CHAPTER 18

Parasites that Manipulate Their Hosts*

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18.1 INTRODUCTION

How a parasite (or its offspring) moves from one host to the next is a central topic in parasitology (see Tables 18.1 and 18.2). Understanding such strategies is at the heart of applied aspects of parasitology such as epidemiology and medicine, but it is also important for resolving more basic biological questions. One strategy of transmission that is especially fascinating is that of host manipulation, which occurs when a parasite enhances its own transmission by altering host behavior or host morphology. Parasites of all kinds have been shown to modify these phenotypic traits of their hosts in ways that appear to enhance the parasite's chances of completing its life cycle. From an evolutionary point of view, these changes are compelling illustrations of the "extended phenotype" concept proposed by Dawkins [31], in which genes in one organism (i.e., the parasite) have phenotypic effects on another organism (i.e., the host). From a medical or veterinary point of view, these phenotypic alterations can also be viewed as an expression of the parasite's virulence. Although more subtle than the gross pathology associated with many parasitic diseases, manipulation of host phenotype is nonetheless harmful to the host.

This chapter has three aims. Using well-documented case studies, we will (1) present an overview of the "manipulation hypothesis," (2) discuss the potential of this hypothesis for providing novel insights into the mechanisms regulating individuals at the organismal and ecological levels, and (3) cover several contentious issues related to this hypothesis.

18.2 HISTORICAL OVERVIEW

According to the manipulation hypothesis, a parasite may be able to alter the behavior of a host for its own selective benefit, usually by enhancing its transmission rate. The hypothesis states that such behavioral modification results from *natural selection* favoring enhanced parasite transmission; it is not simply a sporadic byproduct of other physiological activities of the parasite. Early in the twentieth century, scientists began to suspect that parasites could manipulate their hosts (e.g. [27]). The first field evidence came from cormorants *Phalacrocorax carbo* (definitive hosts), which frequently caught fish that were intermediate hosts of the cestode (worm) *Ligula intestinalis*, whereas fishermen were more likely to capture uninfected fish [151]. In laboratory experiments, Bethel and Holmes [13,14] showed that crustacean amphipod (*Gammarus lacustris)* intermediate hosts of acanthocephalans (worm) (*Polymorphus paradoxus*) behaved abnormally; these behavioral changes resulted in increased predation from ducks (definitive hosts). Since the 1970s, studies of behavioral changes in parasitized animals and the enhanced transmission that frequently accompanies these changes have increased. The phenomenon is not only inherently interesting (witness any one of a number of science fiction stories with manipulated behavior as a central theme), but it also demonstrates the ubiquitous importance of parasites to a broader community of scientists. A wide range of parasites are now known to alter host behavior (see [8,25,26,95,114] for reviews]). These studies have shown that parasites can modify a large range of

*Adapted from [136].

Encyclopedia of Infectious Diseases: Modern Methodologies, by M. Tibayrenc

TABLE 18.1. Major Groups of Protozoan Parasites of Metazoan Hosts, with Representative Genera (from [19])

Parasite taxon	Representative genera
Phylum Microsporida	*Nosema, Encephalitozoon*
Phylum Sarcomastigophora	
Subphylum Mastigophora	*Trypanosoma, Leishmania, Giardia*
Subphylum Opalinata	*Opalina*
Subphylum Sarcodina	*Entamoeba, Naegleria*
Phylum Apicomplexa	
Class Sporozoasida	
Subclass Gregarinasina	*Gregarina*
Subclass Coccidiasina	*Plasmodium, Toxoplasma, Cryptosporidium, Eimeria*
Subclass Piroplasmasina	*Babesia, Theileria*
Phylum Ciliophora	Ciliates

host behavioral traits in ways that can vary in magnitude, from slight changes in activity levels to the production of complex and spectacular behaviors ([95,119], see examples in Section 18.3).

As in many other fields, the early thrill of discovery and ready explanation has later been modulated by circumspection and caution. By the late twentieth century, scientists were bringing more rigor to the manipulation hypothesis, demanding more evidence for the adaptive nature of a behavioral change in an infected organism. Early on, there had been a tendency to accept all behavioral changes in parasitized hosts as beneficial for the parasite, without testing alternative hypotheses. Although acknowledging the fact that numerous alterations in infected hosts were undoubtedly adaptive for parasites, two important papers [96,113] championed a more careful and rigorous approach to the study of the evolution of

TABLE 18.2. Major Groups of Metazoan Parasites of Metazoan Hosts, with Common Names (from [121])

Parasite taxon	Common name	Minimum number of living species
Phylum Mesozoa	Mesozoans	>80
Phylum Platyhelminthes[a]		
Class Cercomeridea		
Subclass Trematoda	Flukes	>20,000
Subclass Monogenea	Monogeneans	>20,000
Subclass Cestoidea	Tapeworms	>20,000
Phylum Nemertinea[a]	Ribbon worms	>10
Phylum Acanthocephala	Thorny-headed worms	>1,200
Phylum Nematomorpha	Hairworms	>350
Phylum Nematoda[a]	Roundworms	>15,000
Phylum Mollusca[a]		
Class Bivalvia[a]	Bivalves	>600
Class Gastropoda[a]	Snails	>5,000
Phylum Annelida[a]		
Class Hirudinea[a]	Leeches	>400
Class Polychaeta[a]	Polychaetes	>20
Phylum Pentastomida	Tongue worms	>100
Phylum Arthropoda[a]		
Subphylum Chelicerata[a]		
Class Arachnida[a]		
Subclass Ixodida	Ticks	>800
Subclass Acari[a]	Mites	>30,000
Subphylum Crustacea[a]		
Class Branchiura	Fish lice	>150
Class Copepoda[a]	Copepods	>4,000
Class Cirripedia[a]		
Subclass Ascothoracida	Ascothoracidans	>100
Subclass Rhizocephala	Rhizocephalans	>260
Class Malacostraca[a]		
Order Isopoda[a]	Isopods	>600
Order Amphipoda[a]	Amphipods	>250
Subphylum Uniramia[a]		
Class Insecta[a]		
Order Diptera[a]	Flies	>2,300
Order Phthiraptera (suborders Ischnocera, Amblycera and Anoplura)	Lice	>3,000
Order Siphonaptera	Fleas	>2,500

[a]Denotes taxa also containing free-living species.

parasite-induced behavioral changes. These papers set forth three questions that persist today: (1) Is a phenotypic change adaptive for a parasite or is it a nonadaptive and accidental result of infection? (2) Is the phenotypic change a host *adaptation* that reduces detrimental *fitness* consequences of infection? (3) What is the role of *phylogeny* in explaining parasite-induced phenotypic change? Behavioral changes can be the products of natural selection in a given host–parasite interaction, but they can also be inherited from an ancestor. In that case, they may or may not continue to confer a selective advantage to the parasite in the present system.

Present day researchers studying parasitic manipulation are cognizant of the problems described above. These difficulties require studies that are collaborations between parasitologists, evolutionary biologists, physiologists, neurobiologists, and biochemists in order to understand the complex process of manipulation.

Fig. 18.1. Adult specimen of *Dicrocoelium dendriticum* (photo: F. Thomas).

18.3 SELECTED EXAMPLES OF MANIPULATION

All adaptive changes in host behavior following parasitic infection are not necessarily manipulation. They can be responses of the host aimed at eliminating the parasite or compensating for its effects. Here, we will focus on changes in infected hosts thought to be cases of adaptive manipulation by the parasite. The list below is far from exhaustive.

18.3.1 Manipulation of Predator–Prey Encounters

There are numerous examples of trophically transmitted parasites that alter the behaviors of their *intermediate hosts* in ways that increase their vulnerability to predatory definitive hosts. Typically, the intermediate host becomes more conspicuous or less able to escape from predators [25,77,95]. The most popular example of trophic transmission in ecological textbooks is the trematode "brainworm" *Dicrocoelium dendriticum*, also called the small liver fluke (Fig. 18.1). This parasite reaches adulthood in large herbivorous mammals but uses ants as second intermediate hosts. The infected ant behaves normally during the day, but when temperatures drop, it ascends blades of grass instead of returning to the nest, and this altered behavior is thought to enhance transmission to grazing sheep. Among crustacean hosts, isopods harboring *cystacanths* of the parasitic worm *Plagiorhynchus cylindraceus* (acanthocephalan) are far more likely than uninfected ones to spend time in areas of relatively low humidity and on white surfaces where they are highly visible to bird predators (definitive hosts) [93,94]. In aquatic habitats, crustacean gammarids (*Gammarus pulex*) infected with avian- or fish- acanthocephalans (*Polymorphus minutus* and *Pomphorhynchus laevis*, respectively) display a range of behavioral changes (e.g., skimming and clinging behavior) that make them more likely to be eaten by aquatic birds and fishes. In contrast to the acanthocephalans, which remain in the host abdomen, the digenean trematode *Microphallus papillorobustus* encysts in the nervous system of the gammarid *Gammarus insensibilis* [56] (Fig. 18.2). Cerebral *metacercariae* of *M. papillorobustus* induce strong behavioral alterations (i.e., positive phototaxis, negative geotaxis, and an aberrant evasive behavior), making infected gammarids (commonly called "crazy" gammarids) more vulnerable to predation by aquatic birds. Trematodes and acanthocephalans are phylogenetically

