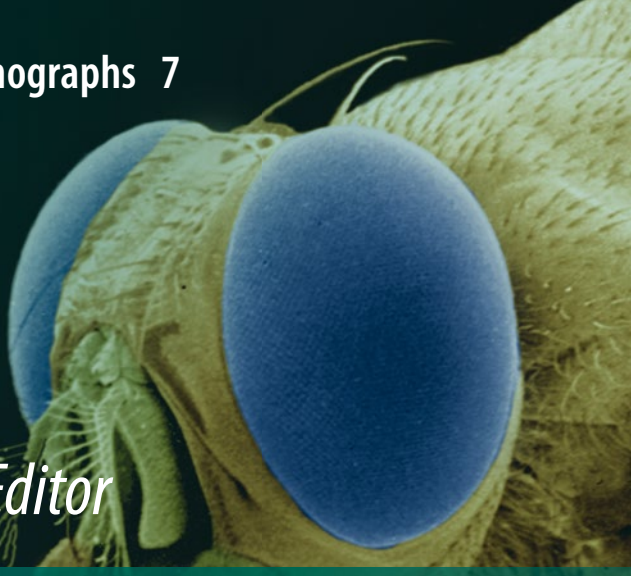
Parasitology Research Monographs 7



Heinz Mehlhorn *Editor*

Host Manipulations by Parasites and Viruses

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Parasitology Research Monographs

Volume 7

Series Editor:
Heinz Mehlhorn
Department of Zoomorphology
Cell Biology and Parasitology
Heinrich Heine University
Düsseldorf
Germany

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The new book series “Parasitology Research Monographs” presents carefully refereed volumes on selected parasitological topics. Parasites have an increasing impact on animal and human health in the present times of globalization and global warming. Parasites may be agents of diseases and- often at the same time- vectors of other agents of disease such as viruses, bacteria, fungi, protozoa and/or worms. The growth in knowledge of parasitic physiology, cell structure, biotechnological and genetic approaches, ecology, therapeutic capabilities, vaccination, immunology, diagnosis, transmission pathways and many other aspects of parasitology is increasing dramatically, even in the face of the breakthroughs that have already been made. Reflecting these most recent achievements and the importance of parasites as a threat to human and animal health, the series’ broad scope concentrates on particularly hot topics that were recently covered by review articles in the journal “Parasitology Research” or in other journals. These reviews offer compact but intense insights into the ongoing research and into the methods and technologies used to control parasites. The volumes in the series will be built on these topics, and the volume editors are well-known experts in their respective fields. Each volume offers 10 to 20 comprehensive reviews covering all relevant aspects of the topic in focus.

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Heinz Mehlhorn
Department of Zoomorphology
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Düsseldorf
Germany

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Düsseldorf, Germany — Heinz Mehlhorn
June 2015

About the Editor

Prof. Dr. Heinz Mehlhorn, Düsseldorf, Germany. He has investigated the transmission pathways of human and animal parasites for over 40 years at German and international universities and he and his university spin-off company Alpha-Biocare have developed many antiparasitic medical products based on more than 20 patents – several in cooperation with big international companies. He has published 25 books, more than 250 original papers, and has served as Managing Editor of the journal Parasitology Research since 1981. A long list of renown international scientists did their PhD work in his laboratory and remain still today interconnected as a large group of lovers of parasitology.

Contents

Contributors

Mhairi E. Alexander Institute for Global Food Security, School of Biological Sciences, Queen's University Belfast, Belfast, UK

Centre for Invasion Biology, Department of Botany and Zoology, Stellenbosch University, Matieland, South Africa

Mandy Bunke School of Biology, University of Leeds, Leeds, UK

Anna Cichy Department of Invertebrate Zoology, Faculty of Biology and Environment Protection, Nicolaus Copernicus University in Toruń, Toruń, Poland

Jaimie T.A. Dick Institute for Global Food Security, School of Biological Sciences, Queen's University Belfast, Belfast, UK

Dorian D. Dörge Institute for Ecology, Evolution and Diversity, Senckenberg Biodiversity and Climate Research Centre, Senckenberg Gesellschaft für Naturforschung, Goethe-University, Frankfurt/Main, Germany

Alison M. Dunn School of Biology, University of Leeds, Leeds, UK

Jaroslav Flegr Section of Biology, Faculty of Science, Charles University in Prague, Prague, Czech Republic

Nina Hafer Department of Evolutionary Ecology, Max-Planck-Institute for Evolutionary Biology, Ploen, Germany

Yue Han Laboratory of Virology, Wageningen University, Wageningen, The Netherlands

Melanie J. Hatcher School of Biology, University of Leeds, Leeds, UK

Regina Klapper Institute for Ecology, Evolution and Diversity, Senckenberg Biodiversity and Climate Research Centre, Senckenberg Gesellschaft für Naturforschung, Goethe-University, Frankfurt/Main, Germany

Sven Klimpel Institute for Ecology, Evolution and Diversity, Senckenberg Biodiversity and Climate Research Centre, Senckenberg Gesellschaft für Naturforschung, Goethe-University, Frankfurt/Main, Germany

Judith Kochmann Institute for Ecology, Evolution and Diversity, Senckenberg Biodiversity and Climate Research Centre, Senckenberg Gesellschaft für Naturforschung, Goethe-University, Frankfurt/Main, Germany

Thomas Kuhn Institute for Ecology, Evolution and Diversity, Senckenberg Biodiversity and Climate Research Centre, Senckenberg Gesellschaft für Naturforschung, Goethe-University, Frankfurt/Main, Germany

Heinz Mehlhorn Department of Zoomorphology, Cell Biology and Parasitology, Heinrich Heine University, Düsseldorf, Germany

Manfred Milinski Department of Evolutionary Ecology, Max-Planck-Institute for Evolutionary Biology, Ploen, Germany

Julian Münster Institute for Ecology, Evolution and Diversity, Senckenberg Biodiversity and Climate Research Centre, Senckenberg Gesellschaft für Naturforschung, Goethe-University, Frankfurt/Main, Germany

Rachel A. Paterson Institute for Global Food Security, School of Biological Sciences, Queen's University Belfast, Belfast, UK

Vera I.D. Ros Laboratory of Virology, Wageningen University, Wageningen, The Netherlands

Stineke van Houte Department of Biosciences, Centre for Ecology and Conservation, Biosciences, University of Exeter, Penryn, Cornwall, UK

Laboratory of Virology, Wageningen University, Wageningen, The Netherlands

Monique M. van Oers Laboratory of Virology, Wageningen University, Wageningen, The Netherlands

Elżbieta Żbikowska Department of Invertebrate Zoology, Faculty of Biology and Environment Protection, Nicolaus Copernicus University in Toruń, Toruń, Poland

Chapter 1
Introduction

Heinz Mehlhorn

The present book deals with interactions of parasitic animals ranging from viruses via protozoans, worms to arthropods that manipulate the behaviour of their various hosts including humans thus enhancing their own chances for propagation inside a given host and/or within a varying host population. In order to be successful in their individual struggle for survival, these animals must develop means for host finding, attachment at the host's surface or offer attractions to become ingested and finally – as most difficult task – create means that help to survive and to reproduce themselves inside a host.

Since about 50 % of the animals on earth live as parasites, it is obvious that already many different strategies have been successfully developed. In the present volume several examples are presented, which show that parasites are even able to manipulate the behaviour of their hosts, which then neglect any care for their own welfare, which is – according to Darwin – the motor of natural selection and thus the basis of survival of a given population of any kind in a peculiar biotope or in a community of similar species. However, also many activities similar to the human behaviour described as altruism occur on both sides (parasites and hosts), when manipulated hosts spend their lives to defend the penetrated parasites or help to propagate the parasites by searching the vicinity of predators and thus become an easy prey. But also single individuals of parasites may show altruistic signs of behaviour, when some stages (e.g. cercariae of several trematodes) enter the "brain" of ants, where they get rid of any further chance for a individual propagation, but make this possible for all other cercariae of its species, that have also entered this intermediate host but are waiting inside its body cavity until it is ingested by the final host. The chapters of this book show several examples, which hopefully induce deeper research activities in this field.

Düsseldorf, June 1st 2015

H. Mehlhorn
Department of Zoomorphology, Cell Biology and Parasitology, Heinrich Heine University, Universitätsstr. 1, 40225 Düsseldorf, Germany
e-mail: mehlhorn@uni-duesseldorf.de

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Chapter 2
Parasites: An Own World of Cross Reactions with Their Hosts

Heinz Mehlhorn

2.1 Introduction

The name parasite has its origin in the Greek term "*parasitos*", which at first describes human beings that tasted food at the tables of noble families in order to find out whether it might be poisoned or is safe. Thus these "*parasitos"* had the privilege to be nourished without working. Therefore the meaning of this term became later transferred to describe animals which take their food from animals or human hosts in a seeming easy way. However, this way of obtaining food seems only easy at the first sight. At the second and third view, however, survival of parasites is highly endangered, since all hosts have developed sophisticated means of self-defense. Thus survival of parasites is only possible, if they develop contra-strategies surmounting the defense activities of possible hosts (Moore 2013). E.g. parasites of any kind have developed means to produce layers on their surface called surface coats, which protect them from intestinal digestive fluids, host's antibodies, attacks of defense cells etc. On the other hand parasites induce the activities of the host immune system at a considerable degree. Examples are larvae of hookworms (e.g. *Necator americanus*, *Ancylostoma duodenale*) and larvae of the whipworm *Trichuris suis*, which stimulate the host's defense system in such a way, that human autoimmune diseases such as Morbus Crohn, ulcerative colitis, multiple sclerosis, allergic rhinitis or even the behavioural disease "autism" are considerably or even totally suppressed (Maizels et al. 2014; Marchan 2014). This effect apparently occurs due to the production of the so-called AcK1 peptide excreted by the worms (Mehlhorn 2016). Even malaria, which kills still nowadays nearly one million

H. Mehlhorn
Department of Zoomorphology, Cell Biology and Parasitology, Heinrich-Heine-University, Universitätsstr. 1, 40225 Düsseldorf, Germany
e-mail: mehlhorn@uni-duesseldorf.de

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patients per year, was shown to protect humans from other diseases. E.g. infected Nigerian people showed significant lower incidences of autoimmune diseases in particular rheumatoid arthritis (Greenwood 1968; Wammes et al. 2014).

It is in the interest of parasites to avoid to kill their hosts, since their death would endanger their own individual existence and would block any chance to become transmitted to other hosts. Thus it can be observed that initial contacts of parasites with new host introduce much higher adverse effects than long-lasting contacts which lead to a balance of host-parasite relationships and mostly to low-graded clinical symptoms. E.g. Egyptians excreting thousands of *Entamoeba histolytica* cysts show often practically no symptoms of disease, while infected tourists may suffer from severe diarrhoeas. Similar effects can be seen after bloodsucking of ectoparasites, since inhabitants of regions with a high pressure of mosquitoes show mostly only very scarce skin reactions after numerous bites, while tourists/foreigners in the same region may suffer from severe skin reactions such as itching, formation of large swellings, allergic shock reactions etc. (Mehlhorn 2015).

2.2 Parasite Activities

Parasites attack their hosts at the surface or at inner organs after entering body cavities such as nose, intestine and lungs. Therefore they are divided into the groups:

- **ectoparasites** with the subgroups **permanent ectoparasites** (such as e.g. scabies and *Demodex* mites, lice (Figs. 2.1, 2.2, and 2.3) and **temporary ectoparasites** (such as mosquitoes, biting flies, fleas, bugs, ticks, several mites etc.) (Figs. 2.4, 2.5, 2.6, and 2.7).
- **endoparasites**, which can be subdivided into groups according to the invaded organs (intestine, body cavities, blood vessels, muscles, brain, lung etc.).

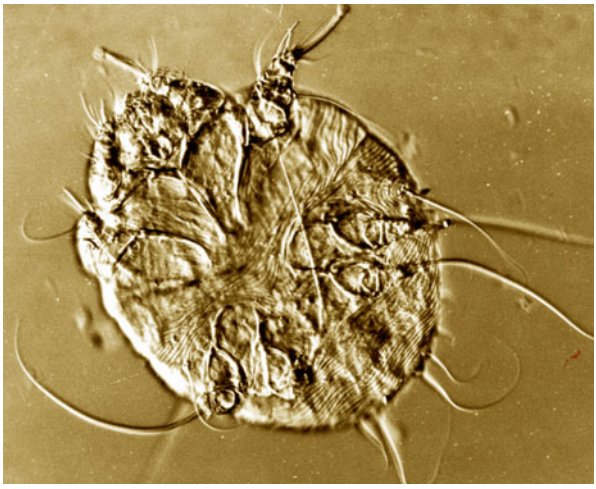

Fig. 2.1 Light micrograph of a *Sarcoptes* scabies mite

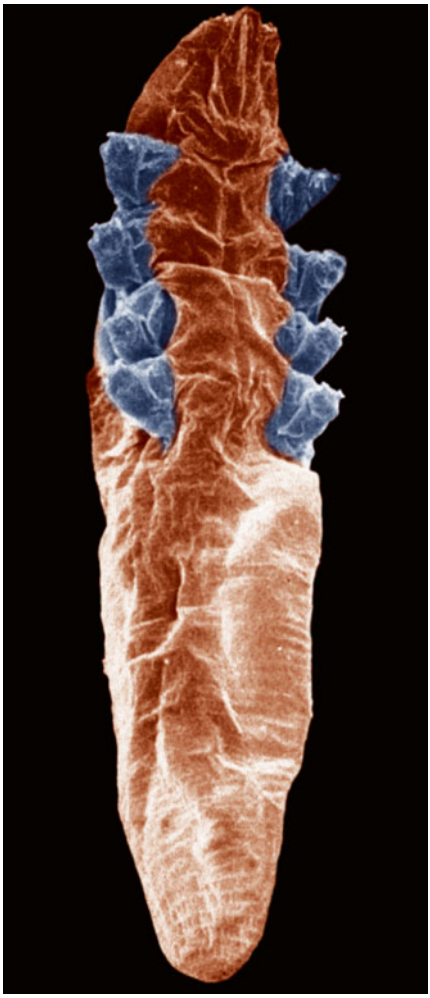

Fig. 2.2 Scanning electron micrograph of a *Demodex folliculorum* mite

Fig. 2.3 Scanning electron micrograph of a head louse (*Pediculus humanus capitis*)

Fig. 2.4 Light micrograph of a female mosquito (*Aedes albopictus*)

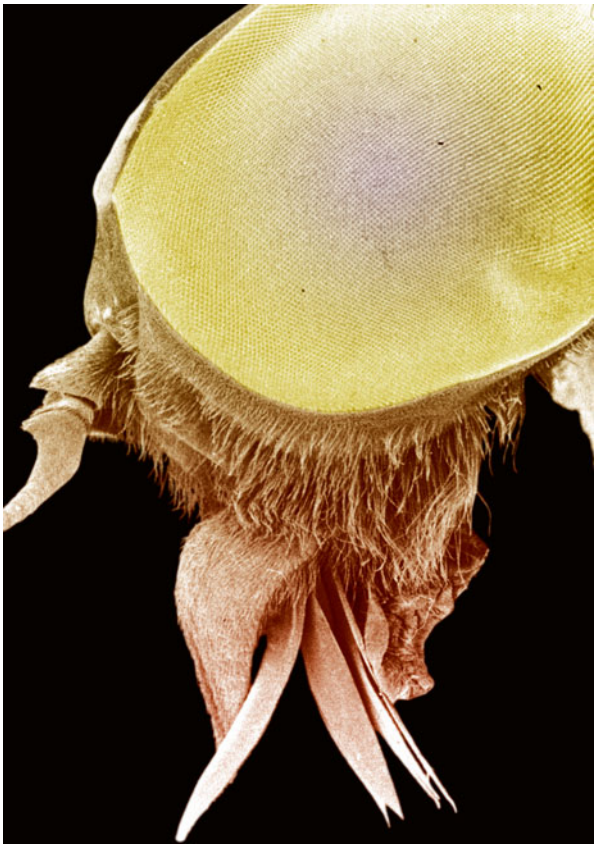

Fig. 2.5 Scanning electron micrograph of the head of a tabanid fly (*Tabanus* sp.)

Ectoparasites are in general highly motile and thus it is rather easy for them to find new hosts, especially since they have developed sophisticated sensory organs such as large compound eyes, thousands of different sensillae, which enable them to detect and to react at different smellings, temperatures and movements of possible hosts (Fig. 2.8).

Fig. 2.6 Light micrograph of a bed bug (*Cimex lectularius*)

Fig. 2.7 Macrophoto of a *Dermacentor reticulatus* tick

Survival of **endoparasites** inside hosts is much more difficult, since this depends on different factors. Parasites that produce eggs depend on the fact, that these stages need to become ingested by a new host. Thus these parasites (mostly worms) produce huge numbers of adult stages, eggs or free larvae (e.g. *Ascaris lumbricoides*, *Ancylostoma duodenale*; Figs. 2.9, 2.10, and 2.11). Another peculiar group of endoparasites needs a vector (e.g. *Plasmodium* species, *Babesia* species, *Trypanosoma* species or filariae; Figs. 2.11, 2.12 and 2.13) and thus they depend on the availability of adapted ectoparasites (mosquitoes, ticks, biting flies, ticks etc.). To overcome these obligate requirements these parasites always produce huge amounts of progeny in order to increase the chances for a successful transmission at least for some individuals (Mehlhorn 2016).

