularly amazing because in the above examples, the altruistic sacrifice of the brain worm is in seeming contrast to the usual pattern of Darwinian evolution. The brain worm triggers the process, but does not gain any fitness advantage for itself, because it is digested and cannot reproduce.

This apparent contradiction is resolved when we realize that all the cercariae entering an ant are probably descended from the same miracidium and are therefore genetically identical. These have been produced asexually in the snail first intermediate host, and transmitted as a group to the same ant. In such cases, the fitness advantage of the entire clone (inclusive fitness) is what really matters – and the full cost is paid by the sacrifice of a single individual with an identical genotype.

There are other cases in which a parasite creates a new predator–prey association to ensure its transmission, by duping a predator into eating what appears to be its normal prey. For instance, trematodes of the genus *Leucochloridium* (Section 3.1.1.6) must be transmitted by ingestion from a snail intermediate host to a bird-definitive host, but bird species that are suitable as hosts for this parasite feed on insects, not snails. In order to overcome this difficulty, the trematode alters the appearance of its snail host: it causes its tentacles to appear swollen and very colorful, and induces them to pulsate rapidly. To a bird in

search of prey, these presumably look like caterpillars, and the bird is fooled into ingesting several parasite larvae as it gobbles up the “caterpillar.” Similarly, the nematode *Myrmeconema neotropicum* must be transmitted by ingestion from an ant-definitive host, probably to a frugivorous bird that spreads the nematode eggs with its feces. The solution: the nematode radically changes the color of the ant’s gaster from black to bright red and causes the ant to hold its gaster in an elevated position. The parasite thus induces its host to mimick a small red berry that attracts hungry birds. These examples further illustrate how strong selective pressures to complete the life cycle can drive the evolution of “extended phenotypes” in parasites.

1.7.3.4 Changes in Habitat Preference

There is another circumstance in which parasites can benefit by modifying the behavior of their host, and that is when the habitat of the host does not overlap with the habitat in which the parasite must emerge from the host. Nematomorphs, or Gordian worms (hairworms), are the best-known examples of this type of manipulation. These worms are larval parasites that develop in arthropods, while the short-lived hairworm adult stages are not parasitic, and mate in water. The hosts of hairworms are often terrestrial arthropods such as beetles, grasshoppers, and praying mantises. Adult hairworms themselves are bound to freshwater – and getting to water is ensured by the mature parasites inside the host. These are typically three to four times longer than their arthropod host, and they force the host to leap into water (Figure 1.61). The worms then break out of the drowned host and look for a sexual partner at the bottom of the body of water, where a “Gordian knot” consisting of several worms may form. Larvae hatch from the eggs produced from the mating and reach their arthropod hosts, either directly or via a paratenic host. The remarkable nature of hairworm infections is the induction of a behavior (throwing themselves in water) that does not occur in the behavioral repertoire of the normal insects. One well-studied model system is the infection of *Meconema thalassinum* – an oak bush cricket commonly



Figure 1.61 Oak bush cricket *Meconema thalassinum* from which the Gordian worm *Spiniochordodes tellini* emerges. (Image: from http://en.wikipedia.org/wiki/Spiniochordodes_tellini.)

found in southern France – with the hairworm *Spinochordodes tellinii*. In this parasite–host system, the behavioral change induced by the parasite occurs only at night. Infected crickets jump into the water – and the factors that trigger this behavioral change have been narrowed down relatively accurately.

Proteome analysis of brains of infected versus uninfected crickets revealed that numerous insect proteins were differentially expressed. The analysis revealed that the leads to production of several proteins with similarity to signal transduction molecules, which could control important brain functions. It is therefore assumed that hairworms secrete products to directly influence the central nervous system of the crickets.

Other pathogens of insects are also capable of modifying habitat selection by their host in order for the parasite to reach a location that is optimal for spreading its offspring. These include nematodes of the family Mermithidae, which have a life cycle similar to that of hairworms and induce the same type of water-seeking in their hosts; and the fungus *Cordyceps* spp., which causes infected insects to climb to the top of vegetation, thus providing the parasite with an ideal perch from which to release its spores into the wind. Several parasitoid wasps are also capable of causing marked changes in their host's behavior and microhabitat choice, in ways that ensure the safety of the parasitoid's emerging pupae.

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Test Questions

1. What is the meaning of the term “extended phenotype” in the context of a parasite infection?
2. Give examples of the alteration of host cells by intracellular parasites.
3. Which types of parasitic castration are found in snails?
4. Why may trematode-infected snails become larger than uninfected individuals?
5. How does *Taenia crassiceps* alter the phenotype of its host?
6. How can parasite-induced damage of the mouthparts of bloodsucking insects lead to an increased transmission of parasites?
7. How does infection with larval tapeworms lead to a host being more easily attacked and eaten?
8. How does *Toxoplasma gondii* manipulate its rodent host?
9. How do the cystacanth larvae of certain Acanthocephala manipulate amphipods?
10. Which stage of the lancet liver fluke influences the life cycle by behavioral change of infected ants?