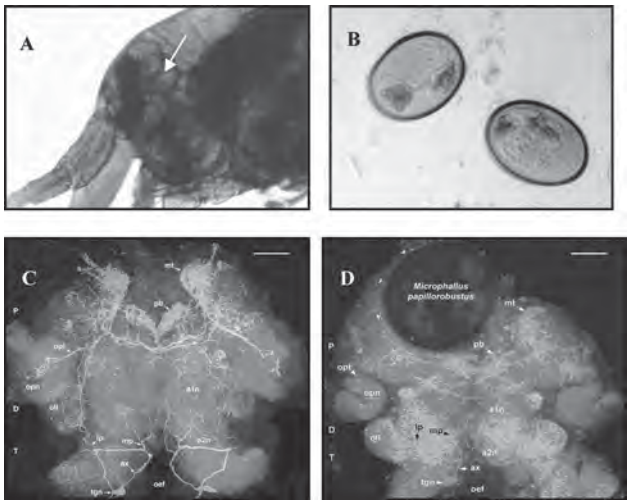


Fig. 18.2. *Gammarus insensibilis* infected by the trematode *Microphallus papillorobustus*. (A) head of a parasitized gammarids, metacercariae correspond to ovoid spheres. (B) Isolated metacercariae of *M. papillorobustus*. (C) Serotonin-containing neurons (yellow) in healthy brain. (D) Serotonin-containing neurons (yellow) in infected brain. (Montage of four stacks of 32 confocal scans showing immunoreactivity for serotonin (green label) and synapsin (red outline of neuropiles). Anterior is at the top. ax, axon of tgn; a1n, antenna 1 neuropile; a2n, antenna 2 neuropile; D, deutocerebrum; lp, lateral projections of tgn; mp, medial projections of tgn; mt, medulla terminalis; oef, oesophageal foramen; oll, olfactory lobe; opn, optic neuropile; opt, optic tract; P, protocerebrum; pb, protocerebral bridge; T, tritocerebrum; tgn, tritocerebral giant neuron. Scale bar, 100 μm.) (From [57].). See color plates.

unrelated, but they evolved under similar ecological constraints on their transmission, that is, they require the predation of the gammarids to complete their life cycle. The similarity of the behavioral changes they induce in their crustacean hosts is an evolutionary *convergence*.

Many parasites alter their hosts' abilities to escape predation. Several studies have also revealed that burrowing bivalves infected with digenean metacercariae may live closer to the surface (e.g., the cockles *Cerastoderma glaucum* and *Austrovenus stutchburyi*, respectively parasitized by *Meiogymnophallus fossarum* [9] and *Curtuteria australis* (Fig. 18.3 and 18.5) [134].

This can be interpreted as a way for the parasite to increase the probability of predation by bird final hosts such as oystercatchers. The life cycle of a different trematode, *Cainocreadium labracis,* which involves two intermediate hosts, illustrates a behavioral change resulting, as in the bivalves above, from a collective action by infective stages. The *cercariae* of the trematode crawl on the sand surface, as does the second intermediate host (generally a gobiid fish). More than 80% of the encysted metacercariae are found in muscles directly involved in gobiid swimming. Accordingly, the ability of infected *Gobius* to escape is compromised when they are attacked by the definitive host, the sea bass *Dicentrarchus labrax* [87]. Similarly, metacercariae of *Diplostomum spathaceum* decrease the visual acuity of freshwater fish by accumulating in the lens of the eye. As a result, infected fish have a reduced ability to detect predators, especially piscivorous birds (definitive hosts) [128]. Aeby [5] demonstrated that the coral-feeding butterflyfish *Chaetodon multicinctus* from Hawaiian reefs significantly prefer foraging on polyps (*Porites* sp.) that are infected by the trematode *Podocotyloides stenometra*. Infected polyps become swollen and pink (Fig. 18.4) and are easier to capture, as they are no longer able to adequately retract into their protective coral skeletons. The cestode *Ligula intestinalis* can grow to be 20 cm long and 1cm wide in the body cavity of cyprinid fishes (intermediate host) (Fig. 18.5). Infected fish not only behave differently from uninfected fish but also develop a rotund shape that is visible to birds [86]. Studies with rats

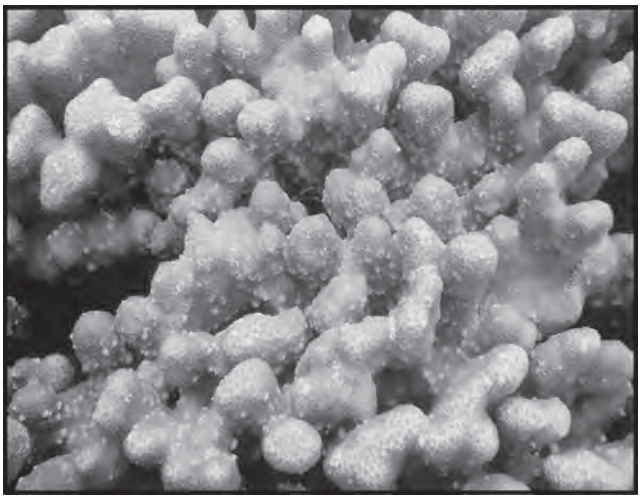
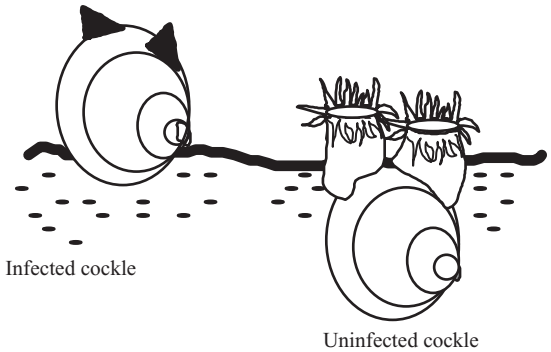


Fig. 18.4. Infection with the trematode *Podocotyloides stenometra* causes coral polyps to become swollen and pink (photo: Greta Aeby). See color plates.

(a)



(b)

Fig. 18.3. Parasitized cockle *A. stutchburyi* lying at the surface of the mud with the two most common invertebrate species living on its shell, the limpet *Notoacmea helmsi* and the anemone *Anthopleura aureoradiata* (photo: F. Thomas).

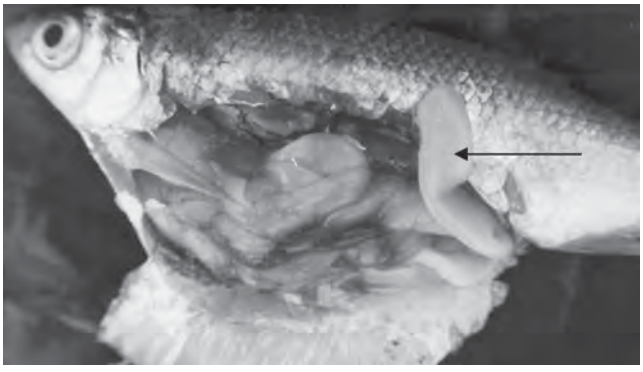


Fig. 18.5. Cyprinid fish infected by *Ligula intestinalis* (photo: Geraldine Loot).

infected with the protozoan parasite *Toxoplasma gondii* also provide compelling evidence for manipulation: *T. gondii* enhances predation of intermediate hosts by the feline definitive host by reducing the rat's innate fear of cats and their associated smells [12].

Limb *autotomy* is a way for parasites to achieve trophic transmission without killing their hosts [77]. The spiny sand crab *Blepharipoda occidentalis*, like most other crabs, has the ability to autotomise a limb to escape predation. Metacercariae disproportionately infect the crab's claws, suggesting that they might become transmitted during one of these successful escapes from an attack. Finally, bivalve mollusks from the genus *Abra* also partially autotomise their *siphons* when the latter are "full" of the metacercariae of *Paratimonia gobii*. Once detached, the siphon moves about on the bottom like *benthic* invertebrate, attracting gobies that then ingest these small parasite-stuffed morsels [87].

18.3.2 Manipulation of Habitat Choice

Parasites can also manipulate host habitat choice. Curtis [28] found that some digeneans such as *Gynaecotyla adunca* drive their molluscan first intermediate hosts toward beaches for the release of cercariae close to amphipods and crabs (second intermediate hosts). Hairworms (phylum Nematomorpha) and mermithid nematodes (phylum Nematoda) are parasitic in arthropods when juveniles, but they are free and aquatic when adults. Insects harboring mature nematomorphs seek water and jump into it, thereby allowing the parasitic worm to reach its reproductive habitat (Fig. 18.6) [146]. A similar water-seeking behavior is observed with the beach hopper amphipod *Talorchestia quoyana* parasitized by the mermithid nematode *Thaumamermis zealandica* (Fig. 18.7): the parasite induces the host to burrow more deeply than healthy amphipods and the adult worm emerges from the host into moist sand at these greater depths. Finally, several fungus species (called "enslaver" fungi) make their insect hosts (such as flies [88] or ants [85]) die perched near the top of plants in a position that facilitates the *dispersal* of *spores* by the wind.