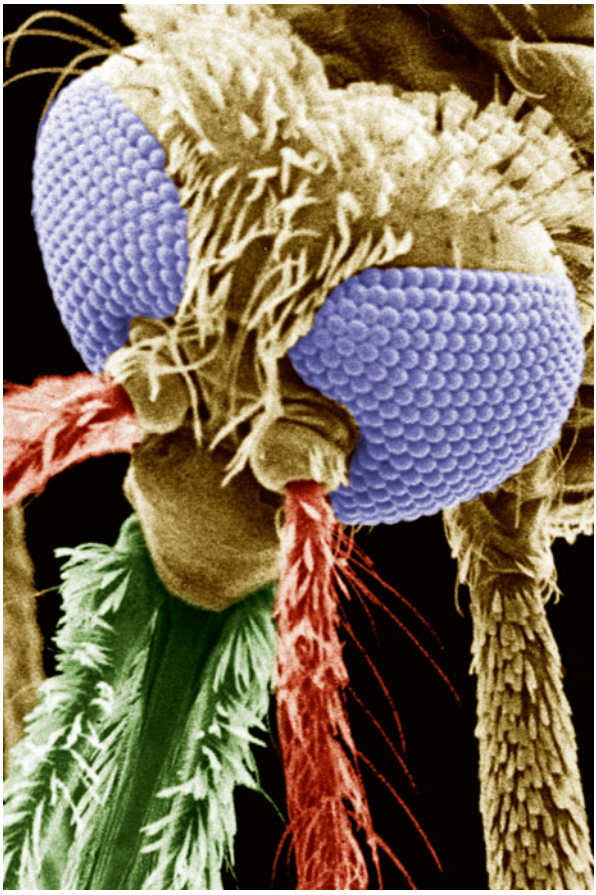

Fig. 2.8 Scanning electron micrograph of the head of an *Anopheles stephensi* mosquito showing hundreds of hair-like sensillae and the huge number of the single facettes of the compound eyes

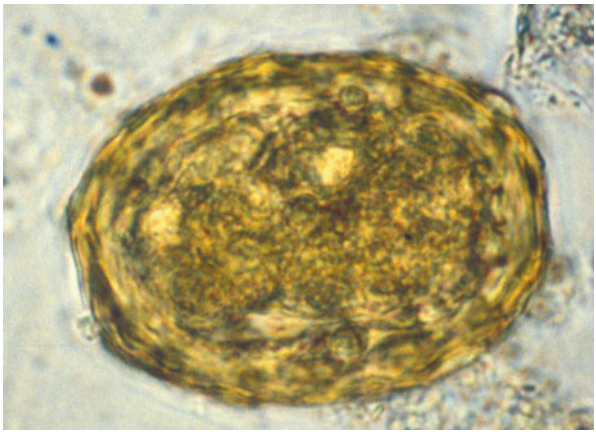

Fig. 2.9 Light micrograph of an egg of *Ascaris lumbricoides*. Note the thick protective egg shell

Fig. 2.10 Macrophoto of adults of *Ascaris lumbricoides*

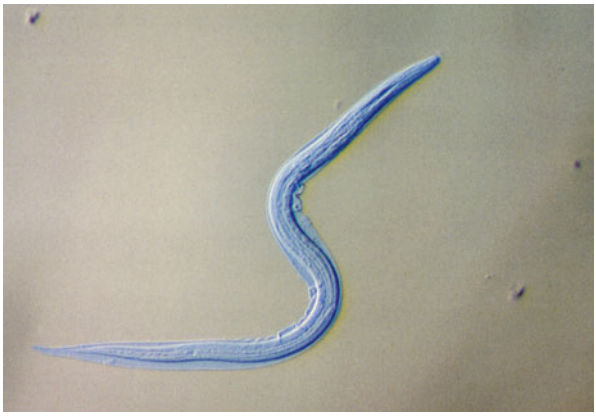

Fig. 2.11 Light micrograph of a larva 3 of the hookworm *Ancylostoma duodenale*

2.3 Requirements for a Parasitic Life

The existence and permanent occurrence of parasites depend on the following main needs:

1. Sophisticated mechanisms of host finding by development of excellent sensory systems.
2. Adaption to tissues within different types of hosts (e.g. final and intermediate hosts, vectors).
3. Protection from host defense systems = development of strategies to survive inside hosts.
4. Production of huge numbers of progeny (eggs, larvae) and placing them in the surroundings of potential hosts.
5. Injection of sufficient numbers of active infectious stages exclusively into suitable hosts.
6. Manipulation of the behaviour of a potential host to enhance the reproduction and transmission of the parasite's progeny (Hatcher 2014).

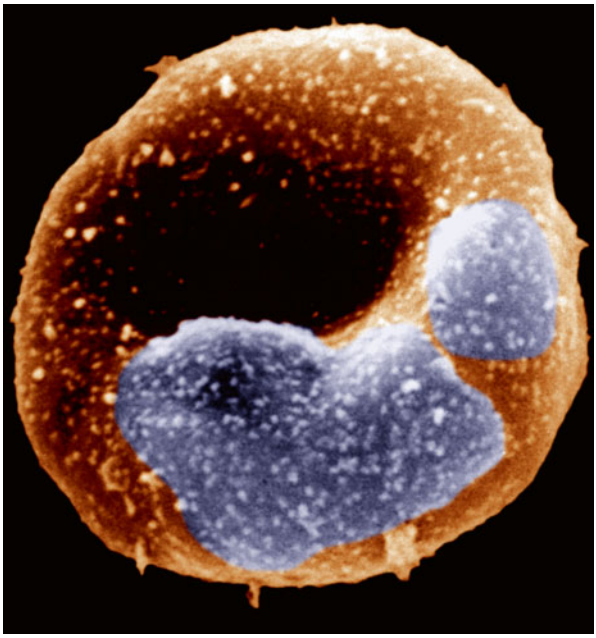

Fig. 2.12 Scanning electron micrograph of an erythrocyte containing two schizonts of *Plasmodium falciparum*, which protrude the surface of the host cell

2.4 Categories of Parasite Manipulations

Parasite-derived host behaviour manipulations have been observed practically in all types of parasite-host relations. Some can be categorized in groups of similar behaviour, others are rather unique. Typical groups of parasitic manipulations are as can be seen in the following examples:

2.4.1 Manipulations Leading to an Increase of Transmission Probabilities

Larval stages (**sporocysts = broodsacs**, Fig. 2.14) of trematodes of the genus *Leucochloridium* change the behaviour of their intermediate hosts (snails of the genus *Succinea*) leading them to creep from hidden places into lighted areas, where they attract their final hosts (birds) by constant pulsating inside the tentacles of the snail. This peculiar behaviour had already been described in Germany in the year 1853 by one of the first typical parasitologists (von Siebold) as is cited in Kagan' review (1951). This example shows two activities: intermediate hosts are urged to crawl onto lighted areas, where they can easily be seen by predators (birds) and become even more visible by the intense pulsating of the parasite stages inside (Lewis 1977). Another example of the same type of parasite-derived host manipulation represents apparently *Toxoplasma gondii* (Figs. 2.15, 2.16, and 2.17). This

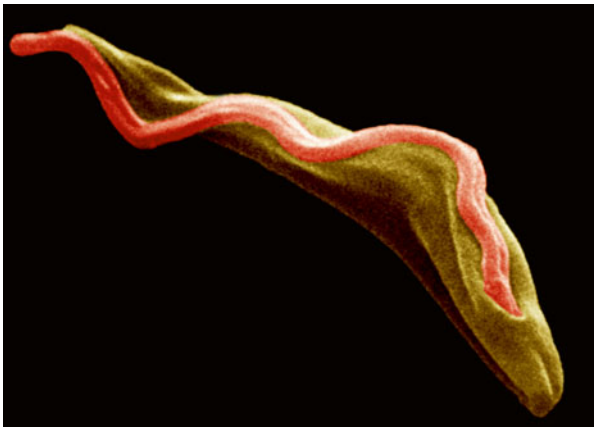

Fig. 2.13 Scanning electron micrograph of a trypomastigote stage of *Trypanosoma* sp. Note the single attached flagellum (*red*)

Fig. 2.14 Macrophoto of a snail containing a pulsating sporocyst inside the protruded tentacle

protozoan parasite, which forms tissue cysts in the brain of intermediate hosts such as mice, rats and humans (see Chap. 6 of Flegr in this book) apparently changes the behaviour of these rodents. While uninfected rats and mice avoid cat-roaming-areas, infected ones are much less shy and seem even to be attracted from cat odours (Webster et al. 1994, 2013; Berdoy et al. 2000). This phenomen enhances the chance that rodents are ingested by cats and *Toxoplasma* tissue cysts become easily transmitted. Another example for a parasite-derived change of host behaviour can be seen in crustaceans (*Gammarus* species) of the group of so-called Amphipoda. Uninfected crustaceans of this group hide themselves in mud, if water movements indicate the arrival of an enemy. In cases of infections with larvae of acanthocephalan worms (e.g. *Polymorphus paradoxus*) gammarids swim to the surface of the water, where they are easily ingested by beavers, rats or ducks, which then become final hosts of the parasite harbouring the adult worms (Bethel and Holmes 1977; Jacquin et al. 2014).

The trematode *Microphallus papillorobustus*, which involves besides final hosts (water birds) two consecutive intermediate hosts. At first a snail is infected by a miracidium larva, which hatches in water from eggs excreted within feces of water

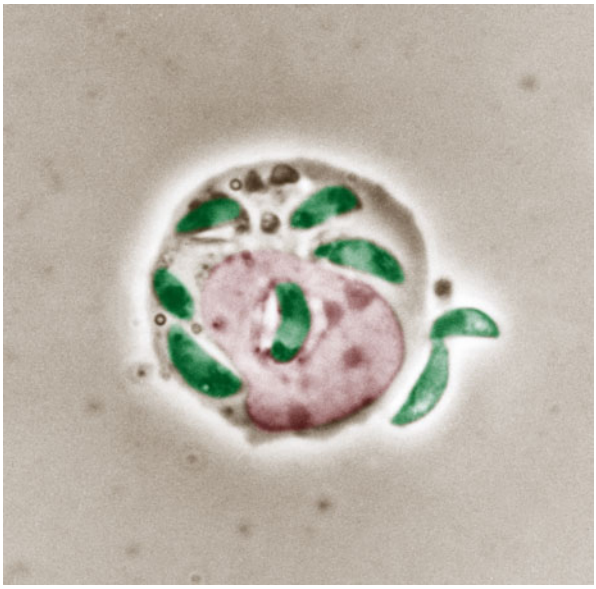

Fig. 2.15 Light micrograph of a lymphocyte parasitized by banana-shaped tachyzoites of *Toxoplasma gondii*. Note the occurrence of parasitophorous vacuoles inside the cytoplasm of the host cell

birds. So-called cercariae leave the snail after a phase of asexual reproduction and are ingested by second intermediate hosts (crustaceans of the species *Gammarus aequicauda* and *G. insensibilis*), where they become encysted in the brain and in the abdomen. The stages in the brain change the behaviour of the gammarids so that they can be easily ingested at the surface of water biotopes by water birds (Hellouy 2013). Apparently the parasites inside the ganglia of the gammarids produce substances which change/manipulate the behaviour of their hosts thus increasing the chances for a successful transmission to the final host.

2.4.2 Manipulations to Use a Parasitized Individuum as Bodyguard

Hereby two different types of effects can be distinguished:

2.4.2.1 Direct Protection

This type e.g. is common in braconid wasps (Hymenoptera). The females inject eggs into the body of larval butterflies (Lepidoptera). The therein hatched larvae feed at first non-essential tissues of their hosts. Then the last larval stages leave the host. As long as the previously parasitized butterfly larva lives, it repells aggressors by intense movements of its forbody thus protecting the unarmed pupa of the parasite (Maure et al. 2013). This behaviour of the parasitized host is apparently induced by excreted compounds of the parasite. Similar effects are seen

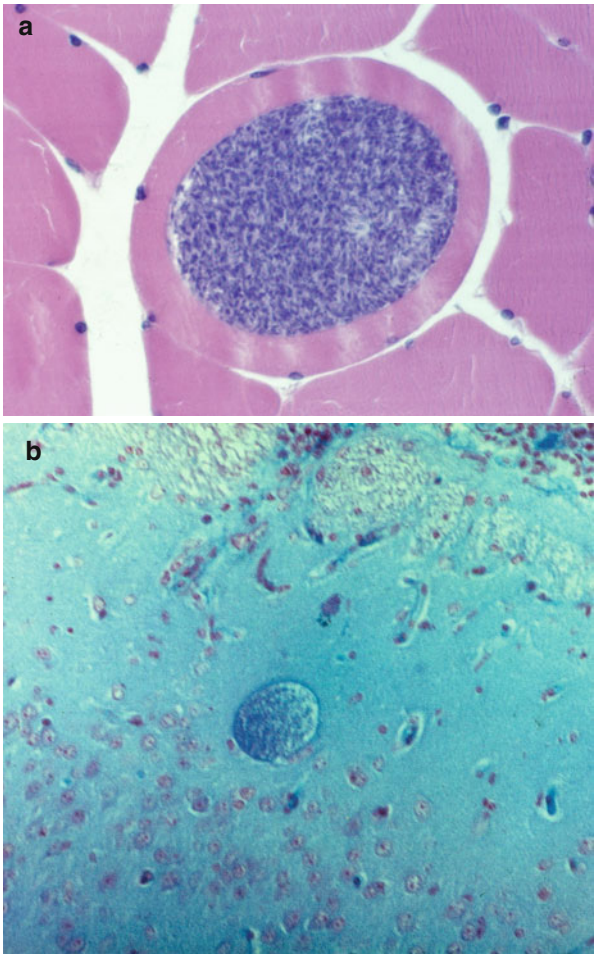

Fig. 2.16 Light micrographs of a section through a *Toxoplasma gondii* cyst in a muscle fibre (**a**) and in the brain (**b**)

when coccinellid beetles (*Coleo megilla maculata* harbour the parasitoid larvae of *Dinocampus coccinellidae*, which also belongs to the family of braconid wasps (Maure et al. 2011).

2.4.2.2 Indirect Protection

Ichneumonid wasps of the species *Polysphincta gutfreundi* paralyze for a short time a spider (*Allocyclosa bifura*) and lays an egg on the spider's back. After recovery the spider lives as usual and the ichneumoid larva feeds by sucking hemolymph from the spider. During this sucking period the parasite apparently injects compounds which lead to the effect, that the spider changes the design of its net and thickens its filaments so that the pupa of the wasp becomes nearly invisible. This effect protects from attacks from enemies of any type (Eberhard 2010; Maure et al. 2013).

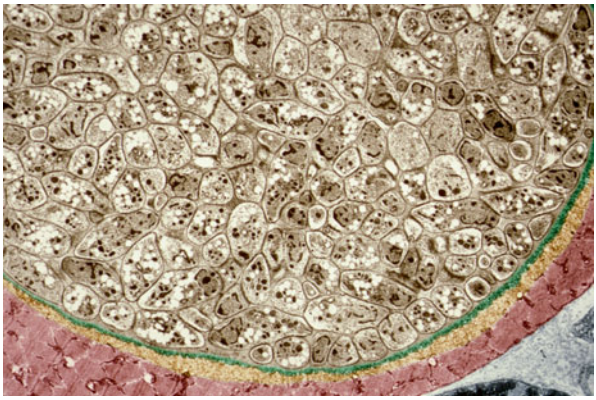

Fig. 2.17 Transmission electron micrograph of a section through a *Toxoplasma gondii* cyst in a muscle fibre

2.4.3 Manipulations of Individuals to Act as Step Parents

The most well-known examples of manipulations of this type are cuckoos (e.g. *Cuculus canorus*, *C. c. bangsii*). The adult female cuckoo enters a foreign bird nest, throws out the host's eggs and places its own egg there, which is bred out by the breeding host parents. The motility signs of the hatched cuckoo stimulate the step-parents to fill up constantly the opened mouth of the insatiable parasite. Apparently the continual gaping and begging of the growing young cuckoo are such a strong manipulatory stimulus for the host parents to feed the completely strange individual replacing their own progeny (Davies and Brooke 1991).

2.4.4 Manipulations to Reach Favourable Sites for Sexual Reproduction

Hairworms (Nematomorpha, Gordiodia) of the species *Chordodes japonensis* live as adult worms in terrestric insects (e.g. in the "Praying mantis" *Tenodera japonensis*). These worms apparently stimulate the worm-bearing terrestric insect to jump into water, where the worms leave the insects and the females start laying eggs after copulation. Larvae hatching from the eggs are ingested by aquatic larvae of dipteran insects (such as mosquitoes, ephemerids etc.) and stay inside their bodies until these insects have finished their metamorphosis and left the water biotope as adults. If e.g. predator insects (e.g. various praying mantids etc.) ingest such larvae-bearing insects (mosquitoes etc.) the nematomorph worms grow up often filling the whole abdominal body and thus become visible as hanging strands outside of the body. These parasites then induce their host insects to enter water, where the adult worms leave the insect that dies inside the water. Uninfected individuals strictly avoid water contact (Schmidt-Rhaesa and Ehrmann 2001; Thomas et al. 2002, 2003). Similar results have been described from hair worms (*Paragordius tricuspidatus*)

parasitizing in *Nemobius sylvestris*) (wood cricket), wherefrom only infected specimens jump into water thus giving the adult hairworms the chance to enter watery biotopes (Thomas et al. 2002, 2003).

2.4.5 Manipulations of Vector Insects

Uninfected female mosquitoes try to suck as often as possible blood since they need it urgently to depone as much eggs as possible. However, female mosquitoes that had just ingested gametocytes of *Plasmodium* species (agents of malaria) visit for a while new hosts much less frequent than uninfected ones (Fig. 2.18). Apparently the malaria parasites influence this behaviour, since they disturb the intestine due to development of their oocysts and disturb also the salivary glands by the presence of numerous sporozoites during their maturation, which need time to obtain full infectivity by producing a protecting surface coat. However, as soon as the sporozoites are fully infectious, it was observed that the female mosquitoes suck more often blood at different hosts (Anderson et al. 1999, 2000; Cator et al. 2012, 2014; Koella et al. 1998; Rossignol

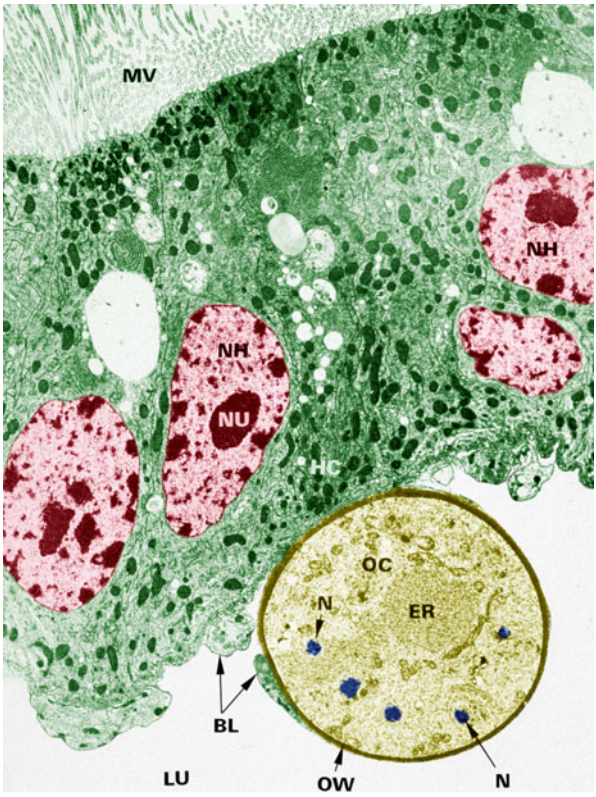

Fig. 2.18 Transmission electron micrograph of a section through an oocyst of *Plasmodium* sp., which is situated at the outer side of the intestine of an *Anopheles* mosquito. *BL* Basal lamina of the intestine; *ER* Endoplasmic reticulum; *LU* Lumen of the body cavity of the mosquito; *N* Nucleus of parasite; *NH* Nucleus of host cell; *NU* Nucleolus; *OC* Oocyst; *OW* Outer wall of oocyst

et al. 1984). This behaviour contributes to the spreading of the parasites among a population of hosts. Similar effects of increasing transmission rates occur due to the fact that host odours become more attractive, when hosts are diseased by malaria (DeMoraes et al. 2014) or when hosts are infected by *Hepatozoon* stages (Ferguson et al. 2013).