18.3.3 Other Kinds of Manipulation

Mermithid nematodes can also feminize the morphology and behavior of male insects when parasite transmission depends on female-specific behavior [152]. Parasitic wasps can make their spider host weave a special cocoon-like structure to shelter the wasp *pupae* against heavy rain [17,39], or can even cause the host to seek refuge within curled leaves to protect pupae from *hyperparasitoids* [16]. Viruses may stimulate superparasitism behavior in solitary parasitoids and thus achieve horizontal transmission [153]. *Sporocysts* of the trematode *Leucochloridium paradoxum* develop in the snails' (*Succinea putris*) tentacles and make them look like colorful caterpillars (Fig. 18.8). These altered tentacles may attract birds (definitive hosts). The rat tapeworm *Hymenolepis diminuta* increases the life span of its intermediate host (the beetle *Tenebrio molitor*), a phenomenon that, in itself, can enhance parasite transmission [63].

18.3.4 Manipulation by Vector-Borne Parasites

Many of the most harmful parasitic diseases of humans are transmitted by blood-feeding insect *vectors*. Selection favors parasites that can manipulate their vectors to enhance transmission [48]. A common strategy used by vector-borne parasites is to increase contact between the vector and the vertebrate host(s) (reviewed in [62]). For instance, in a variety of *Leishmania*/sand fly associations (see Chapter 6), infected flies exhibit increased probing behavior due to difficulties in ingesting the blood meal. An occlusion of the stomodeal valve prevents blood from flowing into the fly midgut. Parasite-induced changes in probing behavior have also been associated with malaria-infected mosquitoes, although a different mechanism is involved [71,72]. As with infected sand flies, parasitized female mosquitoes make many attempts to feed and thus visit many different hosts, each time depositing parasites at the feeding site. Malaria *sporozoites* apparently induce a reduction in salivary apyrase activity, an enzyme that counters host hemostasis and promotes easier and longer blood feeding. At present, it is not known whether this phenomenon results from an inhibitor produced directly by the parasite or from mechanical damage created during tissue invasion. Reduced efficiency of blood meal location has also been attributed to other parasite infections in vectors such as *Rhodnius prolixus* (a blood feeding true bug, vector of Chagas disease in Latin America) infected with *Trypanosoma rangeli*, tsetse flies infected with *Trypanosoma* spp., and the rat flea *Xenopsylla cheopis* infected with the plague bacterium *Yersinia pestis*. Proximal reasons for changes in feeding behavior include physical blockage of the foregut by parasites (plague-infected fleas), obscured phagoreceptors (tsetse flies infected with trypanosomes), and reduced apyrase activity in the salivary glands (*Rhodnius prolixus* infected with *T. rangeli*) (reviewed in [62]).

In many insects, the normal process of *oogenesis* is disrupted by parasites. Fecundity reduction has been frequently reported in *Plasmodium*-infected mosquitoes. Altering vector resource management may increase available nutrient reserves, which, in turn, could enhance vector longevity and hence parasite transmission. Further experiments are however needed to confirm this hypothesis in *Plasmodium*-infected mosquitoes [62].

Finally, there are an increasing number of studies suggesting that vector-borne parasites can render their vertebrate hosts more attractive to vectors, apparently by altering odor profile. *Leishmania*-infected dogs have been shown to be more attractive to sand flies than uninfected dogs [23]. Similarly, hamsters infected with *Leishmania infantum* were shown to be more attractive to female *Lutzomyia longipalpis* [106,123] than noninfected hamsters. It has been also suggested that fever induced by some parasitic infections could increase the attraction of infected individuals to vectors.

18.3.5 Are Humans Manipulated by Parasites?

The rabies virus (genus: *Lyssavirus*) is the classic example of a pathogen that can have a profound impact on human behavior. Rabies remains a serious source of mortality in the

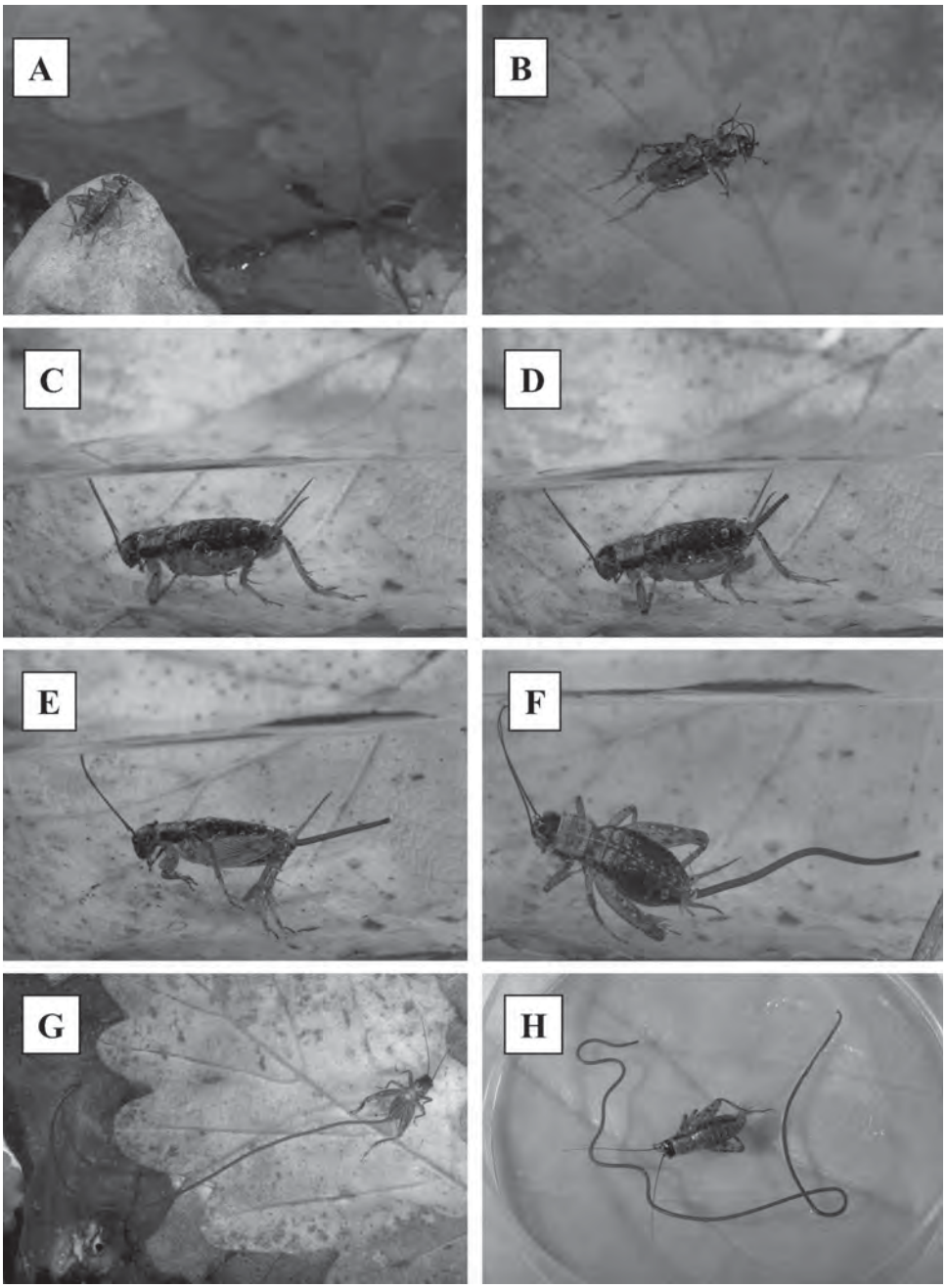


Fig. 18.6. Behavioural sequence illustrating the water seeking behaviour of *Nemobius sylvetris* followed by the emergence of the hairworm *Paragordius tricuspidatus* (photo: F. Thomas and P. Goetgheluck).

developing world, killing more people than yellow fever, dengue fever, and Japanese encephalitis do [59,127]. The rabies virus lives in the brain [127], affording the virus ample opportunity to affect host behavior. Rabid animals and humans do show changes in behavior; for example, dogs exhibiting the encephalitic (furious) form of the disease show increased aggression and biting [148]. Biting is the most effective means of transmitting rabies [127], and therefore this change in host behavior will increase parasite transmission. Rabies in humans does not provide a good example of the manipulation hypothesis, however. Humans are "dead end" hosts and do not typically transmit the disease to others [127]. Perhaps for this reason, the behavioral effects of rabies are highly variable in humans [59,127].