2.4.6 Manipulations to Reduce Adverse Host Reactions

Infections due to parasites affect the host's immune system. This leads to the production of substances like cytokines which also influence neuronal activity and thus also the host behaviour (Dantzer 2004; Dantzer et al. 2008). Parasites are apparently able to influence the production and interrelationships of such cytokines and thus become thereby able to manipulate/decrease adverse reactions against a persistent parasite inside (Adamo 2013; Friberg et al. 2010).

2.4.7 Manipulations due to Increase of the Neurotransmitter Dopamine

It was observed that experimental infections of mice and rats with cysts and bradyzoites of *Toxoplasma gondii* lead to manipulations of the behaviour of the host animals (Berenreiterova et al. 2011). Infected mice and rats do not avoid the nearness of cats, but are apparently attracted by cat's odours and even search their nearness. At the same time it was found that infected mice and rats produce 14 % more dopamine than uninfected ones. Tests with other neurotransmitters showed that they do not influence the cat-approaching behaviour of mice and rats. Therefore Prandovsky et al. (2011) conclude that *Toxoplasma gondii* leads to the increase of the dopamine production in rats, which steers in a not yet fully understood pathway the altered behaviour of *Toxoplasma* infected hosts – especially since injection of dopamine into non-infected animals did not show the same behavioural effects as seen in *Toxoplasma* infected mice (Eskow Jaunarajs et al. 2011). Behaviour changing effects of hosts suffering from *T. gondii* infections were seen due to changing amounts of catecholamines and indoleamines (Stibbs 1985). In addition it is proven that *Toxoplasma gondii* modulates intensively the host cell proteome, so that intense structural changes occur in- and outside of the infected cell (Mehlhorn and Frenkel 1980; Nelson et al. 2008; Plattner and Soldati-Favre 2008) (Figs. 2.15, 2.16, and 2.17).

2.4.8 Manipulations by Parasites That Lead to Transformation of Specialized Host Cells to Tissue Cysts

Most apicomplexan (sporozoan) protozoans live intracellularly inside species specific host cells being included – at least at the beginning – in a parasitophorous vacuole (Fig. 2.16), which finally is transformed into a tissue cyst

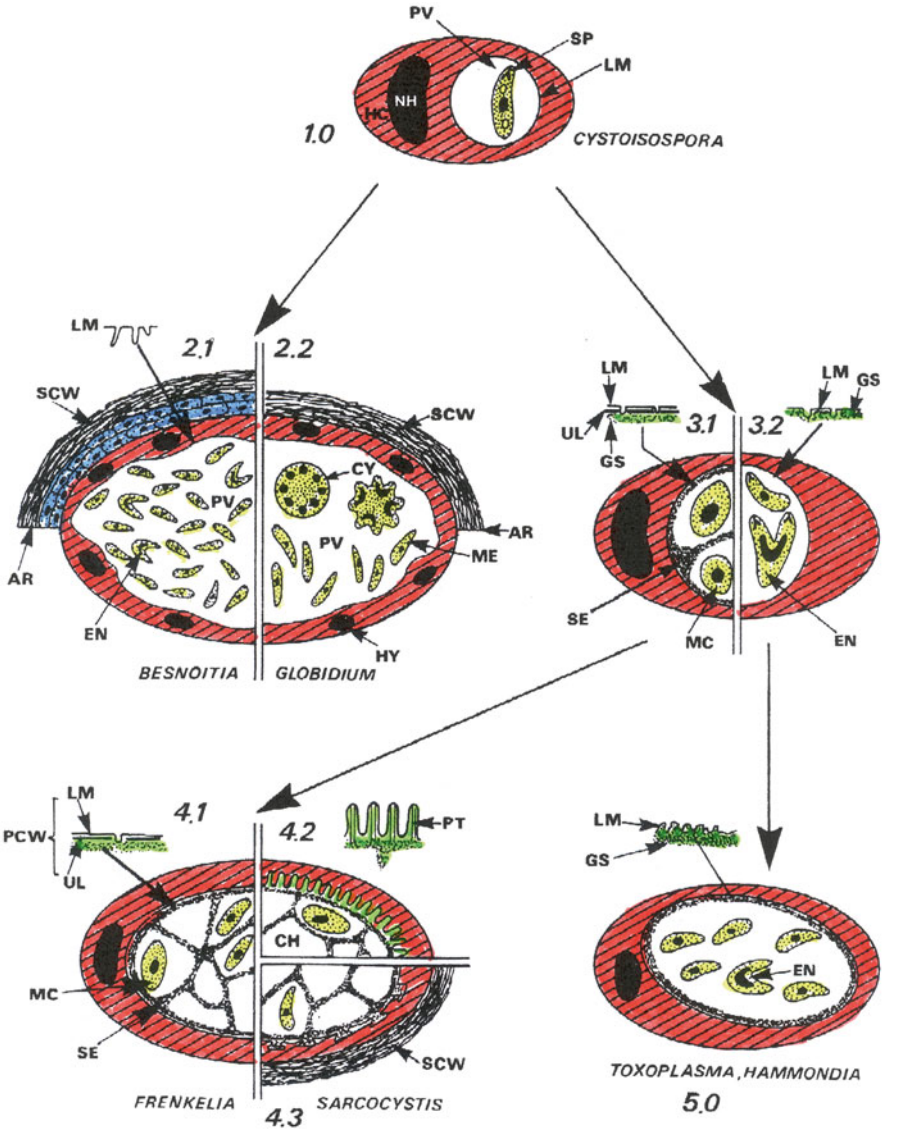

Fig. 2.19 Diagrammatic representation of the development of different tissue cyst types among the Apicomplexa (according to Mehlhorn and Frenkel 1980; Mehlhorn 2016). (*1*) Starting point: After penetration the motile parasitic stage (sporozoite, cyst merozoite etc.) a typical parasitophorous vacuole is formed inside the host cell. (*2.1*, *2.2*) Depending on the species the shape of the parasitophorous vacuole is changed. (*3.1*, *3.2*) Transition stages. (*4.1–4.3*) Cysts with formation of inner chamber-like hollows. (*5*) Cysts without any inner chamber-like hollows. *AR* cut off due to drawing needs, *CH* chamber-like hollow, *CY* cytomere, *EN* endodyogeny, *GS* ground substance, *HC* host cell, *LM* limiting membrane of the PV, *MC* metrocyte, *ME* cyst merozoite, i.e. bradyzoite in *T. gondii, NH* host cell nucleus, *PCW* primary cyst wall, *PV* parasitophorous vacuole, *SCW* secondary cyst wall, *SE* septum, *SP* sporozoite, *UL* underlying material

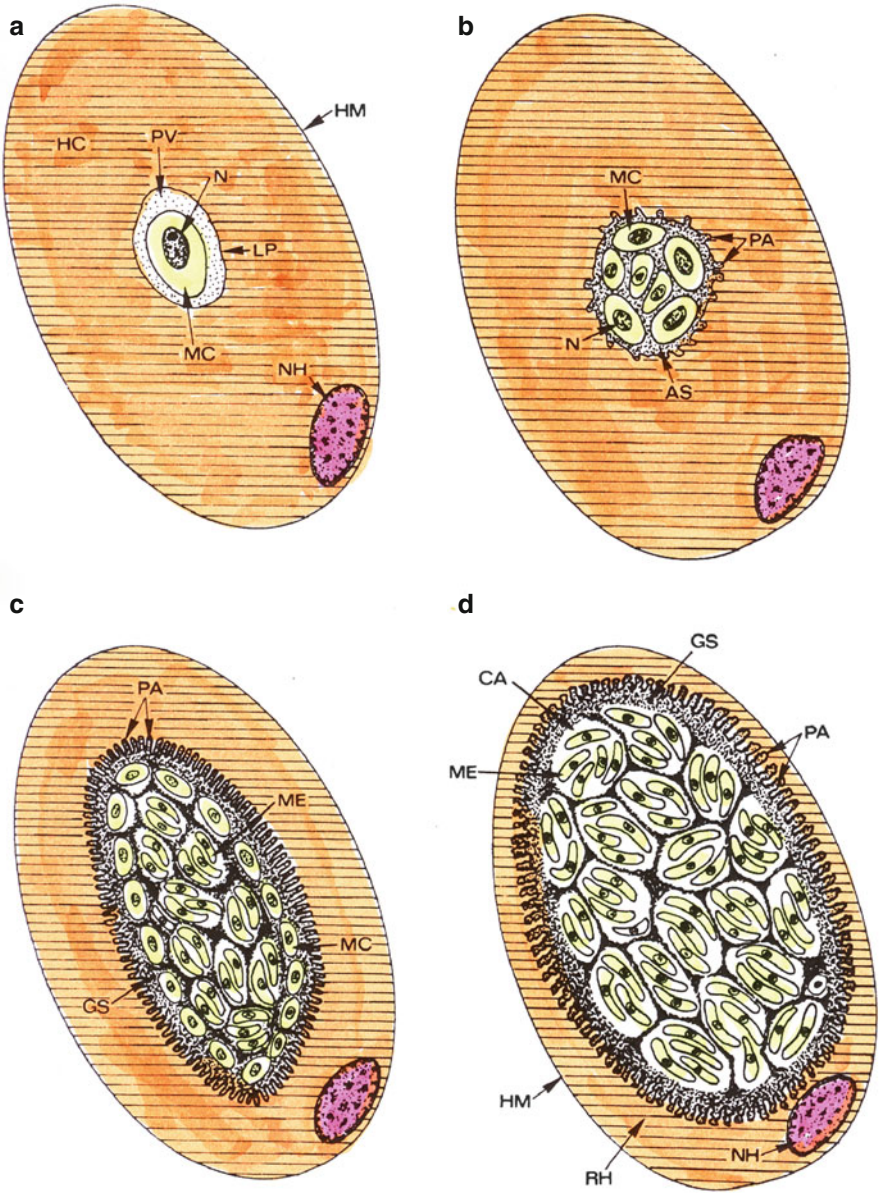

Fig. 2.20 (**a–d**) Diagrammatic representation of the growth of a sarcosporidian cyst within a muscle fibre (protrusions of the primary cyst wall are species specific). Apart from these variations of the shape of the protrusions the developmental process is identical in all *Sarcocystis* species. The development starts about 1 month after infection with the formation of a parasitophorous vacuole and is finished after two further months, when the chamber-like hollows of the ground substance contain numerous banana-shaped, motile cyst merozoites (After Mehlhorn and Heydorn 1978). *AS* amorphous substance, *CH* chamber-like hollow, *GS* ground substance, *HC* host cell, *HM* host cell membrane, *LM* limiting membrane of the parasitophorous vacuole, *MC* metrocyte, *ME* cyst merozoite, *N* nucleus, *NH* host cell nucleus, *PA* palisade-like protrusion of tissue cyst, *PV* parasitophorous vacuole, *RH* -remnants of the host cell cytoplasm (Mehlhorn and Heydorn 1978).

(Figs. 2.19, 2.20, 2.21, and 2.22). This outcome of this transformation is species specific and definitively steered by the parasite. This can be seen by the fact that the tissue cysts have a genus specific appearance so that even in the same genus each species may produce a typical specific appearance. The formation of such cysts is diagrammatically shown in Figs. 2.20 and 2.21. In Figs. 2.23, 2.24, and 2.25 various types of such tissue cysts are depicted in light and electron micrographs (Mehlhorn and Frenkel 1980; Mehlhorn and Heydorn 1978; Mehlhorn 2016).

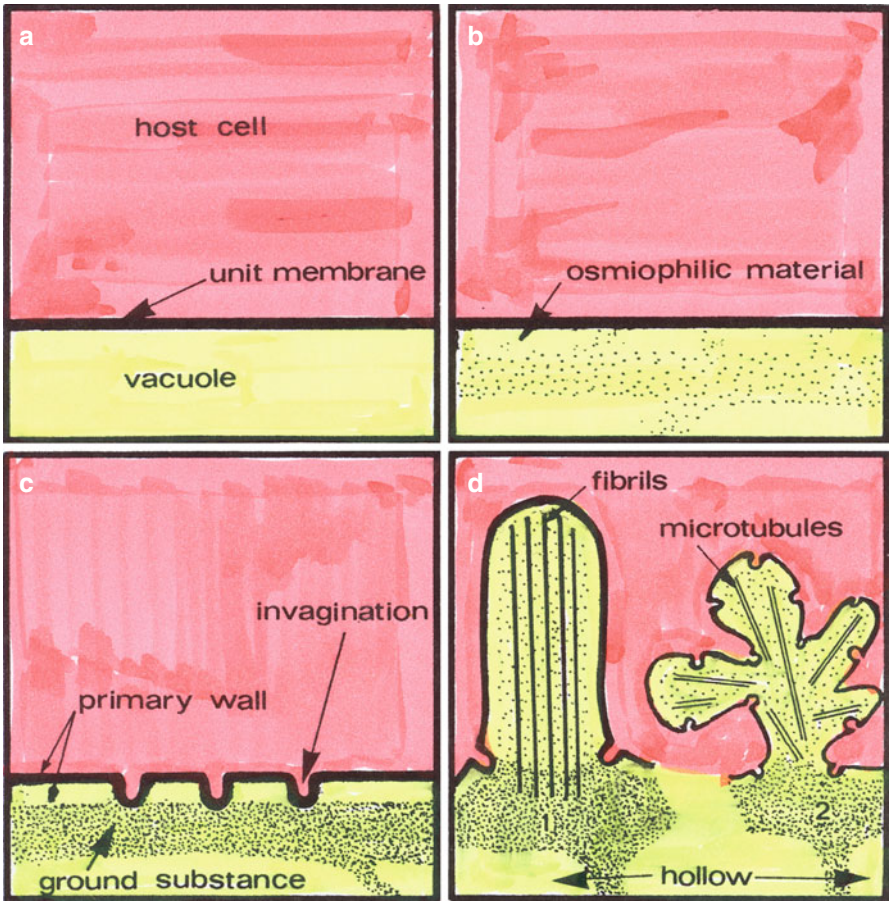

Fig. 2.21 (**a**–**d**) Diagrammatic representation of the growth of the surface of *Sarcocystis* cysts inside a muscle fibre forming species specific protrusions. Diagrammatic representation of the development of the primary cyst wall and the underlying ground substance of the cyst. In mature cysts the primary cyst wall may form species specific protrusions. *d left S. bovihominis* in cattle muscles, *d right S. ovifelis* (From Mehlhorn and Heydorn 1978)

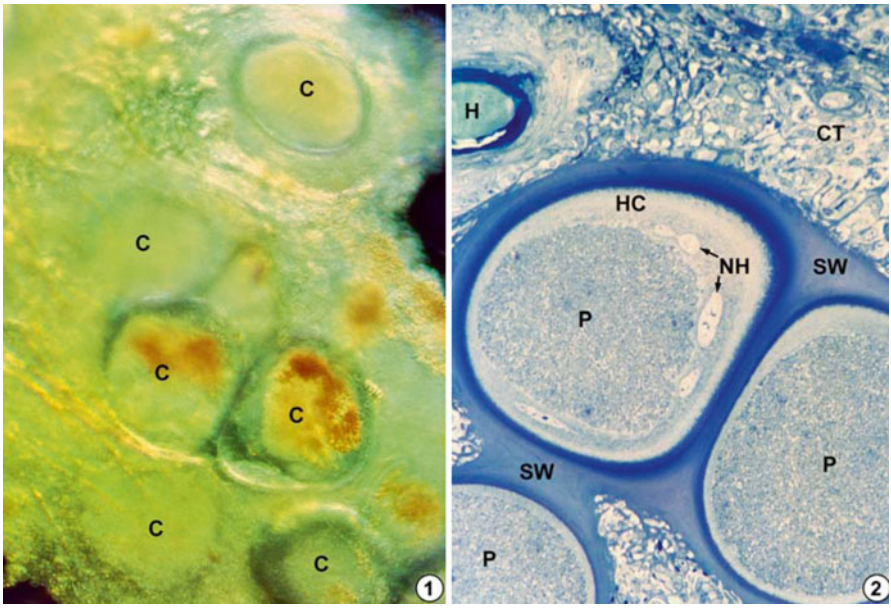

Fig. 2.22 Light micrographs of sections through *Besnoitia besnoiti* cysts inside epidermal cells (**1**-**2**) of cattle: *C* tissue cyst, *CT* dermal remnnants, *H* blood vessel, *HC* host cell, *NH* enlarged nuclei of the host cell, *P* parasites, *SW* secondary cyst wall

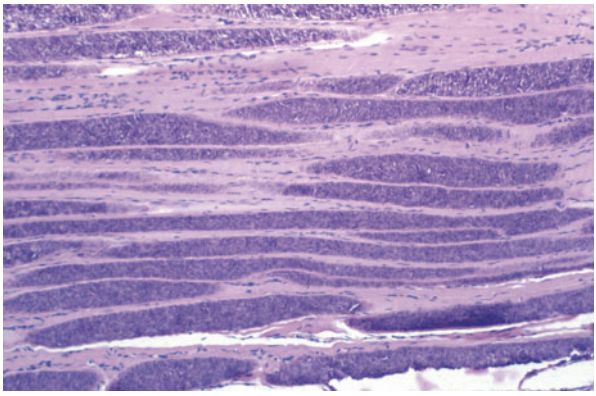

Fig. 2.23 Light micrograph of numerous sarcocysts of a bird *Sarcocystis* species, which would lead to a poor flying ability. Thus this bird becomes easily caught and ingested by a predator bird, which is the final host excreting oocysts

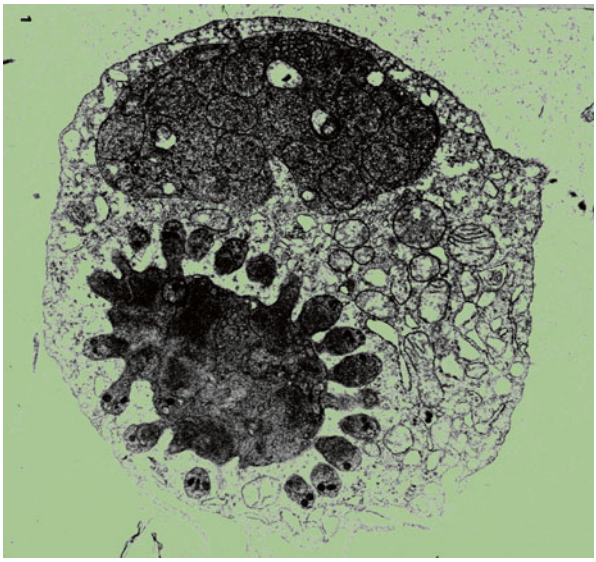

Fig. 2.24 Transmission electron micrograph of two schizonts (a macroschizont and microschizont during formation of merozoites) of *Theileria annulata* in a macrophage of cattle. These stages are not situated in a parasitophorous vacuole, but lay directly in the cytoplasm, after the membrane of the initially formed parasitophorous vacuole has been ruptured (From Mehlhorn and Schein 1984)