However, there are other examples in which a parasite-mediated change in human behavior probably does increase parasitic transmission (e.g., *Trypanosoma brucei*, which causes human African trypanosomiasis, formerly sleeping sickness). For example, Kristensson et al. ([73], Table 1, p. 246) list some of the behavioral effects of *T. brucei* and other parasites, dividing them

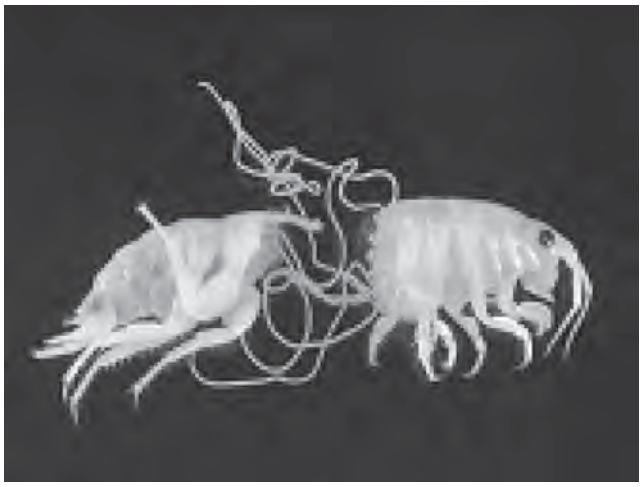


Fig. 18.7. The talidrid amphipod *Talorchestia quoyana* harboring the manipulative nematode *Thaumamermis zealandica* (photo: R. Poulin).

into potential benefits for the person and for the parasite. In some cases, the change in host behavior (e.g., increased lethargy) could benefit both. Unfortunately, most parasite-induced changes in human behavior are identical to various aspects of "sickness behavior," that is, a host response to infection [73], making it difficult to determine whether the change benefits the host or parasite (see also [51]).

Parasites that inhabit the central nervous system (CNS) are in a prime location to manipulate host behavior. In Europe and other parts of the world, one of the most common parasites of humans is the protozoan *Toxoplasma gondii*, and it lives in the nervous system. The normal intermediate hosts of *T. gondii* are rodents, but the parasite develops well in humans, too; cats serve as definitive hosts. The behavioral alterations induced by the parasite in rodents are compatible with the manipulation hypothesis, that is, they lead to an increased risk of predation by cats [12]. In humans, *Toxoplasma* infections result in slight personality changes and reduced psychomotor performance [41–45,53,75,156,157]. Because cats do not normally prey on humans, these behavioral changes are of no apparent value to the parasite. They could be manifestations of mechanisms evolved in the past to manipulate the normal rodent hosts, or they may be mere coincidental pathology shown by infected humans.

Some of the most plausible examples of the manipulation hypothesis in humans are provided by parasites that do not directly interact with the CNS (e.g., see [26]). For example, the pinworm *Enterobius vermicularis* is an intestinal nematode of humans, particularly children. Females of this parasite lay their eggs around the anus and induce an intense itching in the anal area. This behavioral manipulation is simple but very effective. The microscopic eggs of the parasite end up on fingers and are then transmitted to others. Other pathogens and parasites can induce sneezing/coughing or diarrhea (induced by most of the parasites that actively multiply in the intestine, such as *Giardia*), resulting in dissemination of infective stages to the outside environment. We must however remain cautious about assuming that these behavioral changes result in increased parasite transmission without supporting empirical evidence [26]. Finally, some other well-documented behavioral impacts of parasite infection in humans can safely be categorized as nonadaptive for the parasite, and thus be ignored in the context of the manipulation hypothesis. For instance, several intestinal nematodes (*Ascaris lumbricoides*, *Trichuris trichiura*, and hookworms) are ubiquitous parasites in tropical and developing countries. They are also known to impair cognitive function and learning abilities in children, and productivity and wage-earning capacity in adults (e.g., [17,103,104]). These behavioral symptoms are also associated with malnutrition and anemia, and when associated with nematode infections, they are probably only the mere consequences of the parasites' impact on the host's nutritional status and general health.

Fig. 18.8. The snail *Succinea putris* parasitized by *Leucochloridium paradoxum* (photo: P. Vogel).

18.4 HOW DOES THE PRESENCE OF A PARASITE ALTER HOST BEHAVIOR?

Parasites can use both direct and indirect mechanisms to alter host behavior. Parasites can alter host behavior directly by interacting with the host's nervous system or muscle. For example, a parasite may secrete/excrete a neuroactive substance resulting in changes in host behavior. Parasites can have indirect effects on host behavior by affecting host tissues other than neurons and muscles, resulting in host-mediated changes in behavior. For example, the presence of a parasite can influence host development, intermediate metabolism and/or immunity, leading secondarily to an alteration in host behavior.

Both indirect and direct mechanisms can lead to increased transmission of parasites [1]. When researchers discuss "parasitic manipulation" of host behavior, they are usually referring

to an active process in which the parasite expends energy to produce a direct effect on the behavior of its host. However, because changes in host behavior can also be induced indirectly, parasites could alter host behavior with no additional energetic costs beyond those required to survive in the host (e.g., a suppression of host immunity that leads to a fortuitous change in host behavior). Moreover, parasitic waste products may also influence host behavior, and therefore even direct parasitic effects may be energetically cost-free for the parasite. The ecological ramifications of costly parasitic manipulation versus cost-free fortuitous changes in host behavior will be different, even if both are adaptive for the parasite (e.g., [79]). Unfortunately, differentiating between these two possibilities is problematic, as we discuss below.

18.4.1 Direct Effects

Demonstrating that secretions/excretions from a parasite act directly on host neurons has proven difficult. Part of the problem lies with the complex interactions between immunity and the nervous system. When parasites invade any tissue, including the CNS, they typically envoke complex, but poorly understood, immune cascades [73,125,129,149]. Activating these immune cascades also results in the release of neuroactive compounds [29], and these can cause a variety of changes to the brain and behavior [11]. These immune–neural interactions make it difficult to determine whether a change in host behavior is a direct effect of the parasite or a result of the host's immune response. Moreover, some parasites secrete chemicals identical to those secreted by the host's immune system [69,73]. For example, the trematode *Schistosoma mansoni* secretes β-endorphin and other opioid peptides [69]. These substances affect both immune [38] and neural function [69]. In infected hosts, both opiate and opioid levels increase in the serum and CNS, but it is unclear whether the source is the host or the parasite [69,122]. Pharmacological tests show that these compounds play a causal role in the changes in host behavior [69]. Nevertheless, *S. mansoni* has probably been selected to secrete these compounds in order to suppress local immune responses [122], not to induce changes in host behavior. Regardless of whether *S. mansoni* affects host behavior directly or indirectly, the change in behavior may be an unavoidable consequence of parasite-induced immunosuppression.

To further demonstrate the difficulty in determining the roles of parasite and host in mediating host behavioral change, we discuss here the induction of aggressive behavior in mammalian hosts by the rabies virus, already mentioned in Section 18.3. The rabies virus could increase its transmission by infecting and then manipulating areas of the brain important for regulating aggression. This hypothesis is supported by studies showing that rabies virus can alter the neuronal function of infected cells [65,74]. However, closer examination of the evidence reveals complexities in the rabies–host interaction that suggest that a direct parasitic effect on the host cannot entirely explain the increase in host aggression. Virus distribution alone cannot explain the clinical features of rabies [59]. The rabies virus preferentially localizes in the brainstem, thalamus, basal ganglia, and spinal cord [59], areas that are not directly involved in regulating aggression [109]. Therefore, it is unlikely that the virus increases aggression by directly manipulating infected neurons.

Moreover, aggression is frequently absent in infected hosts [127]. Rabies has two classic forms, the "furious" (encephalitic) and the "dumb" (paralytic) [59]. Both forms exhibit increased salivation, but only victims of encephalitic rabies exhibit increased aggression. Virus distribution in the brain is the same in both forms [59]. One difference that has been found between the two forms is that patients with encephalitic rabies tend to have intact T-cell immunity and mount a robust cellular immune response against the virus [59]. Hemachudha et al. [59] argue that it is the immune responses generated by the host that are responsible for the increased aggression seen in some rabies victims. Hemachudha et al. [59] postulate that infection of the brainstem induces production of *cytokines* by the host's immune system and that these compounds then modify the functioning of limbic system structures (brain structures involved in the control of aggression [109]). Further evidence that the increased aggression observed in some rabies victims is due to a host-generated immunopathology is that the increased aggressive behavior that occurs in humans during the final phase of rabies is also seen in other neurological disorders (both infectious and noninfectious) and is not specific to rabies [59]. This change in behavior in neurological patients is probably caused by immune-generated destruction of the CNS (e.g., inflammation [11]). In rabies, the physiological details of an individual host's immune response may play a critical role in determining whether the virus can "manipulate" its host.

In systems in which the host is an invertebrate, the mechanisms mediating host behavioral change may be easier to identify. Nevertheless, even in these systems, demonstrating that a parasite secretes a neuroactive substance, showing that the substance alters neuronal function and finding that the altered neuronal function is causally linked to the change in host behavior are difficult. Recently, Helluy and Thomas [57] suggested that the degeneration of discrete sets of serotonergic neurons in *G. insensibilis* infected by the cerebral trematode *M. papillorobustus* (see Fig. 18.2C and D, Section 18.3) might contribute to host manipulation. However, definitive evidence demonstrating the causal link between serotonin levels and the change in behavior is still lacking. In the *Gammarus lacustris–Polymorphus paradoxus* system, exogenously supplied serotonin can mimic the effect of parasitism on some host behaviors [58], and hosts show an increase in the number of varicosities exhibiting serotonin-like immunoreactivity [89]. Maynard et al. [89] included the important control of examining the CNS of gammarids infected with a different acanthocephalan, *Polymorphus marilis*, which does not induce a change in host behavior. *P. marilis* does not alter serotonergic staining in the host, demonstrating a correlation between the change in host serotonin-like immunoreactivity

and host behavioral change. Holmes and Zohar [60] do not believe that *P. paradoxus* is capable of raising host serotonergic levels sufficiently to alter host behavior. They favor the hypothesis that the parasite induces the host to increase its release of serotonin [60]. However, without biochemical tests demonstrating increased serotonin levels in parasitized individuals, and whether it is the host or parasite that is responsible for its increased secretion, we cannot determine which is paying the cost of altering host behavior.

18.4.2 Indirect Methods

When parasitic alteration of behavior has been examined in detail, the change in host behavior is usually an indirect effect of the parasite [1]. There are two possible reasons for this. First, most parasites are small, and it may be prohibitively expensive for them to secrete behaviorally effective amounts of a neuroactive compound, unless the parasite resides within the CNS. It might be more efficient to induce the host to make them. Second, in order to survive, parasites must evolve mechanisms to allow them to interact with host physiology, especially immunity. It may be a small evolutionary step to co-opt the chemical connections between these systems and the host's nervous system to induce adaptive behavioral change in the host. Immune–neural connections may be especially prone to this type of disruption because of the intimate contact between the parasite and the host's immune system [1,3]. If this is a common mechanism of parasitic manipulation, then most changes in host behavior will resemble host responses to stress or infection, making it difficult to determine whether the parasite is exerting any active effect (i.e., secreting compounds that alter host behavior). For example, the trematode *Trichobilharzia ocellata* suppresses the egg laying of its intermediate host, the snail, *Lymnaea stagnalis* using both direct and indirect methods [33]. Parasitic secretory/excretory products induce the snail's immune system to release schistosomin [32]. Schistosomin decreases the excitability of neuroendocrine cells responsible for releasing the peptide caudodorsal cell hormone (CDCH) that induces egg-laying behavior [61]. Schistosomin probably mediates a stress response in uninfected snails [34]. The parasite also exerts direct effects on gene expression in the snail's CNS [35], and some of these changes may play a role in depressing egg laying in the snail [35]. Many parasites may be like this trematode and use multiple mechanisms to alter host behavior.

18.4.3 Importance of Understanding the Physiological Basis of Host Behavioral Change

Understanding how parasites alter host behavior is important for practical as well as theoretical reasons. Because many parasitic effects on behavior exploit immune–neural connections, studying these systems will increase our insight into the molecular mechanisms underlying sickness behavior (e.g. [73]). Moreover, some parasites appear to be able to induce different behaviors in different hosts by using immune–neural connections (e.g. [59]). Further study of this phenomenon will demonstrate how different types of immune responses induce different types of behavior. Such information could lead to improved therapies for life-threatening host responses such as *cachexia*. Furthermore, infectious diseases of the CNS may underlie some common forms of mental illness [11,82,149]. Studying how parasites alter brain function may aid our understanding of these disorders. Examining how parasites alter social behavior may also tell us something about the evolution of the brain in vertebrates. In a recent review paper, Klein [70] reported several examples of pathogens affecting the proximate mechanisms that mediate the expression of social behaviors in vertebrates (aggressive, reproductive, and parental behaviors) in ways that may increase parasitic transmission. Interestingly, the effects of parasites on social behavior may be retained across several classes of vertebrates because parasites affect the phylogenetically primitive structures of the limbic system and related neurochemical systems [70]. Further research in this area should increase communication and cooperation among neuroscientists, parasitologists, and evolutionary biologists.

18.4.4 Implications about Parasitic Manipulation from Recent Mechanistic Studies

As demonstrated in the preceding sections, changes in host behavior are often a mix of direct and indirect effects of parasites on their hosts' CNS. For example, the host's immunological response to infection can be involved in changing the host's behavior in a manner that favors parasitic transmission (e.g., rabies). Studies attempting to differentiate between host responses (e.g., sickness behavior) and parasitic effects on behavior should keep this observation in mind. Even if a change in host behavior can be mimicked by activating the immune system, this change could still be adaptive for the parasite, and it could still be a direct effect of the parasite (e.g., by the parasitic secretion of cytokines). Furthermore, finding the correct immune challenge to test whether a change in host behavior could be a host response will not be easy. Immune responses can vary depending on the parasite [125], and different immune responses can elicit different types of behavior [4]. For example, parasites that infect the brain may induce specific changes in behavior due to local release of cytokines, a pattern of release that would not be reproduced by a systemic challenge.

In host–parasite systems in which the host exhibits a completely novel behavior (e.g., [146]), the causal connection between a parasitic effect and host behavioral change may be easier to establish. Activation of a unique behavior, rather than the augmentation of a host response or a decrease/increase in a normal behavior, may also be less likely to rely on exploiting a host response to infection. Unfortunately, these types of host–parasite systems are rare and have been largely ignored by physiologists.

18.4.5 New Methods in the Study of How Parasites Manipulate Their Hosts

Proteomics is the study of all the proteins produced by a cell (i.e., the proteome). Instrumental to the study of functional genomics, it incorporates protein separation methods, mass spectroscopy, and bioinformatics on a massive scale (see Chapter 22). Until now, the studies in "Parasitoproteomics" have been done using the expression of the parasite proteome during infection by a given parasite [22,80,98], the reaction of the host proteome following an invasion by a parasite species [22,97,132,155], or the injection of immune elicitors [49,154]. Because proteomics can rapidly provide a comprehensive view of the expression of entire genomes, Biron et al. [15] recently proposed that proteomics would offer an excellent tool to study the host's (and sometimes the parasite's) genomes in action during behavioral manipulation. Current studies using proteomics to identify the mechanisms of parasitic manipulation are in progress, and preliminary results reveal a bright future for such an approach.

18.5 ADAPTIVE VERSUS NONADAPTIVE CHANGES

An important debate concerns the adaptive nature of host manipulation. It is argued that phenotypic changes in infected hosts are not necessarily "true" parasitic (or host) adaptations. These changes may be "byproducts" of infection or ancestral legacies. Adaptation is a complex concept with several possible definitions (see [46] for review). For instance, the definition provided by Reeve and Sherman [124] – an adaptation is a phenotypic variant that results in the highest fitness among a specified set of variants in a given environment – refers only to contemporary effects of the trait on reproductive success. In contrast, the definition of Harvey and Pagel [52] – for a character to be regarded as an adaptation, it must be a derived character that evolved in response to a specific selective agent – explicitly requires an inference about history. Clearly, most researchers interested in manipulation adopt the second, historical definition of adaptation. Such historical definitions of adaptation (e.g. [52]) are reasonable, and even necessary in contexts such as that of comparative analyses; other applications may be more confusing. For instance, what about ancestral, inherited traits that remain advantageous to their bearers in derived groups? This persistent advantage may still exist within several groups of parasites such as acanthocephalans or trematodes (see Section 18.3.1.), where it seems likely that not only has the ability to manipulate host species been inherited from a common ancestor but also that these manipulations have continued to confer a selective advantage in the context of the transmission.

The term "byproducts" of infection refers to at least three types of phenomena. In the first case, the "side effects" of parasite infection are pathological consequences expressed in host behavior that have no adaptive value for the parasite or the host [91]. In the second case, "byproducts" are "coincidentally beneficial" for the parasite. For instance, parasitized hosts may increase their conspicuousness to predators (definitive hosts) if they forage more to satisfy increased energy requirements; this differs from straightforward manipulation [113]. Finally, a third type of change in host phenotype results in "fortuitous payoffs of other adaptations." For example, encysting in the host nervous system is one way to manipulate behavior; such a site may have initially been favored because it affords some protection from the host's immune system [96].

It is reasonable to reevaluate these "byproducts," and the rule of parsimony that has been used to defend the byproduct interpretation. In the first case, it is obviously difficult to demonstrate the absence of anything, be it benefit to parasite or host. In the case of the second and third categories, "coincidental benefits" and "fortuitous payoffs of other adaptations," it is easy to confuse the focus of historical selection (depleted energy? immunological protection?) and concomitant effects on transmission, especially when enhanced transmission itself may be favored by natural selection. In short, if parsimony produces a null hypothesis of "byproduct" as a standard by which to evaluate other interpretations, then that hypothesis must surely be testable [136,147]. Unfortunately, tests of the byproduct explanation of apparent manipulation are not a trivial undertaking. After all, altered behaviors that occur only sporadically are not terribly interesting unless the pattern of appearance/absence itself is somehow informative. On the contrary, if an altered behavior occurs routinely, it is then part of the suite of traits that are subject to natural selection in that association; it is unlikely to be an accident. This does not guarantee that the altered behavior is adaptive; after all, not all traits are adaptive. However, if pathology is linked to transmission, then it is highly likely that natural selection has not been blind to that pathology [7].