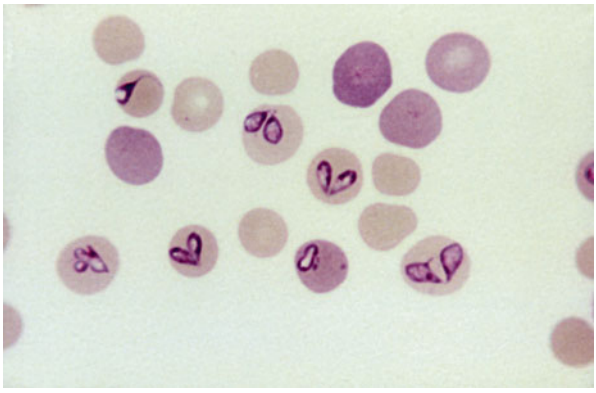

Fig. 2.25 Light micrograph of trophozoites of *Babesia canis* directly inside the red blood cell cytoplasm

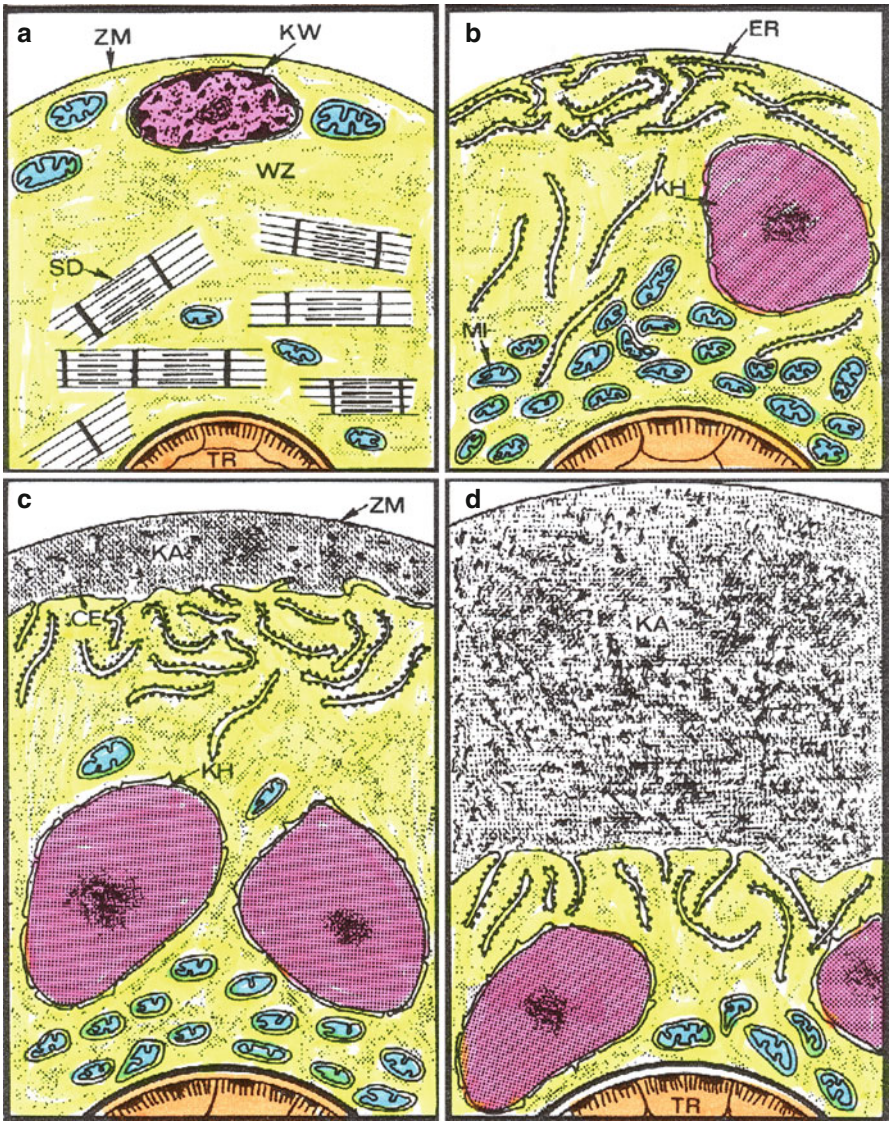

Fig. 2.26 Diagrammatic representation of host cell transformation after infection with larvae of *Trichinella spiralis*. The larva is reduced in the size due to technical reasons of drawing. (**a**) Shortly after larva 1 has penetrated the sarcomeres of the muscle cell start degeneration. (**b**) Zones of increasing mitochondria and lacunes of the ER are formed around the larva. Nuclei start to grow considerably, sarcomeres disappear completely and are replaced by a granular material. (**c**) At the periphery lacunes of the ER become increased and separate a dense outer layer from the inner granular zone. (**d**) The outer dense layer is rather thick starting about 60 days past infection of the cell. In many cases such tissue cysts become additionally surrounded by a layer of degenerated granulocytes of the host. This layer may be calcified after months or even years. However, larvae inside may survive for years inside such tissue cysts. *CE* confluent ER, *ER* endoplasmic reticulum; *KA* capsule appears often as cyst wall in light microscope, *KH* growing host cell nucleus (hypertrophia) *KW* nucleus of host cell, *MI* mitochondrion, *SD* sarcomeres during deformation, *TR Trichinella* larva, *WZ* host cell, *ZM* cell membrane of muscle fibre = host cell

2.4.9 *Manipulations by* Trichinella *Species to Survive Inside Host Muscle Cells*

Nematodes belonging to the genus *Trichinella* enter as larvae 1 typical uninuclear muscle cells (in the heart) or multinucleated muscle fibres and start to transform them, so that the parasites become able to survive for long inside for many years. This transformation process is diagrammatically depicted in Fig. 2.26 and shown in steps in Figs. 2.27, 2.28, and 2.29. At first host cell nuclei start divisions and increase enormously in size. Furtheron the muscle fibres become replaced by granular material starting in the close surroundings of the worm filling finally the whole interior of the considerably enlarged host cell. The host immune system finally adds layers around infected muscle fibers (which may contain several worms, Fig. 2.26) and thus allows survival times of the worms inside up to 20 years (respectively until the infected tissues are ingested by a final host (meat feeding organisms), where finally adult female and male worms are developed. The steering of this peculiar development is only poorly understood (Babal et al. 2011; Wu et al. 2005).

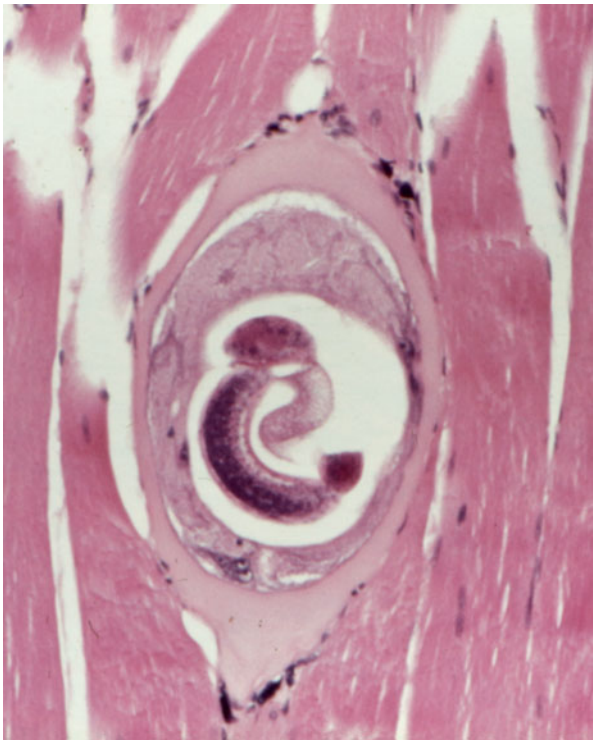

Fig. 2.27 Light micrograph of a section through a muscle fibre, which is on the way to be transformed by the parasite. Most central: the larva of *T. spiralis* is surrounded by amorphous material, which is peripherally surrounded by a pale, dedifferentiated, nuclei containing layer

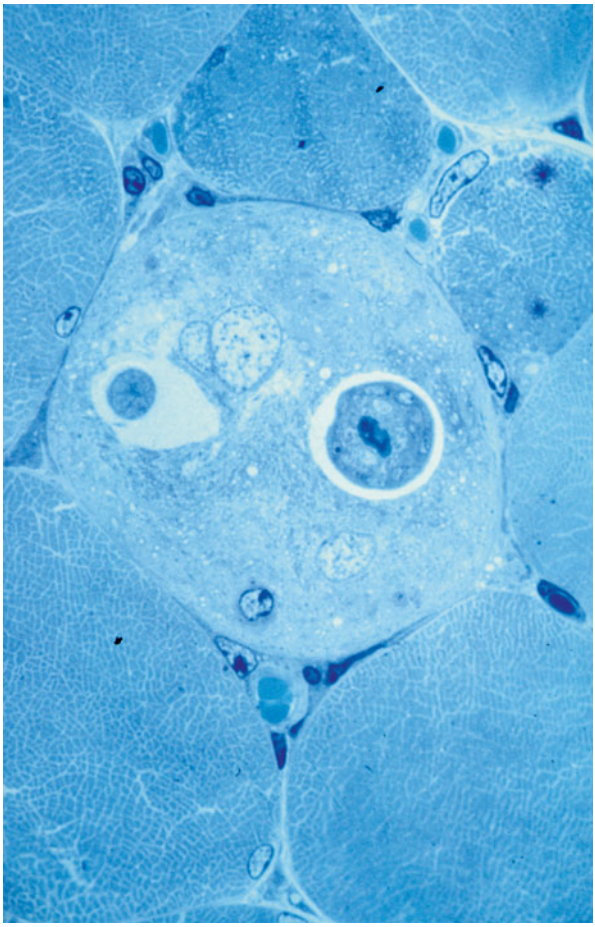

Fig. 2.28 Semithin section through a muscle fibre showing two circular sections of a larva of *T. spiralis*. Note that the typical muscle fibres are transformed to a pale amorphic layer containing highly enlarged nuclei, the number of which has been increased

Fig. 2.29 Macrophoto of a larva of *T. spiralis* filling fully a transformed muscle fibre (Photo granted by Prof. Hinz, Heidelberg)

References

Adamo SA (2013) Parasites: evolution's neurobiologist. J Exp Biol 216:3–10
Anderson RA et al (1999) The effect of *Plasmodium yoelii nigeriensis* infection on the feeding persistence of *Anopheles stephensi* throughout the sporogonic cycle. Proc Biol Sci 266:1729–1733
Anderson RA et al (2000) *Plasmodium falciparum* sporozoites increase feeding associated mortality of their mosquito hosts *Anopheles gambiae*. Parasitology 120:329–333
Babal P et al (2011) Apoptosis as the adaption mechanism in survival of *Trichinella spiralis* in host. Parasitol Res 109:997–1002
Berdoy M et al (2000) Fatal attraction in rats infected with *Toxoplasma gondii*. Proc Biol Sci 267:1591–1594
Berenreiterova M et al (2011) The distribution of *Toxoplasma gondii* cysts in the brain of a mouse with latent toxoplasmosis: implications for the behavioural manipulation hypothesis. PLoS One 6(12)
Bethel WM, Holmes JC (1977) Increased vulnerability of amphipods to predation owing to altered behaviour induced by larval acanthocephalans. Can J Zool 55:110–115
Cator LJ et al (2012) Do malaria parasites manipulate mosquitoes? Trends Parasitol 28:466–470
Cator LJ et al (2014) Alterations in mosquito behaviour by malaria parasites. Malaria J 13:164–170
Dantzer R (2004) Cytokine-induced sickness behaviour: a neuroimmune response to activation of innate immunity. Eur J Pharmacol 500:394–411
Dantzer R et al (2008) From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 9:46–56
Davies NB, Brooke M (1991) Coevolution of the cuckoo and its hosts. Sci Am 264:92–98
DeMoraes CM et al (2014) Malaria induced changes in host odors enhance mosquito attraction. Proc Natl Acad Sci U S A 111:11079–11084
Eberhard WG (2010) Recovery of spiders from the effects of parasitic wasps: implications for fine-tuned mechanisms of manipulation. Anim Behav 79:375–383
Eskow Jaunarajs KL et al (2011) Potential mechanisms underlying anxiety and depression in Parkinson's disease: consequences of l-DOPA treatment. Neurosci Biobehav Rev 35:556–564
Ferguson LV et al (2013) Influence of *Hepatozoon* parasites on host seeking and host choice behaviour of the mosquitoes *Culex territans* and *Culex pipiens*. Int J Parasito Parasites Wildlife 2:69–76
Friberg IM et al (2010) Macroparasites innate immunity and immunoregulation: developing natural models. Trends Parasitol 26:540–549
Greenwood BM (1968) Autoimmune diseases in Nigerians. Lancet 2:573
Hatcher MJ et al (2014) Parasites that change predator or prey behaviour can have keystone effects on community composition. Biol Lett 10:20130879
Hellouy S (2013) Parasite-induced alterations of sensorimotor pathways in gammarids: collateral damage of neuroinflammation? J Exp Biol 216:67–77
Jacquin L et al (2014) Non-specific manipulation of gammarid behaviour by *Polymorphus minutus* parasites enhances their predation by definitive bird hosts. PLoS One 9(7), e101684
Kagan IG (1951) Aspects in the life cycle of *Neoleucochloridium problematicum* and *Leucochloridium cyanocittae*. Trans Am Micros Soc 70:281–318
Koella JC et al (1998) The malaria parasite, *Plasmodium falciparum*, increases the frequencies of multiple feeding of the mosquito vector, *Anopheles gambiae*. Proc Biol Sci 265:763–768
Lewis JD (1977) Adaptations for the transmission of species of *Leucochloridium* from molluscan to avian hosts. Proc Mont Acad Sci 37:70–81
Maizels RM et al (2014) Helminths in the hygiene hypothesis: sooner or later. Clin Exper Immunol 177:38–46
Marchan R (2014) Parasitic Panacea. Lab Times 5:26–29

Maure F et al (2011) The cost of a bodyguard. Biol Lett 7:843–846
Maure F et al (2013) Diversity and evolution of bodyguard manipulation. J Exp Biol 216:36–42
Mehlhorn H (ed) (2016) Encyclopedia of parasitology, 4th edn. Springer, New York
Mehlhorn H, Frenkel JK (1980) Ultrastructural comparison of cysts and zoites of *Toxoplasma gondii*, *Sarcocystis muris* and *Hammondia hammondi* in skeletal muscles of mice. J Parasitol 66:59–67
Mehlhorn H, Heydorn AO (1978) The sarcosporidia: life cycle and fine structure. Adv Parasitol 16:43–102
Mehlhorn H, Schein E (1984) The piroplasms: life cycle and sexual stages. Adv Parasitol 23:38–143
Moore J (2013) An overview of parasite-induced behavioural manipulations – and some lessons from bats. J Exp Biol 216:11–17
Nelson MM et al (2008) Modulation of the host cell proteome by the intracellular apicomplexan parasite *Toxoplasma gondii*. Infect Immun 76:828–844
Plattner F, Soldati-Favre D (2008) Hijacking of host cellular functions by the Apicomplexa. Annu Rev Microbiol 62:471–487
Prandovsky E et al (2011) The neurotropic parasite *Toxoplasma* increases dopamine metabolism. PLoS One 6(9)
Rossignol PA et al (1984) Increased dermal probing time in sporozoite-infected mosquitoes. Am J Trop Med Hyg 33:17–20
Schmidt-Rhaesa A, Ehrmann R (2001) Horsehair worms (Nematomorpha) as parasites of praying mantids with a discussion of their life cycle. Zool Anzeiger 24:167–179
Stibbs HH (1985) Changings in brain concentrations of catecholamines and indoleamines in *Toxoplasma*-infected mice. Ann Trop Med Parasitol 79:153–157
Thomas F et al (2002) Do hairworm (Nematomorpha) manipulate the water seeking behaviour of their terrestrial hosts? J Evol Biol 15:356–361
Thomas F et al (2003) Parasitic manipulation: where are we and where should we go? Behav Process 68:185–199
Wammes LJ et al (2014) Helminth therapy or elimination: epidemiological, immunological, and clinical considerations. Lancet Inf Dis 14:1150–1162
Webster JP et al (1994) Effect of *Toxoplasma gondii* on neophobic behaviour in wild brown rats. Parasitology 109:37–43
Webster JP et al (2013) *Toxoplasma* infection, from predator to schizophrenia. J Exp Biol 2016:99–112
Wu Z et al (2005) A spectrum of functional genes mobilized after *Trichinella spiralis* infection in skeletal muscle. Parasitology 130:561–573

Chapter 3
Trait-Mediated Effects of Parasites on Invader-Native Interactions

Melanie J. Hatcher, Jaimie T.A. Dick, Rachel A. Paterson, Mhairi E. Alexander, Mandy Bunke, and Alison M. Dunn

3.1 Introduction

Most work on parasite-induced behavioural change in hosts focuses on the mechanisms underlying these changes and their direct consequences for parasite and host fitness (see other chapters in this volume). However, infected hosts do not exist in isolation; they form part of a community of organisms that interact through an array of trophic links. Here, we broaden the focus of parasite-modified behaviour to examine the indirect consequences of such behavioural changes for species that interact with the host, and explore how this may impact community structure. In particular, we review our work on crustacean host-parasite systems where we find that parasites affect a range of trophic interactions between invasive and native host species. We examine the potential significance of these parasite-induced behavioural effects in the biological invasion process.

M.J. Hatcher (✉)
School of Biological Sciences, University of Bristol, Bristol BS8 1TH, UK

School of Biology, University of Leeds, Leeds LS2 9JT, UK
e-mail: pab6mjh@leeds.ac.uk

J.T.A. Dick • R.A. Paterson
Institute for Global Food Security, School of Biological Sciences, Queen's University Belfast, Belfast BT9 7BL, UK

M.E. Alexander
Institute for Global Food Security, School of Biological Sciences, Queen's University Belfast, Belfast BT9 7BL, UK

Centre for Invasion Biology, Department of Botany and Zoology, Stellenbosch University, Matieland 7602, South Africa

M. Bunke • A.M. Dunn
School of Biology, University of Leeds, Leeds LS2 9JT, UK

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From a population perspective, we usually think of the direct effects of parasitism on the host – the morbidity and mortality induced by the parasite in hosts. However, recent theoretical and empirical research suggests that the indirect effects of parasitism may be equally important in structuring communities (Hudson et al. 2006; Hatcher and Dunn 2011). Indirect interactions occur when the impact of one species on another affects populations of a third species, with these interactions being density- or trait-mediated. Change in population density has been regarded as the main mechanism driving such indirect interactions. For example, the decline in the Iberian Lynx was an indirect result of parasite (myxamatosis & rabbit haemorrhagic disease) induced decline in its rabbit prey (Ferrer and Negro 2004). However, indirect interactions can also be caused by changes in behaviour, development or physiology; for example parasite (nematode) induced vulnerability to predation mediates population cycles in snowshoe hares (Murray et al. 1997). Such effects, known as trait-mediated indirect effects (Werner and Peacor 2003) can theoretically be as important as density-mediated effects for community structure and function (Abrams and Matsuda 1996) and are now considered an important driving factor in community ecology (Ohgushi et al. 2012).