18.6 COST(S) OF MANIPULATION FOR PARASITES

If manipulation offers a selective advantage, does it also exact a cost in fitness? This possibility has been the focus of some discussion. Although suitable systems exist with which hypotheses about cost might be tested, no such tests have been conducted, and many workers seem to assume the existence of costs. The existence and amount of such costs are probably closely linked to the mechanism that underlies manipulation (see Section 18.4). In addition, in a broader evolutionary context, one must consider manipulative costs not only at a physiological level, but also at the ultimate level, in terms of fitness [116]. For instance, Thomas et al. [139] found that although amphipods (*Gammarus aequicauda*) are capable of mounting an immune response against invading parasites (involving both encapsulation and melanization), they use this cellular defense reaction only against the manipulative trematode *M. papillorobustus* and never against three other species of non-manipulative trematodes commonly

found in the abdomen. Further, encapsulation is targeted almost exclusively at *M. papillorobustus* metacercariae encysting in the host's cerebral region, that is, at those individual parasites inducing the manipulation, and not at their non-manipulative conspecifics encysting in the abdomen. In this case, manipulating the host is thus associated with higher risk of mortality for the parasite.

Assuming that manipulation is costly for parasites, then the potential for cost-sharing by manipulative parasites poses other basic questions [112]. Despite theoretical expectations of cooperation among manipulative conspecifics, very few studies have explored this issue. From data collected in the field, Brown et al. [18] found no evidence that co-occuring metacercariae of *M. papillorobustus* benefit from the presence of conspecifics in the brain of gammarids; instead, individuals in larger *infrapopulations* suffered reduced size and fecundity. The issues of cost and of adaptation versus byproduct, as well as other questions about parasite-induced behavioral changes, may have much to gain from attention to mechanisms.

18.7 MAFIA-LIKE STRATEGY OF MANIPULATION

The complexity of the interactions between hosts and parasites suggests that we may not yet fully understand host–parasite interactions. Theoretically, parasites may select for collaborative behavior in their hosts by imposing extra fitness costs on recalcitrant hosts. This interaction has been called a mafia-like strategy [130]. This process was initially proposed as a possible explanation for why several bird species accept cuckoo eggs and nestlings in their nest despite the dramatic cost to their own fitness. Cuckoos may force the bird host to tolerate non-self eggs by making the consequences of rejection more damaging than the consequences of acceptance ([159], Table 1, p. 246). In a study of the great spotted cuckoo and its magpie host, Soler et al. [130] provided empirical evidence of this phenomenon: ejector magpies suffer from considerably higher levels of nest predation by cuckoos than acceptors do, suggesting "punishment" of the ejector host when the cuckoo retaliates and destroys its clutch (see Fig. 18.9). Such retaliation favors an

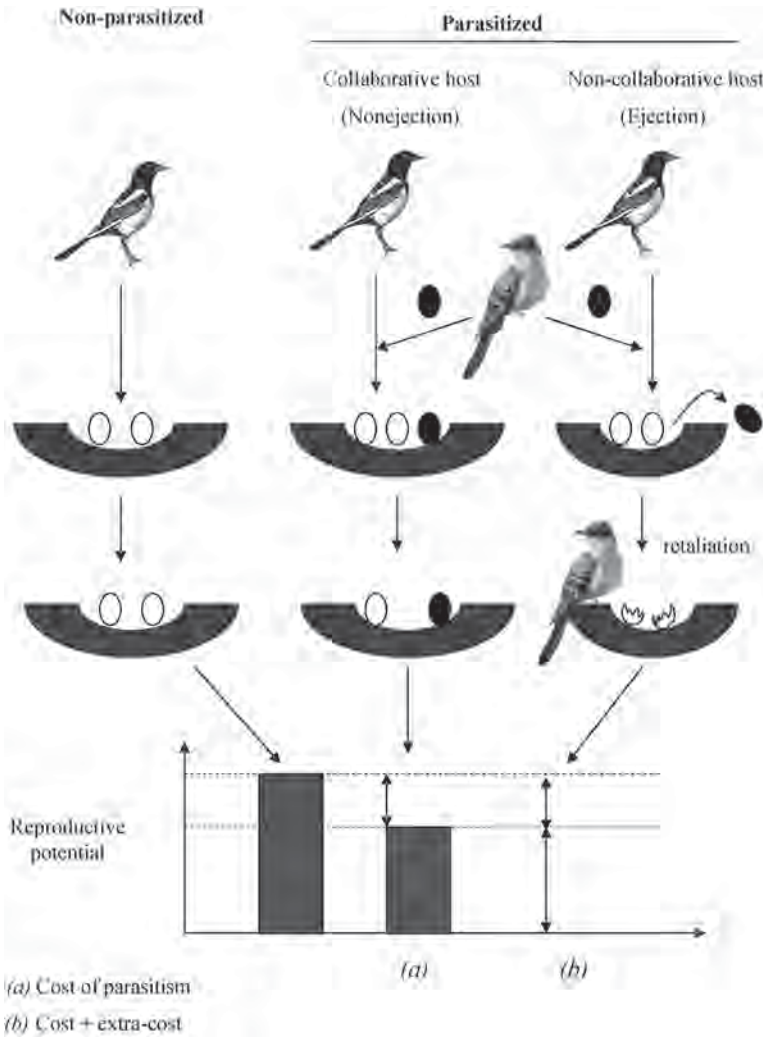


Fig. 18.9. Mafia behavior in the cuckoo *Clamator glandarius* parasitizing the magpie host *Pica pica*.

increase in "acceptor genes" relative to "rejector genes" in the host population. Such interactions could be far more common among host–parasite systems than the few existing studies might indicate.

Host species are under selective pressure not only to eliminate parasites but also to compensate for the effects of parasites when elimination is impossible. When parasites can respond to recalcitrant hosts by increasing their virulence, then host–parasite cooperation, rather than resistance, might mitigate fitness costs associated with parasitism. This scenario implies that both host and parasite can perceive a large set of fitness-related environmental cues and adjust their life history decisions (*sensu lato*) accordingly. Increasing evidence suggests that this faculty is indeed present (see [84,137,115] for parasite examples and [2,6,92,110,] for host examples). Theoretically, mafia-like strategies may evolve even when manipulative parasites strongly reduce host survival. From an evolutionary point of view, reduced survival and reduced fitness are not synonymous. Net fitness, not survival, is the primary consideration. Thus, a host that cooperates with the parasite, even to the point of "suicide" (manipulated behavior, see Section 18.3), may be better off with reduced fecundity compared to total castration inflicted by a retaliatory parasite on an uncooperative host.

Parasites affect fecundity over a wide range of outcomes, from slight reduction to total, irreversible castration. This range invites further investigations of mafia-like strategies of manipulation. For instance, noncompliance could be imposed by an investigator, and the fitness of those noncompliant hosts could then be compared to that of hosts allowed to express parasite-induced behavior. This would reveal differences between a collaborative host and a truly manipulated one, and would allow measurement of the relative costs. From an evolutionary point of view, this approach suggests that phenotypic changes in infected hosts, even when they result in clear fitness benefits for the parasite, are not necessarily an illustration of the extended phenotype of the parasite alone (*sensu* [31]). They can also be the direct product of natural selection acting on the host genome as well.

18.8 MULTIPLE PARASITES WITHIN MANIPULATED HOSTS

Another area of increasing interest is the study of the influence of manipulative parasitic species on the evolution of sympatric parasite species. Lafferty et al. [79] offer a series of ecologically based predictions about transmission strategies that should be favored by natural selection in these multispecies situations. For instance, when manipulation is costly and when both non-manipulative and manipulative parasites have a similar transmission agenda (i.e., they have the same intermediate and definitive hosts), non-manipulator parasites should increase their chance of transmission by preferentially infecting hosts that are already manipulated (hitch-hiking strategy [140,144]). In the case of two manipulative parasites that have such shared interests and produce different manipulations (e.g., color changes, behavioral changes) in ways that increase transmission additively, co-occurrence of these "co-pilots" in intermediate hosts should be favored by natural selection [79]. Finally, if an intermediate host is shared by one or more parasite species that require different definitive hosts, conflicts of interests will emerge. At least three evolutionary solutions to such a conflict have been proposed: (1) avoiding intermediate hosts containing a manipulator, (2) killing the manipulator, (3) overpowering the manipulation of the manipulator. The last instance is called "hijacking," in the case of a second trophically transmitted manipulator [79], and "sabotage" when the second parasite is not a manipulator, is not trophically transmitted, and benefits most from being in a host with a normal phenotype [138]. The number of empirical studies focusing on multiple parasites within manipulated hosts is low, but increasing (but see [20,29,36,37,40,78,107,118,117,120,140,142,144]). In order to understand these interactions, it is desirable for the entire community of parasites in manipulated hosts to be examined. In addition, a better understanding of the proximate causes of parasitic manipulation will clarify the potentially complex interactions that mediate cooperative and conflicting relationships among parasites sharing a manipulated host (see [117] for a unique example).

18.9 HOW COMPLEX ARE "PARASITICALLY MODIFIED ORGANISMS"?

A full understanding of the manipulation process requires the study of other phenotypic traits in hosts in addition to the most obviously altered behaviors. Indeed, there are several reasons to think that we have until now only studied the visible part of the iceberg; manipulated hosts may be vastly more complex than traditionally viewed.