Trait-mediated interactions may be especially relevant in parasite-host systems because parasites do not necessarily kill their hosts, at least not immediately, but frequently modify host behaviour or development (reviewed in Lefevre et al. 2009; Thomas et al. 2010 and chapters in this issue). Such trait changes may have no apparent deleterious effect on hosts measured in isolation. However, if these trait modifications reduce host fitness when interacting with other species, we can nevertheless regard them as aspects of virulence; we have referred to such characteristics as "cryptic virulence" (MacNiel et al. 2003c; Hatcher and Dunn 2011).

In our laboratories at The University of Leeds and Queen's University Belfast, we are particularly interested in the roles played by parasites in biological invasions (Prenter et al. 2004; Dunn 2009; Hatcher and Dunn 2011; Dunn et al. 2012). Parasites (here we use the term to include macro- and microparasites and parasitoids) are an important consideration in biological invasions for a number of reasons (Fig. 3.1). Firstly, some invasions may succeed partly because the introduced species leaves behind its parasites (and their deleterious effects) in the native range (a mechanism known as enemy release; Mitchell and Power 2003; Torchin et al. 2003). In other cases, introduced species arrive with their parasites, but the parasites go on to infect populations of related host species in the recipient range (the phenomenon of spillover; Daszak et al. 2000), often with highly deleterious effects on the new host. Parasite spillback or dilution may also occur (from an invasions perspective, where native parasites in the invaders new invaded range cross into introduced hosts; Kelly et al. 2009). These can be considered as direct effects in that they influence host (novel or original) survival directly via presence (or absence) of the parasite. In addition, many parasites are themselves invasive, and the process of disease emergence shares many similarities with that of biological invasion (Hatcher et al. 2012a, b; Dunn and Hatcher 2015).

Furthermore, the importance of parasite-induced indirect effects in the process of biological invasion has now been recognized for a range of terrestrial

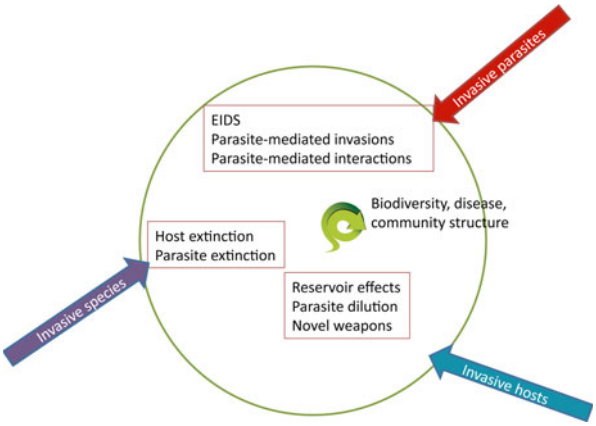

Fig. 3.1 Alternative ways in which invaders cause ecological novelty through their interactions with parasites. *Green circle*: native community. *Red arrow*: invasive parasites can drive changes in host abundance and extinction and can mediate native/invader interactions leading to changes in biodiversity and community structure. *Blue arrow*: invasive hosts can co-introduce parasites which may act as novel weapons; invasive species may also acquire endemic parasites resulting in parasite amplification or dilution. *Purple arrow*: extinctions and changes in community structure as a result of biological invasions can affect native parasite-host interactions. *Green spiral*: feedback between parasite prevalence and biodiversity (From Dunn and Hatcher 2015)

and aquatic, plant and animal systems (White et al. 2006; Dunn et al. 2012). Parasite-induced trait effects have been reported as important in ongoing biological invasions in diverse taxa and ecosystems, including wild oat (*Avena fatua*) in Californian grasslands, fire ants (*Solenopsis invicta*) in North America and amphipods in UK freshwaters (Dunn et al. 2012; Dunn and Hatcher 2015). Here, we review the importance of trait-mediated effects, with particular focus on the crustacean invasions studied in our laboratories in the UK. We use a community module-based approach (Holt 1997; Hatcher et al. 2006) to structure this review, allowing us to examine systematically the potential "targets" of indirect effects.

3.2 Crustacean Invasion Study Systems

Amphipod crustaceans are often keystone species in freshwater ecosystems. Through processing nutrients and providing prey for larger invertebrates and vertebrates, they provide important ecosystem services (MacNeil et al. 1997). They process the primary basal energy resource (leafy detritus) through shredding, with strong impacts on community structure. They also consume smaller invertebrate species in the food web, influencing macroinvertebrate species richness and diversity, and are key prey for commercial and recreational fish stocks, and for wildfowl. Furthermore, amphipod species differ in their propensity towards predation and

detritus processing, and thus from an ecosystem perspective, there is unlikely to be equality of functionality between invader and native. Therefore, the impact of parasitism on amphipod population dynamics or invasion outcomes could have profound ramifications for the diversity and structure of aquatic communities as well as having eco-economic costs.

3.2.1 Amphipod Invasion

In rivers and streams in Ireland, the native amphipod *Gammarus duebeni celticus* is being replaced by the European *Gammarus pulex.* In addition to influencing native amphipod populations, *G. pulex* invaded rivers also have lower macroinvertebrate abundance and diversity (Kelly et al. 2006). A further two species of non-native amphipods also co-occur; *Gammarus tigrinus* and *Crangonyx pseudeogracilis*, despite being weaker competitors and being predated by the other invasive and native amphipods. In mainland Europe, the invasive *Dikerogammarus villosus* is a voracious predator of macroinvertebrates including native and other invasive amphipods (Dodd et al. 2014), with invaded regions showing a decrease in macroinvertebrate abundance and diversity (Rewicz et al. 2014).

Comparison of invasive and native amphipods reveal differences in detritivory, in predation on native invertebrates, as well as a hierarchy of competition and intraguild predation (i.e., predation of ecological guild members, that is, potential competitors; Polis et al. 1989) between these amphipods (Fig. 3.2).

Amphipods are host to a suite of parasites including viruses (Bojko et al. 2014; Arundell et al. 2015), microsporidia (Terry et al. 2003), trematodes (Arundell et al. 2015) and acanthocephala (MacNeil et al. 2003a), which modify competitive and trophic interactions of their hosts. There is correlative evidence that enemy release may be a factor in both *G. pulex* and *D. villosus* invasions. In Ireland, Dunn and Dick (1998) have shown that parasite diversity is higher in the native *G. duebeni celticus* than in the invading *G. pulex.* Five species of parasite were detected, of which three were shared but two, the microsporidian *Pleistophora mulleri* and the acanthocephalan *Polymorphus minutus*, were restricted to the native host. For two species (*Embata parasitica* and *Epistylus* sp.) that infected both native and invading species, parasite prevalence and burden was higher in native hosts. However, this pattern was not universal; prevalence of the acanthocephalan *Echinorhynchus truttae* was found to be higher in the invasive *G. pulex* (Dunn and Dick 1998; Hatcher and Dunn 2011). A recent study of newly invasive *D. villosus* populations in the UK provides evidence of enemy release from viral, metazoan and microsporidian parasites that are highly prevalent in the (invasive) continental range (Bojko et al. 2014; Arundell et al. 2015), although there is also evidence that parasite diversity has increased in the 5 years since this species has been reported in the UK (Bovey et al. unpublished).

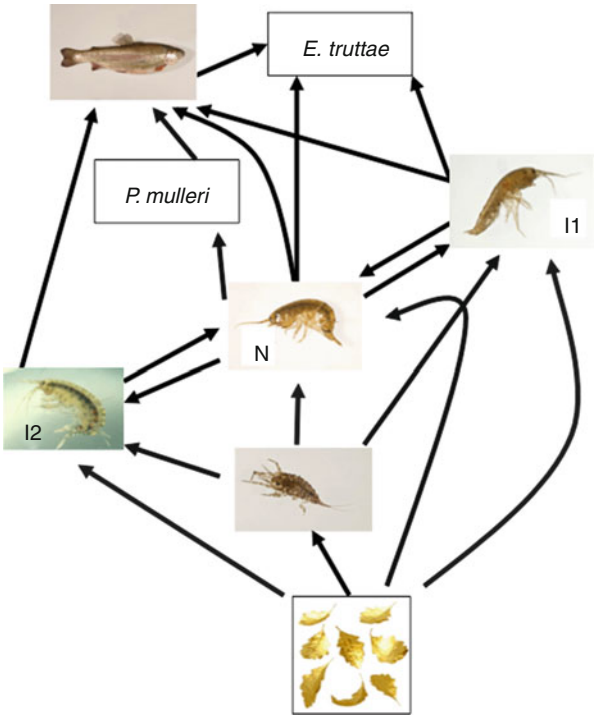

Fig. 3.2 Simplified food web depicting amphipod invader-native interactions in Ireland. The native *Gammarus duebeni celticus* (*N*) sits mid-way in an intraguild predation hierarchy between the invasives *G. pulex* (*I1*) and *G. tigrinus* (*I2*). Amphipods prey on smaller invertebrates (e.g. *Asellus aquaticus*, shown) and process leafy detritus. They are prey to salmoniid fish (e.g. *Salmo trutta*, shown). Two parasites modify gammarid interactions: *Pleistophora mulleri* infects *G. d. celticus*, and *Echinorhynchus truttae* infects *G. d. celticus* and *G. pulex* as intermediate hosts, utilizing salmoniid fish as the definitive host. *Arrows* depict direct trophic interactions; *direction of arrow* indicating direction of energy flow

3.2.2 Crayfish Invasions

In Europe, the decline of the native white-clawed crayfish (*Austropotamobius pallipes*) and its replacement by the North American signal crayfish *(Pacifastacus leniusculus)* is at least partly mediated by parasitism (Dunn 2009). The fungal parasite *Aphanomyces astaci* (which causes crayfish plague) was co-introduced with the signal crayfish (Holdich and Poeckl 2007), whilst an endemic microsporidian parasite *Thelohania contejeani* affects the endangered native species (Oidtmann et al. 1997).

3.3 Module Approach to Indirect Interactions

To examine how parasites influence invasion dynamics and impact, we need an understanding of the potential for indirect effects of parasitism on other species in the invaded community. Analysis of community modules helps to categorize all the potential indirect effects that may ramify from a focal host-parasite pairing (Fig. 3.3). Community modules (Holt 1997) are sets of three or more strongly

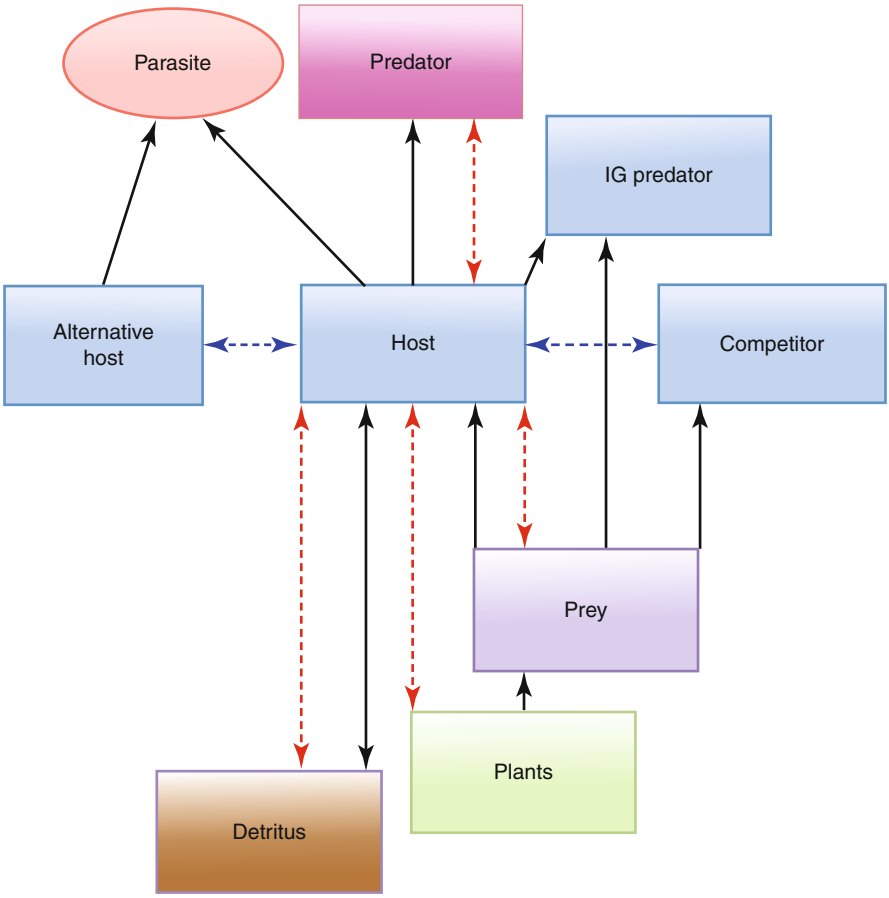

Fig. 3.3 Parasite-induced indirect interactions in community modules. Interaction links between a focal host (*blue*, *bold border*) and closely linked community members are shown. *Bold arrows* depict direct interactions between species; the direction of energy flow is indicated by the *arrow*. Crustacean amphipods are involved in many trophic interactions, as predators and prey, and as detritoves and processors of detritus, as well as being hosts to parasites. *Dashed arrows* depict sample indirect interactions with other species; the examples show where a parasite (*red*) may indirectly affect interactions between the host and other species by modifying host behaviour. Conceivably, interactions between any species pair may be modified; *red arrows* indicate vertical indirect interactions, *blue* show horizontal indirect interactions

interacting species, providing a bridge between simple single population or two-species dynamics and the inherent complexity of complete communities. Modules provide a basis for analysing indirect interactions mediated by a third species, and how interactions such as predation and parasitism themselves interact.

All the major trophic interactions in an ecosystem may be affected by parasitism (Hatcher and Dunn 2011). From the perspective of understanding invasions, we can distinguish between two relevant facets of module structure where parasites may have impact (Dunn et al. 2012):

Horizontal interactions between species on the same trophic level. These may include competitive interactions (which may be influenced by parasites in one or more host species at that level) or apparent competition and related interactions (for instance, where two species do not compete directly for resources, but are host to the same parasite species). Via their effects on competitive strength or apparent competition, parasites may therefore influence invasion rate/success, and coexistence/species replacement dynamics.

Vertical interactions between species at different trophic levels. These include consumptive predator-prey, herbivory and detritivory interactions. Such vertical interactions are relevant to understanding ecological impact in invasion biology, as some of the most devastating invasive species have been demonstrated as more voracious consumers than native counterparts (Dick et al. 2014). As we will review, parasites influence predation rates on or by their hosts, and therefore may strongly influence the strength of these interactions.

Here, we review evidence for each of these indirect interactions in the crustacean-parasite systems we study, along with a brief examination of evidence from other systems.

3.4 Trait Effects of Parasites on Trophic Interactions

3.4.1 Detritivory

In many aquatic ecosystems, leafy detritus provides the primary basal energy resource. Amphipods and isopods play an important role in processing this detritus, converting it from coarse to fine particulate organic matter that can be consumed by filter feeders and collector-gatherers (MacNeil et al. 1997). Parasitism has been shown to modify detritivore interactions in some of these systems. Infection by the acanthocephalan parasite *Acanthocephalus tahlequahensis* was found to cause a reduction in detritus processing by its isopod host, *Ceacidotea communis* in streams in North America (Hernandez and Sukhdeo 2008). This trait effect has community-wide ramifications, with parasites predicted to reduce detritus processing by up to 50 %, affecting energy transfer throughout the ecosystem. Biological invaders may have different rates of detritus processing than the native species that they replace. For example, leaf shredding function of the invasive *Dikerogamarus villosus* was

lower than that of 3 native species MacNeil et al. (2011), and current work is exploring whether parasites can also influence detrital processing.

Trait-mediated effects can be both subtle and context-dependent. For example, larval *Drosophila melanogaster* compete with the fungus *Aspergillus niger* for dead organic matter; *D. melanogaster* larvae suppress fungal growth, whilst the fungus secretes toxins that inhibit the fly larvae. Infection with the parasitoid *Asobara tabida* reduces feeding by *D. melanogaster* larvae, and this influences its interaction with the fungus; this form of cryptic virulence leads to complex interactions between the competitors (Rohlfs 2008).

3.4.2 Herbivory

Herbivory *per se* has not been studied in our crustacean systems. However, as herbivory is key to processing the basal energy resource in many ecosystems, it would be remiss not to discuss some key findings from other systems, especially as parasitism of herbivores is well documented as having profound effects on community structure. Disease outbreaks in vertebrate populations have led to some dramatic examples of cascading effects. For instance, myxomatosis and rinderpest have led to population declines of dominant grazers (rabbits *Oryctolagus cuniculus* and wildebeest, *Connochaetes taurinus,* respectively), with consequent effects on both plant and predator communities (reviewed in Hatcher and Dunn 2011). In these examples, parasitism has its impact via classical density-mediated effects (reduced host survival); however, recent work suggests that less obvious trait-mediated effects on host fitness may also have cascading effects in communities. For example, endophytes of grasses which reduce host palatability to herbivores can have knock-on effects for plant community composition and succession, and also appear to influence herbivore, detritivore and predator communities. Because these endophytes protect hosts from herbivory, infection with endophytes may underlie the invasive success of some grass species (Rudgers et al. 2007). The trematode C*ryptocotyle lingua* does not kill its intermediate host, the algal grazing periwinkle *Littorina littorea*, but damages the host digestive system. As a result, per capita algal grazing was reduced by 40 % in infected periwinkles, leading to a 65 % increase in algal cover, which is likely to influence the recruitment of other species that require a rocky surface for colonization (Wood et al. 2007).

3.4.3 Competition

Parasite-mediated effects on competition provide some of the most-cited cases of parasite impact on community structure. Parasite-induced density effects have long been recognized as having potential to drive community structure via their effects

on competitors (Elton 1958). Indeed, seedling mortality induced by specialist pathogens could be one of the chief drivers of plant biodiversity in tropical rainforests (Freckleton and Lewis 2006) and may explain aspects of global diversity patterns today (Kulmatiski et al. 2008). In contrast, multi-host parasites may reduce biodiversity, preventing coexistence or speeding the replacement of one host species by another. One well-documented case is that of squirrel poxvirus (SQPV) in the red squirrel *Sciurus vulgaris*, which is under threat of replacement by the grey squirrel *Sciurus carolinensis* in the UK (Tompkins et al. 2003). SQPV has a direct, strongly pathogenic effect on red squirrels (Tompkins et al. 2003) and can potentially be spread through multiple routes (Collins et al. 2014). In England, where the virus is present, decline in red squirrels is up to 25 times more rapid than in Scotland and Italy, where the virus is absent (Rushton et al. 2006).