As shown in studies on *phenotypic plasticity* and evolution, a single phenotypic change (for instance, one induced by a minor genetic mutation) can secondarily produce additional important phenotypic changes as a result of compensatory responses *via* a shift in the expression of related traits (see [102,158]). Poulin and Thomas [119] argued that the ability of infected hosts to undergo large phenotypic alterations, such as a change of microhabitat, may depend on the capacity for auxiliary traits to accommodate this novelty. To our knowledge, the idea that manipulative parasites could act as a developmental switch for several associated traits remains to be investigated.

In addition to changes resulting from plastic adjustments of the hosts to novel conditions, complex alterations of the host phenotype could result from parasites being able to manipulate several traits in their hosts. Because studies on manipulation have usually focused on the most spectacular change displayed by infected hosts, this idea has rarely been explored (but see [54,81]). When possible, manipulation of several host traits by parasites either simultaneously or in sequence should

be favored by selection. For instance, the efficiency of a behavioral manipulation could, in many situations, be enhanced by a physiological manipulation. Indeed, the display of an aberrant behavior is not only likely to be an energetically costly task for the host, but is also a period during which foraging may be reduced. Because the window of manipulation is larger for hosts with high levels of energy reserves than for those with poor reserves, natural selection should favor parasites that cause hosts to increase energy reserves. In fact, this is hypothesized to be an advantage for parasitic castrators – they are thought to shift resource allocation from reproductive to somatic (and hence, parasite) uses [114]. If intermediate hosts are "vehicles" transporting the parasites to their definitive hosts, then parasites should make sure that the "gas tank" is full. Further research is likely to reveal that parasitically modified hosts are not simply normal hosts with one aberrant trait (e.g., behavior), but instead are deeply modified organisms with a range of modifications, some of which may favor parasites, and some of which may favor hosts. Such integrative study requires collaboration among parasitologists and researchers from other disciplines, especially physiology, morphology, and developmental biology.

18.10 INTRASPECIFIC VARIATION IN MANIPULATIVE PROCESSES

Substantial variation in the intensity of the phenotypic changes is typical of many infected hosts, even when they are collected in the same environment and at the same time. As pointed out by Perrot-Minnot [108], the analysis of the intraspecific variability in these patterns is essential to understand their evolution. Two individuals may differ because they differ in *genotype*, because they differ in environmental experiences, or both. Unfortunately, the extent to which different individual parasites display different manipulative abilities and the variability in the ability of individual hosts to oppose manipulation is poorly documented. Despite the difficulty of maintaining parasites with complex life cycles in the laboratory, we need more studies aimed at identifying not only the relationship between phenotype and fitness but also the phenotypic variance and the degree to which manipulation is heritable. Such efforts will undoubtedly provide a much better basis for understanding the evolution of traits involved in the manipulative process.

18.11 MANIPULATIVE PARASITES AND ECOSYSTEM FUNCTIONING

Over the past 15–20 years, considerable progress has been made in understanding the functional importance of parasites in *ecosystems*. Much theoretical and empirical evidence has demonstrated that parasites, in spite of their small size, are biologically and ecologically important in ecosystems [24,90,99,111,131,133,135]. Little is known, however, about the more specific role(s) of manipulative parasites in these processes [79].

Parasite manipulation can first influence community structure and biodiversity in ecosystems by apparently interfering with competition between hosts. This scenario has been illustrated in salt marshes of southern France for the association between the trematode *M. papillorobustus* and the two congeneric and syntopic amphipods *G. insensibilis* and *G. aequicauda* (see also [10]). As reported in Section 18.3 (Fig. 18.2), cerebral metacercariae of *M. papillorobustus* induce strong behavioral alterations making infected gammarids more vulnerable to predation by aquatic birds. In *G. insensibilis*, metacercariae always alter behavior, as they are always cerebral [56]. Conversely, in *G. aequicauda*, metacercariae can also be abdominal; in this case, they have no particular effect on the host behavior [55]. In the field, two distinct infection patterns are observed in the two amphipod species (Fig. 18.10) [145], indicating that the manipulation exerted by *M. papillorobustus* probably acts as an important mechanism regulating the density of *G. insensibilis* populations versus that of *G. aequicauda* (see [126]). Because the higher reproductive success of *G. insensibilis* [66] is offset by its lower tolerance to *M. papillorobustus*, the *sympatric* coexistence of the two amphipod species is likely to be mediated by this manipulative parasite [145].

A second process through which manipulative parasites could influence community structure in ecosystems is through their influence on the predator community. As seen in Section 18.3, many trophically transmitted parasites adaptively change the phenotype of their hosts in a way that increases their probability of being captured by definitive hosts [25,26,77]. Predators sometimes risk infection when feeding on manipulated prey, but they also often benefit from enhanced prey capture [64,76,93,105]. In addition, most manipulative parasites in intermediate hosts apparently cause little harm to definitive hosts [76,77], so we can safely assume that predators not only have no *a priori* reason to avoid manipulated prey, they should even prefer foraging on those prey (see [5,76,93]). By increasing accessibility of prey that is normally difficult to capture, the net effect of manipulative parasites in ecosystems may be the enhancement of the trophic potential of these habitats. Unfortunately, this idea remains to be tested; there are no reports of possible positive relationships among the local abundance of manipulative parasites, food accessibility for predators and their local *richness/diversity*.

A third important mechanism by which manipulative parasites may influence processes of community ecology is through their interference with engineering processes. Ecosystem engineers are organisms that directly or indirectly modulate the availability of resources to other species by causing physical state changes in biotic or abiotic materials [67,68]. Manipulative parasites, by altering the phenotypes of their host, can either have impacts on existing ecosystem engineers or act as engineers themselves [141]. The idea that parasites could create new resources for other species by shifting

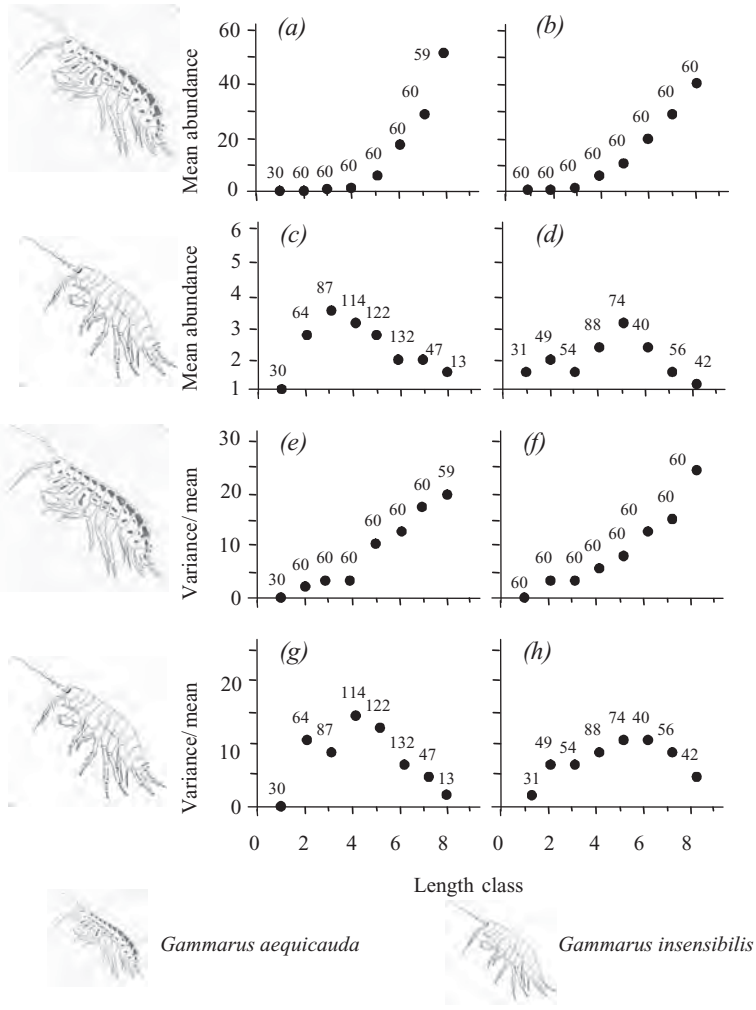


Fig. 18.10. Infection patterns (mean abundance and variance to mean ratio) of the trematode *Microphallus papillorobustus* in relation to host size in *Gammarus aequicauda* (a,b,e,f) and *G. insensibilis* (c,d,g,h). The number of hosts analyzed in each length class is indicated above each dot. Left-hand column presents data for males, the right-hand column for females (based on [145]).

the phenotype of the host from one state to another is well illustrated by the association between the cockle *A. stutchburyi*, the trematode *C. australis* and various epibiotic invertebrates ([143], see also Section 18.3, Fig. 18.3B).

A. stutchburyi lives just under the surface of the mud in many sheltered shores of New Zealand. This abundant mollusk can be considered an autogenic engineer, as its shell is the only hard substrate where invertebrates such as sea anemones (*Anthopleura aureoradiata*) and limpets (*Notoacmae helmsi*) can attach (Fig. 18.3). This cockle is also the second intermediate host of the trematode *C. australis*, a manipulative parasite that enhances its transmission to oystercatchers by altering the burrowing behavior of cockles (infected cockles remain at the surface of the mud) [134]. Manipulated cockles apparently provide a new kind of substrate for the fouling community of invertebrates. Indeed, limpets, which are normally outcompeted for space on burrowed cockles by sea anemones, significantly prefer surface cockles [143] (Fig. 18.3B). Conversely, manipulated cockles support fewer anemones than burrowed cockles do because of their greater exposure to desiccation at low tide. The manipulation exerted by the trematode *C. australis* clearly turns living material (the cockle) from one physical state (buried) into a second physical state (surface), and this act of engineering modifies both the availability and the quality of habitats for invertebrates. It seems likely that the net effect of this manipulation on the local biodiversity is positive; by reducing competition for space between invertebrates, the local coexistence of limpets and anemones is likely to be facilitated. The effect of the trematode *C. australis* extends beyond the fouling invertebrates living on the cockle shell. The presence of numerous manipulated cockles lying on the sediment modifies seabed hydrodynamics, and the reduced burrowing of infected cockles decreases bioturbation of the sediments, with the net impact being that sediment characteristics in areas of high parasite abundance differ from those in adjacent areas of low

parasite abundance. In a field experiment, the species richness and the overall density of benthic invertebrates (polychaetes, crustaceans, etc.) settling in plots with high parasite abundance were higher than in control plots with low parasite abundance [101]. Thus, a single manipulative parasite can have measurable effects on biodiversity of an entire intertidal ecosystem.

The parasite community (the trematodes *M. papillorobustus*, *Maritrema subdolum*, and the nematode *Gammarinema gammari*) harbored by the brackish gammarid *G. insensibilis* provides an interesting system for exploring how parasite manipulation can have both positive and negative effects on species richness. As seen above, the trematode *M. papillorobustus* is a manipulative parasite that increases the vulnerability of gammarids to predation by aquatic birds (definitive hosts of the parasite). Using the terminology of Jones et al. [67], this manipulation can be said to turn gammarids from a phenotype A (normal behavior) to a phenotype B (altered behavior). Thomas et al. [140] showed that the trematode *Maritrema subdolum*, which also completes its life cycle in an aquatic bird but does not alter the behavior of the intermediate host, preferentially infects phenotype B gammarids [140]. The manipulator and the "hitch-hiker" *M. subdolum* therefore seem to share interests, but the situation is quite different with the nematode *G. gammari*. Indeed, because this parasite uses the amphipod as a habitat and source of nutrition but not as an intermediate host, there is a clear conflict of interest between the nematode and the trematode. In accordance with theoretical expectations, the manipulator and the nematode are negatively associated in the field, suggesting that *G. gammari* prefer phenotype A gammarids [138]. Finally, laboratory experiments suggest that the nematode is able to "sabotage" the manipulation exerted by *M. papillorobustus*, reversing gammarids from a phenotype B to a phenotype A [138].

Many studies of parasitic manipulation have been performed without considering the ecological context in which they occur. This is unfortunate, for it compromises both our understanding of the evolution of parasitic manipulation and our understanding of the ecological consequences of manipulation within ecosystems. A full understanding of the evolution of parasitic manipulation requires knowledge of the selective pressures experienced by both the host and the parasite. Conditions used in laboratory studies as well as in semi-natural experiments may be poor approximations of processes that occur in the field. For instance, the proportion of manipulated hosts/uninfected hosts often used in predation experiments is huge compared to that frequently observed in natural conditions. How this affects the behavior of predators, and hence the conclusions derived from these studies, is not known. Most experiments do not take into account the fact that, in natural conditions, other predators unsuitable as hosts may also take advantage of the manipulation (see for instance [100]), or that several suitable host species may vary in their predation efficiency. These phenomena are nonetheless critical to our understanding of the costs and the benefits of parasitic manipulation. In some cases, certain features of parasite-induced behavioral changes seem more relevant to limiting the risk of predation by the wrong (non-host) predator than to increasing transmission to appropriate hosts (e.g. [83]). Such altered behavior in intermediate hosts cannot be understood outside its ecological context.

Finally, an important limitation of virtually all recent theoretical and experimental studies of the evolution of parasitic manipulation is the fact that these phenomena occur in a metapopulational context (e.g. [150]). Like most animal species, host and parasite species are likely to exhibit a classical *metapopulation* structure over their entire geographic range, occupying habitats that are fragmented and heterogeneous in space and/or time. In heterogeneous environments, local populations might be permanently maladapted because of migration from other habitats with contrasting selection pressures (e.g., sink populations, see [50]). Such concepts have not been tested in the context of manipulative changes, but research in this direction could well provide examples of adaptive changes that are locally maladapted. For instance, given that predator communities frequently vary in space and/or time, the fitness benefits for trophically transmitted parasites that result from manipulation differ from one place to another, with some sink populations being net importers of individuals and genes. In similar fashion, adaptive baseline behaviors of uninfected animals may vary across host ranges, thus changing the behavioral substrate on which the manipulative parasite may work [95]. General conclusions about the possible adaptive value of host changes induced by parasites must therefore be considered with caution when derived from local and/or short-term field studies. Consideration of the spatial structure of both host and parasite populations as well as the heterogeneity of environmental conditions is as desirable as it is daunting.

18.12 CONCLUDING REMARKS

The path to understanding the evolution of manipulation is a long and winding road [21]. The trait of interest is the product of the interaction between the genotypes of two different organisms, the host and the parasite. The host–parasite interactions that form the core of this research reflect evolutionary processes that have been ongoing, often for more years than we can measure. The interdisciplinary scientific interactions required to understand them have just begun.

GLOSSARY

Adaptation: A trait that evolved because it improved reproductive performance.

Autotomy: The ability of certain lower animals, such as lizards and starfish, to cast off injured body parts, such as the tail and, usually, to regenerate new ones.

Benthic: Organisms that live at the bottom of a river, lake or ocean.

Byproduct: Something that is made in the process of making something else.

Cachexia: A clinical condition in which there is a depletion of blood proteins, and fat deposits. Tissue proteins are eventually catabolized with the ultimate possibility of severe tissue atrophy and muscle wasting. There is a progressive weight loss.

Cercaria: An immature digenean, usually free swimming, produced by a sporocyst or a redia.

Congeneric: Species of the same genus.

Convergence: Two species resemble each other not because they shared common ancestors but because evolution has adapted them to similar ecological conditions.

Cystacanth: Juvenile stage of acanthocephalans that is infective to the definitive host.

Cytokines: Cytokines are chemical messengers (proteins) made by cells that influence that influence the behavior of other cell types. Cytokines produced by lymphocytes are also referred to as lymphokines or interleukins.

Dispersal: Movement of living organisms away from their previous home range. Often refers to the movement of an organism away from the home range where it was born when it matures.

Diversity: An ecological concept that incorporates both the number of species in a particular sampling area and the evenness with which individuals are distributed among the various species.

Ecosystem: A community of organisms and its environment.

Hyperparasitoid: A parasitoid that uses another parasitoid as a host.

Fitness: For a start, relative lifetime reproductive success, which includes the probability of surviving to reproduce. In certain situations, other measures are more appropriate. The most important modifications to this definition include the inclusion in the definition of the effects of age-specific reproduction, and of fluctuations of density dependence.

Genotype: The genetic constitution of an individual.

Horizontal transmission: The transmission of a virus, parasite, or other pathogens from one individual or one cell to another within the same generation, as opposed to vertical transmission through the germ line.

Infrapopulation: All of the individuals of a single species within a single host at a particular time.

Intermediate host: That host in a parasite's life cycle required by the juvenile parasite to complete its life cycle and in which some morphological change or development occurs.

Metacercaria: A developmental stage of digeneans between a cercaria and an adult; usually sequestered within a cyst in a second intermediate host.

Metapopulation: A set of partially isolated populations belonging to the same species. The populations are able to exchange individuals and recolonize sites in which the species has recently become extinct.

Natural selection: A non-zero correlation of trait variation with variation in reproductive success. The process in nature by which, according to Darwin's theory of evolution, only the organisms best adapted to their environment tend to survive and transmit their genetic characters in increasing numbers to succeeding generations, whereas those less adapted tend to be eliminated.

Oogenesis: The formation and growth of the egg or ovum in an animal ovary.

Phenotype: Observable characteristics of an organism produced by the interaction of the organism's genotype and its environment. For example, hair type, eye color, height.

Phenotypic plasticity: Sensitivity of the phenotype to differences in the environment.

Phylogeny: The history of a group of taxa described as an evolutionary tree with a common ancestor as the base and descendent taxa as branch tips.

Pupa: The last immature stage in an insect's life, just before the adult stage.

Richness: The number of species in a biological community.

Siphon: Opening in molluscs or in urochordates which draws water into the body cavity. In many molluscs, the siphon may be used to expel water forcibly, providing a means of propulsion.

Spore: Reproductive body of fungi and other lower plants, containing one or more cells.

Sporocyst: An intramolluscan, asexual developmental stage of digeneans.

Sporozoite: The motile, infective stage often present within a cyst or shell produced during sporogony.

Sympatry: Occurring in the same geographic area.

Vector: A micropredator that transmits a parasite from host to the next. Development in the vector may, or may not, occur.

Virulence: The degree of pathogenicity of a microorganism as indicated by the severity of the disease produced and its ability to invade the tissues of a host. By extension, the competence of any infectious agent to produce pathologic effects.

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