However, trait-mediated competitive interactions are also known to affect both animal and plant invasions. For instance, plant pathogens can potentially influence plant community composition and grassland diversity via trait-mediated indirect effects on competition; Barley Yellow Dwarf Virus (BYDV) modifies competition between native perennial bunchgrasses and invasive annual grass species in the Californian plains. In field plot experiments, BYDV infection did not affect bunchgrass survivorship when grown alone, but halved survivorship of bunchgrass grown with invasive species (Malmstrom et al. 2006). This effect may facilitate the ecological replacement of bunchgrasses by invasive competitors (Borer et al. 2007). A further example of the power of parasite-induced trait effects concerns parasitic phorid flies. Phorids have surprising effects on their ant hosts, causing direct virulence effects in infected hosts, but indirectly exerting trait effects in *uninfected* hosts that exhibit parasite avoidance behaviour. These parasitoids develop in the head capsule of worker ants – leading to decapitation before the fly pupates and emerges as an adult. The presence of the phorid *Apocephalus* sp. induces refuge seeking behaviour in potential hosts, preventing defensive behaviour towards the competing ant species (Lebrun and Feener 2007). In the presence of phorid flies, an otherwise dominant species may be outcompeted by an inferior competitor. Interestingly, ant species that are dominant competitors experience higher levels of infection as host alarm and foraging trail pheromones are used by the parasitoid to detect hosts in which they will lay their eggs. Fear of parasitism may be more widespread than we appreciate: in the 2003 SARS pandemic, in addition to state-imposed contact control measures, there were notable decreases in social behaviour (such as restaurant usage and attendance of social events) as people attempted to reduce their risk of infection (Blendon et al. 2004).

In the Ireland *Gammarus* system, we suspect that trait effects of parasites may act via competition on the invasion process. For instance, parasite-induced changes in predation on shared invertebrate prey could release or exacerbate invader-native competition. However, intraguild predation is also key to invader-native interactions, thus it is difficult to tease apart the importance of competition versus predation (including intraguild predation between competing gammarids) in these community modules; these processes are discussed below.

3.4.4 Predation

Parasites can influence predation via trait effects in two ways; parasites of predators may alter the predatory behaviour of such hosts, whereas parasites of prey species can alter the likelihood of the host being consumed. Both scenarios are found in crustacean systems we study.

3.4.4.1 Predation by the Host on Lower Trophic Levels

In laboratory experiments, the microsporidian *P. mulleri* causes little direct mortality or reduction in fecundity to its host, the native *G. d. celticus*. However, this parasite leads to reduced predatory ability on smaller sympatric amphipods and isopods (MacNeil et al. 2003b; Fielding et al. 2005). The effects of a second parasite, the acanthocephalan *E. truttae,* on its host the invasive *G. pulex,* are more complex and depend on prey size and species (Dick et al. 2010; Paterson et al. 2015). Analyses of predator functional responses (the per capita prey consumption as a function of prey density; Holling 1966; Dick et al. 2014) reveal that, when provided with juvenile *A aquaticus*, *E. truttae*-infected *G. pulex* exhibited a significantly higher functional response asymptote (i.e., exhibit higher predation rates) than uninfected individuals (Dick et al. 2010).

For both the invasive *G. pulex* and the native *G. d. celticus*, parasitism (with *E. truttae* and *P. mulleri* respectively) influenced foraging mostly through effects on prey handling time (Paterson et al. 2015). Whilst functional responses to some more mobile species (e.g. mayfly nymphs, *Baetis rhodani*) were lower for infected amphipods, predation was increased on the more sessile *Simulium* species. Furthermore, additional trait-mediated effects (the presence of higher-order fish predators) further modified foraging behaviour and the impact of parasites (Paterson et al. 2015). These findings, together with those for detritivory and cannibalism (see below), are strong indicators that parasites not only influence appetite, they influence prey choice and may induce trophic shifts in the host. This may be particularly relevant for our understanding of parasite impact in communities in general, as well as their role in invasion success and impact (Dick et al. 2014; Dunn and Hatcher 2015).

Parasitism also mediates interactions between invasive and native crayfish and their native prey (Dunn 2009). The invasive signal crayfish, *P. leniusculus,* which was introduced to Europe for aquaculture, is driving extirpation of native European crayfish including the endangered white clawed crayfish *A. pallipes*. Crayfish plague (caused by the fungus *Aphanomyces astaci*) is asympotamatic in the signal crayfish. However, the invader acts a reservoir for the parasite which causes mass mortality in the native species (Holdich and Poeckl 2007). In contrast, the microsporidian parasite *Thelohania contejeani* (Imhoff et al. 2011) mediates predation by the host through trait effects. *T contejeani* causes porcelain disease, a chronic infection in the native crayfish, which suffer muscle damage and a reduction in their predatory abilities (Haddaway et al. 2012). Comparison of predatory functional

responses revealed that native crayfish had a lower prey intake rate than did the invasive species, reflecting a longer prey handling time. This difference is exacerbated by the parasite, which induced muscle damage leading to a reduced attack rate and increased prey handling time, contributing to a 30 % reduction in prey intake by parasitised native crayfish (Haddaway et al. 2012).

The effects of parasites on predator survival and/or behavior can have knock-on effects for prey species (Hatcher et al. 2006). In some cases, the effects can long outlive the duration of active infection in a population, and would be missed in contemporary experiments. For instance, an outbreak of canine parvovirus in grey wolves (*Canis lupus*) in the US National Park of Isle Royale 20 years ago precipitated a population crash from which the wolf population has never recovered (probably because the crash reduced genetic diversity in the wolf population). This density-mediated effect has shifted the balance of population regulation of the chief prey species (moose, *Alces alces*) away from predation and towards correlation with climatic factors (Wilmers et al. 2006). Whether trait-mediated effects can have such lasting impact has yet to be examined.

3.4.4.2 Predation on the Host by Higher Trophic Levels

In some cases, predators attack infected prey more frequently than healthy prey because parasitism weakens hosts making them easier to catch. This parasite-induced vulnerability to predation may determine population dynamics and community structure in some natural systems (Packer et al. 2003; Holt and Roy 2007). If infected prey provide an "easy" resource for predators to exploit, parasitism can enhance persistence of a predatory species (Hethcote et al. 2004). Alternatively, predators and parasites can interact to determine prey population persistence and dynamics. For instance, parasite-predator interactions can drive cyclic population dynamics in the snowshoe hare (*Lepus americanus*). Murray et al. (1997) found that hare populations prone to strong predation more than doubled their survival rates when treated with anthelminthics. Infection with nematode parasites had no other measurable effects on host fecundity or direct mortality, thus increased predation on infected hosts appears to be the sole cause of virulence in this system. Similarly, red grouse *Lagopus lagopus* killed by predators had significantly higher burdens of the caecal nematode *Trichostrongylus tenuis* and worm burden reflected the level of gamekeeper control of predators (Hudson et al. 1992).

Many of the behavioural changes described above represent "by products" of infection (Poulin 1995). Nonetheless, in the community context, their outcomes may be far from "boring" (Poulin 1995). Other changes in prey/host behavior may be adaptive, resulting from selection on the host to avoid infection, or selection on the parasite to enhance transmission. For example, parasites can influence predation via effects on the avoidance behavior of potential hosts. Tadpoles of the toad *Bufo americanus* exhibit an adaptive "fear" response of hyperactivity to chemical cues from cercariae of the trematode *Echinostoma trivolvis*, which reduce their chances of becoming infected (Rohr et al. 2009). This increased activity could potentially offset

adaptive predator avoidance strategies (predator presence elicits a decrease in activity) and lead to suboptimal foraging and developmental rates (Raffel et al. 2010).

Trophically transmitted parasites have indirect life cycles and are transmitted to the definitive host when it preys upon an infected intermediate host. Many species of acanthocephalan and trematode parasites have been found to manipulate the anti-predator behaviour of the intermediate host, thereby increasing its vulnerability to predation (Moore 2002; Lefevre et al. 2009). For example, the acanthocephalan parasites *E. truttae* and *P. minutus* both induced changes in activity and photophilic behaviour of their amphipod hosts: infected hosts show higher motility and are more photophilic than uninfected hosts (MacNeil et al. 2003a), enhancing transmission to the definitive fish and duck hosts. Although both the native and invasive species are used as intermediate hosts, *E. truttae* prevalence is higher in the invasive *G. pulex,* which could have ramifications for invasion dynamics as well as having the potential to increase parasite frequency in commercially important fish (Hatcher and Dunn 2011).

3.4.5 Intraguild Predation

Intraguild predation, that is, predation between potential competitor species, is widespread in ecological communities (Polis et al. 1989). For example, wolves compete with hyenas for prey, but also prey upon them, whilst invasive and native amphipods show mutual intraguild predation whilst perhaps also competing for other invertebrate prey. Intraguild predation is a special case wherein predation by and of focal host species need to be considered together. In the N. Ireland amphipod system, intraguild predation is key to understanding invasion and coexistence (Dick et al. 1993). The two species of parasite (the microsporidium *P. mulleri* and the acanthocephalan *E. truttae.*) have been shown to influence both the prey and predatory components of intraguild predation between these amphipods, with *P. mulleri* infecting the abdominal musculature in the native *G. d. celticus,* thus reducing host motility (MacNeil et al. 2003b). In field enclosure experiments, *P. mulleri* had no impact on *G. d. celticus* survival whether in single populations or in mixed species populations with the smaller *G. tigrinus*. However, infection of *G. d. celticus* resulted in increased survival of the smaller intraguild prey species*;* whilst *G. tigrinus* kept in mixed populations with *G. d. celticus* showed 90 % mortality over 2 weeks, this species was able to coexist with infected *G. d. celticus*. Laboratory experiments confirmed that coexistence was facilitated by a reduction in intraguild predation by infected *G. d. celticus* on *G. tigrinus* (Fig. 3.4). Similarly, infected *G. d. celticus* showed less intraguild predation of another smaller amphipod, *C. pseudogracilis.* In addition to modifying the intraguild predatory abilities of its host, *P. mulleri* infection also increased host vulnerability to becoming the intraguild prey of the larger invasive species *G. pulex*.

For *G. pulex*, infection by the acanthocephalan *E. truttae* not only modifies host predatory abilities on smaller invertebrate species, it also reduces predation on its intraguild prey, including the native *G. d. celticus* (MacNeil et al. 2003a). Field

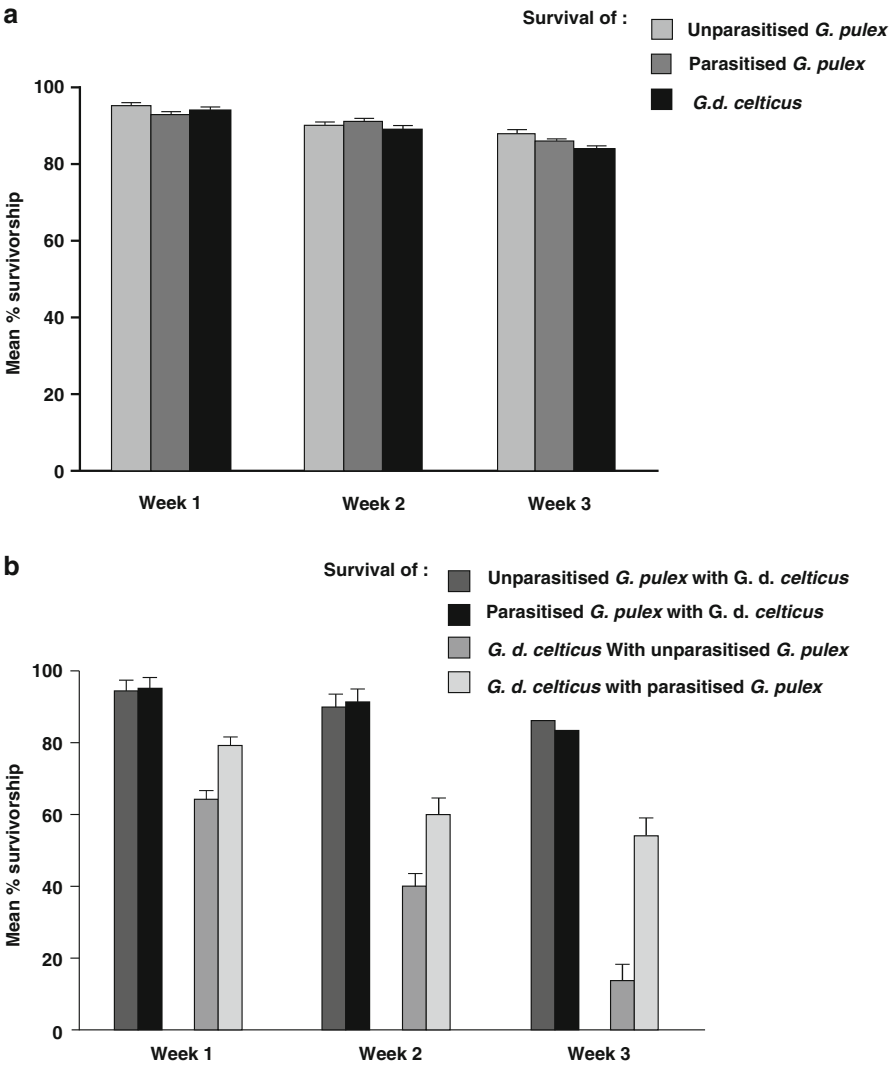

Fig. 3.4 Survival of the native species *Gammarus duebeni celticus* and of uninfected and *Echinorhyncus truttae*-infected *Gammarus pulex* (invader) in (**a**) single and (**b**) mixed species enclosures. Parasitism did not direct affect survival of the host *Gammarus pulex* but enhanced survival of the native species (From MacNeil et al. 2003a)

enclosure experiments were used to assess the impact of parasitism on the native and invading hosts in single and mixed species populations. In single species populations, *E. truttae* did not directly affect the survival of the native or the invader. In mixed species populations, the survival of *G. pulex* was again unaffected. However, parasitized *G. pulex* were less likely to attack the native species leading to higher survival of the native species (MacNeil et al. 2003a). This reduction in intraguild

predation can theoretically facilitate species coexistence, limiting spread of the invader (Hatcher et al. 2008, 2014).

Mathematical models of this process demonstrate that the trait-mediated effects of parasites on predation can act as a strong force on co-existence dynamics, equal to that generated by density effects (Hatcher et al. 2008, 2014). Intraguild predation is a curious population module because it is theoretically rather unstable, predicted in many cases to disintegrate to extinction of either the intraguild predator or prey. Whilst parasites with density (mortality) effects can promote coexistence of predators and prey (Hatcher et al. 2008), we have also found that parasites with trait effects can have an equally strong impact on coexistence (Hatcher et al. 2014). Indeed, parasites with zero classical virulence, but cryptic virulence in the form of altered vulnerability to or propensity for predation, can have as pronounced an impact as density in promoting or inhibiting coexistence (Fig. 3.5). Parasites can thus have strong ecological impacts, even if they have negligible classical virulence, underscoring the need to consider trait-mediated effects when predicting effects of parasites on community structure in general and biological invasions in particular.

3.4.6 Cannibalism

One further trophic interaction could be important in understanding the dynamics of these amphipod systems. Cannibalism is a frequent occurrence in many systems, being both stage- and sex-specific; adults frequently consume immature conspecifics, and adults at moult – in particular females that may be held in precopula – are also vulnerable to cannibalism (MacNeil et al. 2003c; Bunke et al. 2015). In *G. d. celticus*, infection with *P. mulleri* can cause increased vulnerability to cannibalism, which also leads to enhanced transmission of the parasite as it is transmitted directly *per os* (MacNeil et al. 2003b). Although more vulnerable to being cannibalized themselves, recent work has shown that infected individuals become more cannibalistic, eating twice as many conspecifics in laboratory experiments. This may reflect the metabolic demand of the parasite; infected individuals are less able to consume prey of different species, and it may be that smaller conspecifics are an easier food item to capture and handle (Bunke et al. 2015). Interestingly, choice experiments indicate that uninfected *G. d. celticus* preferentially cannibalise uninfected conspecifics (Bunke et al. 2015). The parasite is transmitted via cannibalism, thus it seems that this behavior is an adaptive mechanisms to avoid the risk of parasitic infection.

3.5 Conclusions

Our crustacean study system is one of few systems where the impact of parasites on a range of different community modules has been studied, and we have seen that trait-mediated indirect effects have the potential to ramify both horizontally and

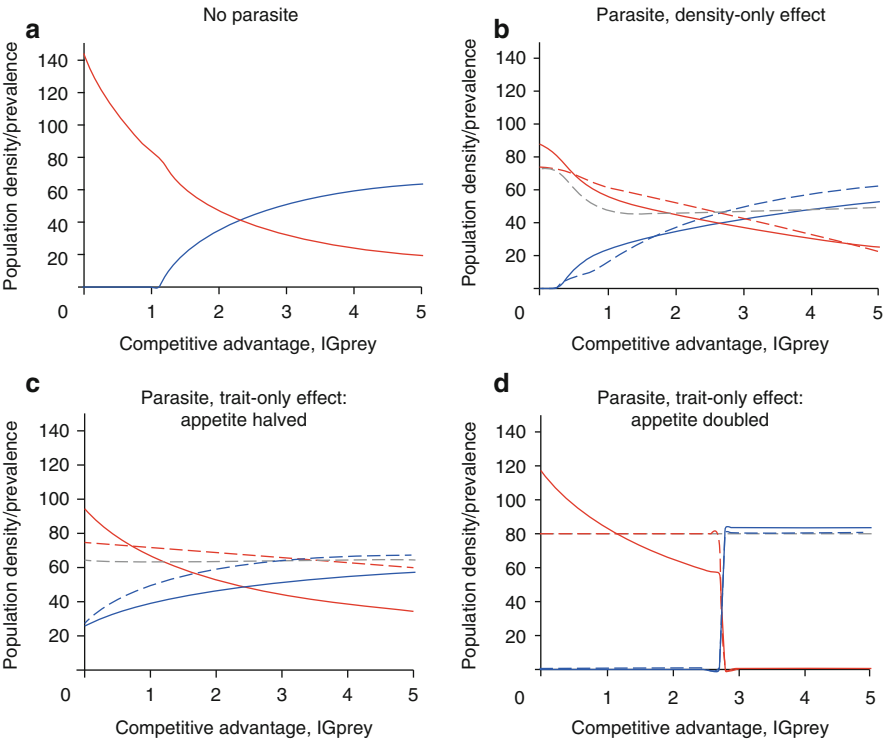

Fig. 3.5 Trait-mediated effects of parasitism on IGP systems. Equilibrium population densities (*solid lines*) and parasite prevalence (*dashed lines*) in the more predatory species (*intraguild predator*; *red*) and the weaker predator (*intraguild prey*, *blue*) plotted against the relative competitive advantage of the intraguild prey. (**a**) in the absence of parasitism, a strong intraguild predator excludes competitively weak intraguild prey; (**b**) virulent parasites (inducing 10 and 30 % mortality in the prey and predator respectively) enable coexistence of predator and prey over a broader parameter range; (**c**) parasites with no mortality effect but which reduce predatory ability strongly enhance coexistence whereas (**d**) parasites that increase predation strongly reduce coexistence (From Hatcher et al. 2014)

vertically in these modules. It is likely, therefore, that such effects underpin other systems. In particular, since parasites are known to have a wealth of effects on feeding behaviour and vulnerability to predation, it seems likely that they will strongly influence vertical trophic interactions. We have good evidence that, for a broad range of systems, invasion impact is related to the predatory propensity or resource consumption by the introduced species (Dick et al. 2014). Hence, parasites could potentially be important in modifying predation/consumption in a number of these systems, contributing to invasion success and impact. It is therefore important to study trait-mediated effects from the practical perspective of understanding and predicting invasion outcomes and also to understand the impact of parasites on biological invasion in particular and community ecology in general.

With the increasing realization that parasites are important components of ecosystems (Hudson et al. 2006; Lafferty et al. 2008), the potential importance of behavioural effects of parasites in a community context now deserves recognition (Lefevre et al. 2009). We have shown these community effects to be important both empirically and theoretically at the community module level (MacNeil et al. 2003c; Dick et al. 2010; Hatcher et al. 2014). Parasitologists and ecologists need to examine further the community and ecosystem-level consequences of trait-mediated effects and the cryptic virulence to which they lead. There is increasing recognition that parasites play important roles in ecosystem functioning, by influencing species coexistence patterns, biological invasions, energy flow and community stability (Hudson et al. 2006; Hatcher et al. 2012a, b). Underpinning all these ecosystem-level effects are the interactions between species in community modules. However, whilst we can demonstrate parasite-induced trait-mediated interactions at the level of modules, scaling up to the ecosystem level is a challenging proposition, both theoretically and empirically.

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References

Abrams PA, Matsuda H (1996) Positive indirect effects between prey species that share predators. Ecology 77:610–616

Arundell K, Dunn A, Alexander J, Shearman R, Archer N, Ironside JE (2015) Enemy release and genetic founder effects in invasive killer shrimp populations of Great Britain. Biol Invasions 17:1439–1451

Blendon RJ, Benson JM, DesRoches CM et al (2004) The public's response to severe acute respiratory syndrome in Toronto and the United States. Clin Infect Dis 38:925–931

Bojko J, Stebbing PD, Bateman KS, Meatyear JE, Bacal-Spychalaska K, Dunn AM, Stentiford GD (2014) Baseline histopathalogical survey of a recently invading island population of 'killer shrimp' *Dikerogammarus villosus*. Dis Aquat Organ 106:241–253

Borer ET, Hosseini PR, Seabloom EW, Dobson AP (2007) Pathogen-induced reversal of native dominance in a grassland community. Proc Natl Acad Sci U S A 104:5473–5478. 0027–8424

Bunke M, Alexander ME, Dick JTA, Hatcher MJ, Paterson R, Dunn AM (2015) Eaten alive: cannibalism is enhanced by parasites. R Soc Open Sci 2:140369

Collins LM, Warnock ND, Tosh DG, McInnes C, Everest D, Montgomery WI, Scantlebury M, Marks N, Dick JTA, Reid N (2014) Squirrelpox virus: assessing prevalence, transmission and environmental degradation. PLoS One 9:e89521

Daszak P, Cunningham AA, Hyatt AD (2000) Wildlife ecology – emerging infectious diseases of wildlife – threats to biodiversity and human health. Science 287:443–449

Dick JTA, Montgomery I, Elwood RW (1993) Replacement of the indigenous amphipod *Gammarus duebeni celticus* by the introduced *Gammarus pulex* – differential cannibalism and mutual predation. J Ani Ecol 62:79–88

Dick JTA, Armstrong M, Clarke HC, Farnsworth KD, Hatcher MJ, Ennis M, Kelly A, Dunn AM (2010) Parasitism may enhance rather than reduce the predatory impact of an invader. Biol Lett 6:636–638

Dick JTA, Alexander ME, Jeschke JM, Ricciardi A, MacIsaac HJ, Robinson TB, Kumschick S, Weyl OLF, Dunn AM, Hatcher MJ, Paterson RA, Farnsworth KD, Richardson DM (2014)

Advancing impact prediction and hypothesis testing in invasion ecology using a comparative functional response approach. Biol Invasions 16:735–753
Dodd JA, Dick JTA, Alexander MA, MacNeil C, Dunn AM, Aldridge DC (2014) Predicting the ecological impacts of a new freshwater invader: functional responses and prey selectivity of the 'killer shrimp', Dikerogammarus villosus, compared to the native Gammarus pulex. Freshw Biol 59:337–352
Dunn AM (2009) Parasites and biological invasions. Adv Parasitol 68(68):161–184. 0065–308X
Dunn AM, Dick JTA (1998) Parasitism and epibiosis in native and non-native gammarids in freshwater in Ireland. Ecography 21:593–598
Dunn AM, Hatcher MJ (2015) Parasites and biological invasions; parallels, interactions and control. Trends Parasitol 31:189–199
Dunn JC et al (2009) Competition and parasitism in the native White Clawed Crayfish *Austropotamobius pallipes* and the invasive Signal Crayfish *Pacifastacus leniusculus* in the UK. Biol Invasions 11:315–324
Dunn AM et al (2012) Indirect effects of parasites in invasions. Funct Ecol 26(6):1262–1274
Elton CS (1958) The ecology of invasions by animals and plants. Methuen, London
Ferrer M, Negro JJ (2004) The near extinction of two large European predators: super specialists pay a price. Conserv Biol 18:344–349
Fielding NJ, MacNeil C, Robinson N, Dick JTA, Elwood RW, Terry RS, Ruiz Z, Dunn AM (2005) Ecological impacts of the microsporidian parasite Pleistophora mulleri on its freshwater amphipod host *Gammarus duebeni celticus*. Parasitology 131:331–336. 0031–1820
Freckleton RP, Lewis OT (2006) Pathogens, density dependence and the coexistence of tropical trees. Proc R Soc B Biol Sci 273:2909–2916. 0962–8452
Haddaway NR, Wilcox RH, Heptonstall REA, Griffiths HM, Mortimer RJG, Christmas M, Dunn AM (2012) Predatory functional response and prey choice identify predation differences between native/invasive and parasitised/unparasitised crayfish. PLoS One 7(2)
Hatcher MJ, Dunn AM (2011) Parasites in ecological communities: from interactions to ecosystems. Cambridge University Press, Cambridge
Hatcher MJ, Dick JTA, Dunn AM (2006) How parasites affect interactions between competitors and predators. Ecol Lett 9:1253–1271
Hatcher MJ, Dick JTA, Dunn AM (2008) A keystone effect for parasites in intraguild predation? Biol Lett 4:534–537
Hatcher MJ, Dick JTA, Dunn AM (2012a) Disease emergence and invasions. Funct Ecol 26(6):1275–1287
Hatcher MJ, Dick JTA, Dunn AM (2012b) Diverse effects of parasites in ecosystems: linking interdependent processes. Front Ecol Environ 10:186–194
Hatcher MJ, Dick JT, Dunn AM (2014) Parasites that change predator or prey behaviour can have keystone effects on community composition. Biol Lett 10(1):e20130879
Hernandez AD, Sukhdeo MVK (2008) Parasite effects on isopod feeding rates can alter the host's functional role in a natural stream ecosystem. Int J Parasitol 38:683–690
Hethcote HW, Wang WD, Han LT, Zhien M (2004) A predator-prey model with infected prey. Theor Popul Biol 66:259–268
Holdich DM, Poeckl M (2007) Invasive crustaceans in European inland waters. In: Gherardi F (ed) Biological invaders in inland waters: profiles, distribution and threats. Springer, London, pp 29–75
Holling CS (1966) The functional response of invertebrate predators to prey density. Mem Entomol Soc Can 48:1–87
Holt RD (1997) Community modules. In: Gange AC, Brown VK (eds) Multitrophic interactions in terrestrial systems. Blackwell Science, Oxford, pp 333–350
Holt RD, Roy M (2007) Predation can increase the prevalence of infectious disease. Am Nat 169:690–699. 0003–0147
Hudson PJ, Dobson AP, Newborn D (1992) Do parasites make prey vulnerable to predation – red grouse and parasites. J Anim Ecol 61:681–692
Hudson PJ, Dobson AP, Lafferty KD (2006) Is a healthy ecosystem one that is rich in parasites? Trends Ecol Evol 21:381–385

Imhoff EM, Mortimer RJG, Christmas M, Dunn AM (2011) Porecelain disease in white-clawed (*Austromotamobius pallipes* (Lereboullet)) and signal (*Pacifastacus lenuisculus* (Dana)) crayfish in the UK. Crayfish Conservation in the British Isles. In: Brickland J, Holdich DM, Imhoff EM (eds) Proceedings of a conference held 2009, Leeds, pp 49–56

Kelly DW, Bailey RJ, MacNeil C, Dick JTA, McDonald RA (2006) Invasion by the amphipod *Gammarus pulex* alters community composition of native freshwater macroinvertebrates. Divers Distrib 12:525–534

Kelly DW, Paterson RA, Townsend CR, Poulin R, Tompkins DM (2009) Parasite spillback: a neglected concept in invasion ecology? Ecology 90:2047–2056

Kulmatiski A, Beard KH, Stevens JR, Cobbold SM (2008) Plant-soil feedbacks: a meta-analytical review. Ecol Lett 11:980–992. 1461–023X

Lafferty KD, Allesina S, Arim M, Briggs CJ, De Leo G, Dobson AP, Dunne JA, Johnson PTJ, Kuris AM, Marcogliese DJ, Martinez ND, Memmott J, Marquet PA, McLaughlin JP, Mordecai EA, Pascual M, Poulin R, Thieltges DW (2008) Parasites in food webs: the ultimate missing links. Ecol Lett 11:533–546

Lebrun EG, Feener DH (2007) When trade-offs interact: balance of terror enforces dominance discovery trade-off in a local ant assemblage. J Anim Ecol 76:58–64

Lefèvre T, Lebarbenchon C, Missé D, Poulin R, Thomas F (2009) Ecological significance of manipulative parasites. Trends Ecol Evol 24:41–48

MacNeil C, Dick JT, Elwood RW (1997) The trophic ecology of freshwater Gammarus aspp. (Crustacea: Amphipoda): problems and perspectives concerning the functional feeding group concept. Biol Rev 72:349–364

MacNeil C, Fielding NJ, Dick JTA, Briffa M, Prenter J, Hatcher MJ, Dunn AM (2003a) An acanthocephalan parasite mediates intraguild predation between invasive and native freshwater amphipods (Crustacea). Freshw Biol 48:2085–2093

MacNeil C, Dick JT, Hatcher MJ, Terry RS, Smith JE, Dunn AM (2003b) Parasite-mediated predation between native and invasive amphipods. Proc Biol Sci 270:1309–1314

MacNeil C, Dick JTA, Hatcher MJ, Fielding NJ, Hume KD, Dunn AM (2003c) Parasite transmission and cannibalism in an amphipod (Crustacea). Int J Parasitol 33:795–798

MacNeil C, Dick JTA, Platvoet D, Briffa M (2011) Direct and indirect effects of species displacements: an invading freshwater amphipod can disrupt leaf-litter processing and shredder efficiency. J N Am Benthol Soc 30:38–48

Malmstrom CM, Stoner CJ, Brandenburg S, Newton LA (2006) Virus infection and grazing exert counteracting influences on survivorship of native bunchgrass seedlings competing with invasive exotics. J Ecol 94:264–275

Mitchell CE, Power AG (2003) Release of invasive plants from fungal and viral pathogens. Nature 421:625–627

Moore J (2002) Parasites and the behavior of animals. In: Parasites and the behavior of animals. Oxford University Press, Oxford

Murray DL, Cary JR, Keith LB (1997) Interactive effects of sublethal nematodes and nutritional status on snowshoe hare vulnerability to predation. J Anim Ecol 66:250–264

Ohgushi T, Schmitz OJ, Holt RD (2012) Trait-mediated indirect interactions: ecological and evolutionary perspectives. Cambridge University Press, Cambridge

Oidtmann B, El-Matbouli M, Fischer H, Hoffmann R, Klarding K, Schmid I, Schmidt R (1997) Light microscopy of Astacus astacus L. under normal and selected pathological conditions, with special emphasis to porcelain disease and crayfish plague, Lafayette: International Assoc Astacology. 3230-9642382-3-3323

Packer C, Holt RD, Hudson PJ, Lafferty KD, Dobson AP (2003) Keeping the herds healthy and alert: implications of predator control for infectious disease. Ecol Lett 6:797–802

Paterson RA, Dick JTA, Pritchard DW, Ennis M, Hatcher MJ, Dunn AM (2015) Predicting invasive species impacts: a community module functional response approach reveals context dependencies. J Anim Ecol 84:453–463

Polis GA, Myers CA, Holt RD (1989) The ecology and evolution of intraguild predation – potential competitors that eat each other. Annu Rev Ecol Syst 20:297–330

Poulin R (1995) “Adaptive” changes in the behaviour of parasitized animals: a critical review. Int J Parasitol 25:1371–1383
Prenter J, MacNeil C, Dick JTA, Dunn AM (2004) Roles of parasites in animal invasions. Trends Ecol Evol 19:385–390
Raffel TR, Hoverman JT, Halstead NT et al (2010) Parasitism in a community context: trait-mediated interactions with competition and predation. Ecology 91:1900–1907
Rewicz T, Grabowski M, MacNeil C, Bacela-Spychalska K (2014) The profile of a ‘perfect’ invader – the case of killer shrimp, *Dikerogammarus villosus*. Aquat Invasions 9:267–288
Rohlfs M (2008) Host-parasitoid interaction as affected by interkingdom competition. Oecologia 155:161–168
Rohr JR, Swan A, Raffel TR, Hudson PJ (2009) Parasites, info-disruption, and the ecology of fear. Oecologia 159:447–454
Rudgers JA, Holah J, Orr SP, Clay K (2007) Forest succession suppressed by an introduced plant-fungal symbiosis. Ecology 88:18–25
Rushton SP, Lurz PWW, Gurnell J, Nettleton P, Bruemmer C, Shirley MDF, Sainsbury AW (2006) Disease threats posed by alien species: the role of a poxvirus in the decline of the native red squirrel in Britain. Epidemiol Infect 134:521–533
Terry RS, MacNeil C, Dick JTA, Smith JE, Dunn AM (2003) Resolution of a taxonomic conundrum: an ultrastructural and molecular description of the life cycle of *Pleistophora mulleri* (Pfeiffer 1895; Georgevitch 1929). J Eukaryot Microbiol 50:266–273
Thomas F, Poulin R, Brodeur J (2010) Host manipulation by parasites: a multidimensional phenomenon. Oikos 119:1217–1223
Tompkins DM, White AR, Boots M (2003) Ecological replacement of native red squirrels by invasive greys driven by disease. Ecol Lett 6:189–196
Torchin ME, Lafferty KD, Dobson AP, McKenzie VJ, Kuris AM (2003) Introduced species and their missing parasites. Nature 421:628–630
Werner EE, Peacor SD (2003) A review of trait-mediated indirect interactions in ecological communities. Ecology 84:1083–1100
White EM, Wilson JC, Clarke AR (2006) Biotic indirect effects: a neglected concept in invasion biology. Divers Distrib 12:443–455
Wilmers CC, Post E, Peterson RO, Vucetich JA (2006) Predator disease out-break modulates top-down, bottom-up and climatic effects on herbivore population dynamics. Ecol Lett 9:383–389
Wood CL, Byers JE, Cottingham KL, Altman I, Donahue MJ, Blakeslee AMH (2007) Parasites alter community structure. Proc Natl Acad Sci U S A 104:9335–9339. 0027–8424

Chapter 4
Cooperation or Conflict: Host Manipulation in Multiple Infections

Nina Hafer and Manfred Milinski

4.1 Introduction

Many parasites from various taxa have the ability to alter the phenotype of their host in a variety of ways to enhance their own fitness. Complex life cycle parasites, for example, use such host manipulation to increase trophical transmission to a subsequent host by altering host behavior and appearance (Holmes and Bethel 1972; Poulin and Thomas 1999; Moore 2002; Poulin 2010; Moore 2013). Parasites for which predation of their host would be fatal, e.g. because they have not yet completed their development can induce protection from predation (Koella et al. 2002; Hammerschmidt et al. 2009; Dianne et al. 2011; Weinreich et al. 2013). There is increasing evidence that even symbionts or commensals may influence their host's behavior (Feldhaar 2011; Ezenwa et al. 2012). Their interaction with co-infecting macroparasites remains largely unexplored (reviewed by Cézilly et al. 2014). Given the ubiquity of parasites, symbionts and commensals hosts may no longer be in full control of their own behavior but rather might display a compromise of all parties' interests (Milinski 2014). Humans, too, are subject to host manipulation, both as potentially manipulated host (e.g. Lafferty 2006; Flegr 2013) and as definitive host (e.g. Lacroix et al. 2005; Koella et al. 2006).

Most (experimental) studies of host manipulation to date have focused on infections by single parasites. This does not reflect nature where nearly every host is infected by multiple parasites (e.g. Petney and Andrews 1998). A number of previous reviews has identified the potential for multiple infections to affect host manipulation (Rigaud and Haine 2005; Koella et al. 2006; Thomas et al.

N. Hafer (✉) • M. Milinski
Department of Evolutionary Ecology, Max-Planck-Institute for Evolutionary Biology, August-Thienemann-Strasse 2, Ploen D-24306, Germany
e-mail: hafer@evolbio.mpg.de

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2010, 2011; Syller 2012; Mauck et al. 2012; Cézilly et al. 2014). So, how do parasites deal with co-infecting parasites with the same or different aims? From an ecological perspective, an already infected potentially manipulated host may no longer be the same environment as an uninfected non-manipulated host. Parasites could hence act as ecosystem engineers, modifying the host environment for all co-infecting parasites (Thomas et al. 1998b; Poulin and Thomas 1999; Lefèvre et al. 2009).

In this chapter we review the empirical evidence for the effect of multiple infections on host manipulation and try to identify emerging patterns. Depending on the aims of each of the parasites involved, co-infections might lead to cooperation or conflict over host manipulation (Fig. 4.1). This could affect infection patterns if parasites seek out hosts co-infected by suitable manipulators and avoid co-infections by unsuitable ones. Once two parasites enter the same host with at least one of them able to manipulate host behavior, cooperation or conflict might ensue. Cooperation can occur between parasites with the same interest. However, agreeing interests could also be exploited by free-riders saving the cost of manipulation. Conflict can exist between parasites with different aims. This includes two parasites of different species with different definitive hosts, different developmental stages of the same or different parasite species or two different parasite species with different transmission strategies (e.g. vertically transmitted parasites and parasites that require trophic transmission). Any such conflict might result in one parasite sabotaging the other parasite's manipulation.

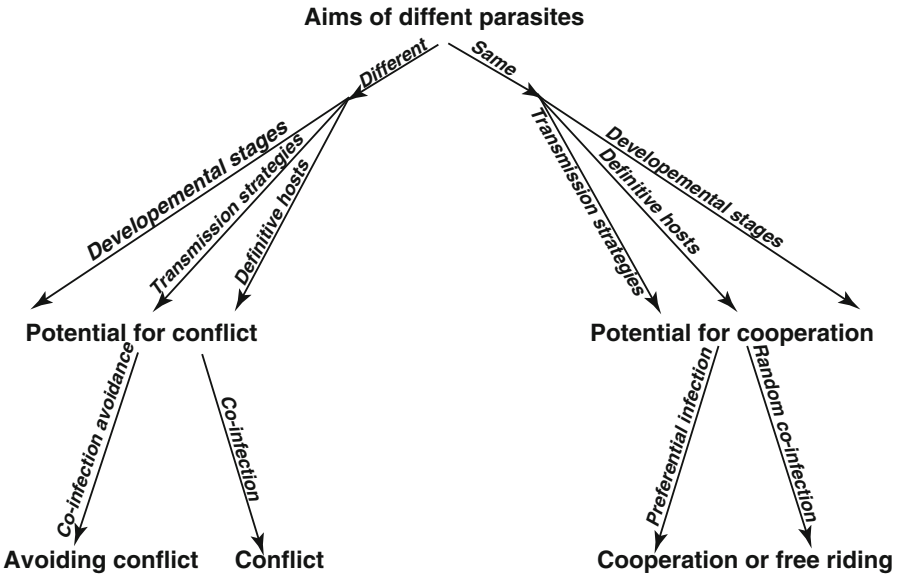

Fig. 4.1 Overview of potential consequences of multiple infections with regards to host manipulation

Box 4.1. How to test for parasite manipulation

Unjustified conclusions from observational (i.e. correlational) data

If the behavior of a wild-caught animal that harbors parasite A differs in a "meaningful" way from that of unparasitized wild-caught animals, it is tempting to conclude that the observed difference in behavior has been caused by parasite A – it might have manipulated the behavior of its host. This conclusion is not justified. One cannot exclude the possibility that pre-existing individual differences have caused both the altered behavior and the susceptibility to parasite A. The parasite might have no influence on its host's behavior. Alternatively, the host might be parasitized by an undetected additional parasite B that actually manipulates its host's behavior in the observed way. In both cases the altered behavior correlates with the possession of parasite A, which has not necessarily caused the behavioral change. Thus, we cannot conclude any causation of the changed behavior (e.g. Milinski 1997). Similarly, if a host harboring parasite C known to manipulate from previous experimental studies, fails to show this manipulation when naturally co-infected by another parasite, parasite D, this does not necessarily imply sabotage of the manipulation by parasite C through parasite D. Observational data, again, cannot rule out alternative explanations. For example, parasite D might preferentially infect less manipulated hosts (Thomas et al. 2002).

Is correlational evidence of any value? An interesting correlation that is found unexpectedly, e.g. animals that happen to be infected with parasite A differ in their behavior from uninfected ones, might help to generate hypotheses for a decisive experiment (see below). Furthermore correlational evidence can be used as a predictor: animals with changed behavior are likely to be parasitized, in the same way a time table at the railway station is a predictor for the arrival times of trains. To exclude a causal relationship you can change the time table with a pen. There will be no train at the altered time.

Only an experiment allows to conclude a cause-effect relationship

What can be done if one wants to determine whether an observed trait A (e.g. parasite A) has caused an observed trait B (e.g. altered behavior)? One must do an experiment, in which one removes the possibility that a difference in behavior between unparasitized animals and animals with parasite A is caused by any other (undetected) trait that parasitized individuals usually possess (e.g. weak immune response). One determines randomly which of e.g. 50 lab-bred, *i.e.* parasite-free animals has to be exposed to parasite A and which are to be sham-exposed, *i.e.* be handled in the same way as the exposed animals without including parasite A. It would be a mistake to expose the first 25 animals caught to parasite A and to sham-expose the second 25, because the first may be slower, less easily frightened thus easier to catch than the ones caught thereafter. So randomization is indispensable to ensure that all other traits which may affect an individual's behavior were assigned randomly to the to be exposed and sham-exposed individuals. Make sure, that each exposed animal is actually parasitized

by parasite A. Now wait until parasite A is ripe to be transmitted to the next host and record the behavior of each exposed and each sham-exposed animal separately.

We assume that the experiment has been performed properly in all other respects, e.g., in order to avoid experimenter bias the person handling and testing the animals must not know which has been exposed to parasite A and which has been sham-exposed. If there is a significant difference in behavior between exposed and sham-exposed individuals, parasite A must have caused the difference. We can, however, not conclude parasite A has manipulated its host's behavior. The behavioral change might be simply a side-effect of the energy drain caused by the parasite (Milinski 1990). To conclude manipulation additional experiments have to be performed. Accordingly, to show that parasite D alters, *i.e.* sabotages the host manipulation of parasite C, there has to be a significant difference between individuals experimentally exposed to parasite D and C and those experimentally exposed only to parasite C.

4.2 Cooperation – When Parasites Agree

4.2.1 Facilitating Cooperation: Hitch-Hiking

If host manipulation is beneficial but costly and baseline transmission rates are low, then parasites should seek out opportunities to co-infect hosts infected by other parasites with appropriate host manipulation (Thomas et al. 1998b). This should result in non-random associations between parasites (Cézilly et al. 2014). Preferential infection of suitably manipulated hosts, termed hitch-hiking, can be considered an adaptation if it is genetically determined and has become prevalent by conferring a selective advantage (Thomas et al. 1998b). In order to show that hitch-hiking occurred, preferential infections of already infected hosts need to be shown to increase fitness through enhanced transmission, ideally under experimental conditions (Thomas et al. 1998b). To our knowledge, this has never been done. Indeed, experimental studies testing whether parasites associate with each other according to their manipulation are missing entirely. In a survey of different naturally infected fish species, those larval helminthes that used the same host subsequent to the present fish host showed stronger associations than those that did not (Poulin and Valtonen 2001). Poulin and Valtonen (2001) suggested associations due to appropriate host manipulation as one possible explanation for the pattern they observed. Other studies have focused on one specific host species and investigated patterns of association including at least one parasite known to manipulate host behavior. Some did indeed find positive associations between parasites with the same interests (Thomas et al. 1997; Dezfuli et al. 2000; Poulin et al. 2003; Leung and Poulin 2007; Wisenden et al. 2012), but others did not (Thomas et al. 1998a; Poulin et al. 2003; Lagrue and Poulin 2008; Leung and Poulin 2010; Rauque et al. 2011). Infecting already infected hosts comes at some costs: the co-infecting parasites will compete over the host's resources (Thomas et al. 1998b; Vickery and Poulin 2009).

This cost has to be paid also by the manipulator whose host is hitch-hiked, but unlike the hitch-hiker it stands nothing to gain from it in return (Thomas et al. 1998b). Many parasites need to undergo a certain time of development within their intermediate host, during which ingestion even by the correct consecutive host would be fatal (e.g. Hammerschmidt et al. 2009; Dianne et al. 2011). To benefit fully from hitch-hiking timing would be crucial. Infecting the right host when it already manipulates its host might increase disastrous premature predation rather than transmission. It should in any case result in a conflict over host manipulation. Accordingly, hitch hiking should only work in fast developing parasites (Thomas et al. 1998b).

Hitch-hiking is not the only possible explanation for associations between parasites with parallel life cycles. The concurring life cycles themselves could cause associations between parasites. Parasites accumulate in their definite host. They (or their eggs) leaving it via defecation are likely to do so together with parasites using the same definite host. Hence, such parasites are more likely to develop in the same area contrary to those from different definitive hosts making it more likely that they will eventually infect the same host (Poulin and Valtonen 2001). Since associations have only been studied using naturally infected hosts, we cannot conclude anything about how such associations may come about. One possibility to distinguish associations due to parallel life cycles from actual hitch-hiking might be to study patterns of associations and relate them to host manipulation. If associations are due to hitch-hiking, they should be strongest in associations that involve both manipulators and non-manipulators but absent if no manipulators are present.

4.2.2 Cooperation

Once two manipulating parasites with the same aim with regards to host manipulation have co-infected the same host, they have a high potential to cooperate. The simplest case of cooperation involves multiple parasites of the same species at the same developmental stage. A number of theoretical models have predicted what should happen in this case. They all assume that host manipulation bears both costs and benefits (Poulin 1994; Brown 1999; Vickery and Poulin 2009). Benefits, *i.e.* altered predation risk, have been shown in a few systems (Wedekind and Milinski 1996; Mouritsen and Poulin 2003; Dianne et al. 2011; Weinreich et al. 2013). Evidence for costs, especially energetic costs, has remained largely elusive and is limited to indirect, correlational evidence (Franceschi et al. 2010; Maure et al. 2011).

If costly, host manipulation should not be maximized but optimized (Poulin 1994). Accordingly, parasites should adjust the extent of manipulation to the (expected) presence of other parasites. Thus, individual investment into host manipulation should decrease as within host parasite population size increases (Fig. 4.2, red line, Poulin 1994; Brown 1999; Vickery and Poulin 2009), though exceptions may occur if both benefits and relatedness between parasites are very high. In this case the already very high benefits are received by close kin likely to share the genes responsible for this manipulation with the manipulator (Vickery and Poulin 2009). In either case, total manipulation should still increase with increasing parasite

number (Fig. 4.2, blue line, Poulin 1994; Brown 1999; Vickery and Poulin 2009). Individual investment into host manipulation has never been measured and doing so might proof challenging. By contrast, total host manipulation has often been recorded as the total extent of (behavioral) change induced by parasites. In naturally infected hosts, total host manipulation often correlates with parasite number for at least some traits (Giles 1987; LoBue and Bell 1993; Brown et al. 2001; Mouritsen 2002; Latham and Poulin 2002; Addino et al. 2010; Seppälä et al. 2011; Fredensborg and Longoria 2012; Rode et al. 2013; Corrêa et al. 2014b). This seems to hold in both mass exposed (Urdal et al. 1995; Seppälä et al. 2005; Luong et al. 2011) and individually infected (Benesh et al. 2009; Cox and Holland 1998, 2007; Dianne et al. 2012; Franceschi et al. 2008; Hafer and Milinski 2015; Santos et al. 2011; Santos and Santos 2013) hosts. Some effect of parasite number on the strength of host manipulation, though it does not always seem to be linear, seems particularly consistent in parasites that usually infect their hosts in high numbers (Cox and Holland 1998, 2007; Mouritsen 2002; Latham and Poulin 2002; Seppälä et al. 2005; Addino et al. 2010; Santos et al. 2011; Seppälä et al. 2011; Luong et al. 2011; Fredensborg and Longoria 2012; Santos and Santos 2013; Corrêa et al. 2014b). Parasite number should correlate with manipulation strength, if host manipulation results from the impairment of a certain organ (Thomas et al. 2011). Brown (1999) predicted that host manipulation should only occur once a certain threshold in parasite population size within a host was reached. Such a threshold might be automatic if host manipulation depends on the impairment of a certain organ, which cannot be accomplished by a single parasite. The trematode *Diplostomum* sp. encysts in the eyes of fish obscuring their vision and thereby making them more vulnerable to predation especially at higher parasite numbers within one host (Fig. 4.3, Seppälä

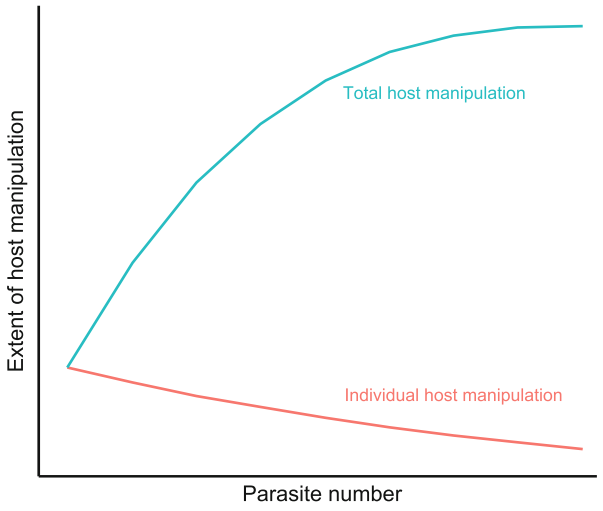

Fig. 4.2 Theoretical expectations of host manipulation resulting from cooperation over host manipulation (Based on Poulin 1994; Brown 1999; Vickery and Poulin 2009)

et al. 2005). This, however, only takes effect when a considerable number of parasites has encysted inside the eye (Seppälä et al. 2011).

In parasite species in which the number of individual parasites per host is usually very low and single infections may be the rule, evidence for an effect of parasite number on host manipulation is less clear. Some studies did find it (Brown et al. 2001; Dianne et al. 2012; Franceschi et al. 2008; Giles 1987; Hafer and Milinski 2015; LoBue and Bell 1993; Rode et al. 2013; Urdal et al. 1995), but others did not, including both studies using naturally infected (Cézilly et al. 2000; Latham and Poulin 2002) and experimentally exposed (Poulin et al. 1992; Benesh et al. 2005; Franceschi et al. 2010; Dianne et al. 2014) hosts. The cestode *Schistocephalus solidus* first reduces host activity to avoid premature predation and then increases it to enhance predation to continue its life cycle (Hammerschmidt et al. 2009). In a strictly experimental study, we (Hafer and Milinski 2015) found that two cestodes did not manipulate their first intermediate copepod host more than a single one did when they suppressed predation risk before they had reached infectivity for the next host. Once the parasites were infective to the next host and should enhance predation risk, they did enhance each other's manipulation (Fig. 4.4a, b). These findings confirmed previous correlational evidence from the same system (Urdal et al. 1995). We (Hafer and Milinski 2015) speculated that manipulation after reaching infectivity could be caused only through energy drain by the procercoid, which is a potential mechanism whenever predation risk needs to be increased (Milinski 1990). In cestodes energy drain might be a frequent mechanism resulting in host manipulation (Lafferty and Shaw 2013). Interestingly, most of the studies that found a correlation between parasite number and manipulation in systems with usually low parasite numbers per host used cestodes (Brown et al. 2001; Giles 1987; Hafer and

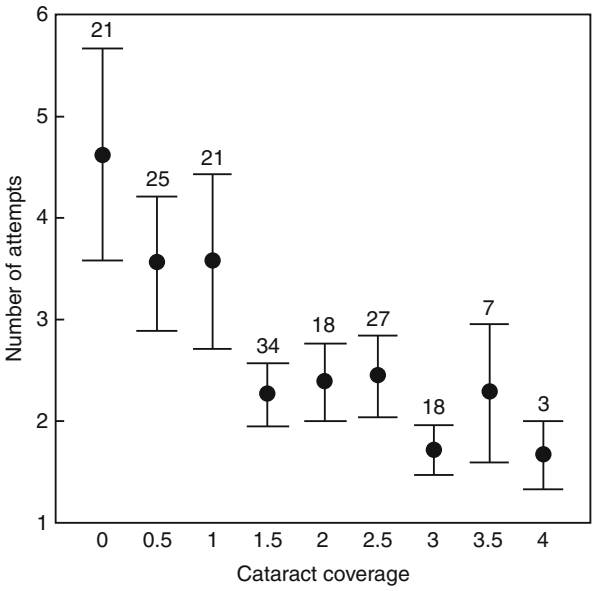

Fig. 4.3 Number of attempts (Mean ± SE) needed to catch rainbow trout mass exposed to the trematode *Diplostomum* sp. by dip netting. Cataract coverage indicates the average level for both eyes of cataract formation caused by the parasite. *0* = no cataract; *1* = cataract covering less than 50 %; *2* = cataract covering 50–100 %; *3* = cataract covering 100 %; and *4* = opaque cataract covering 100 % of the lens area. Numbers above the error bars indicate sample sizes (After Seppälä et al. 2005)

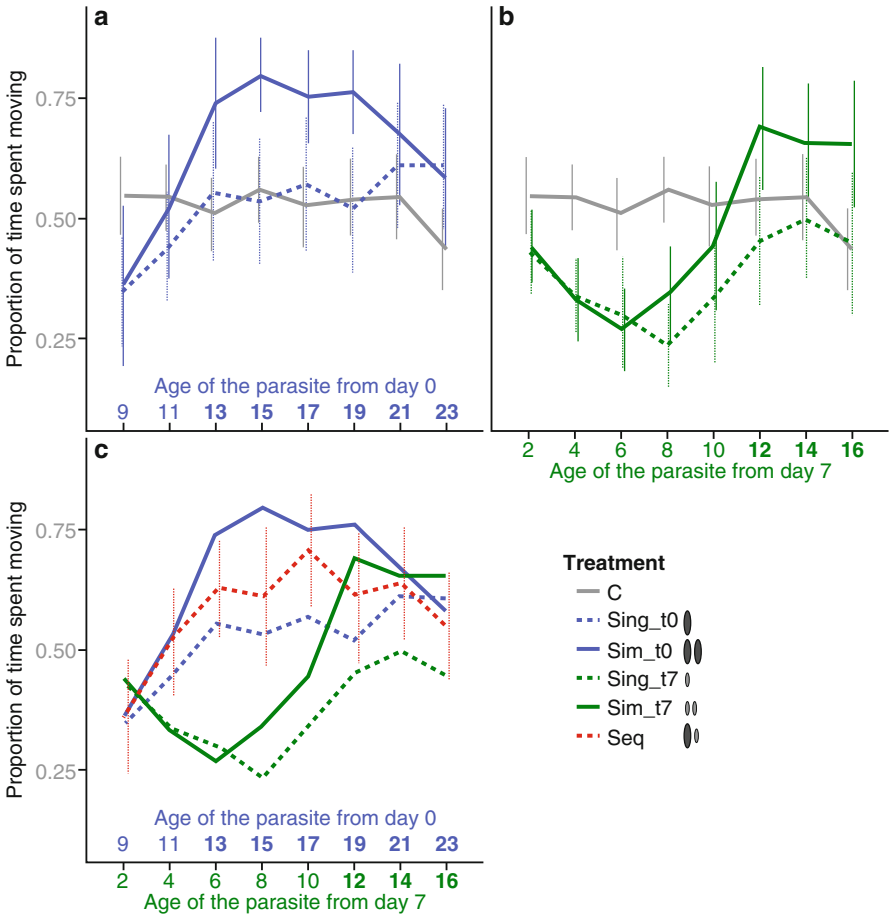

Fig. 4.4 The effect of multiple infections of the cestode *Schistocephalus solidus* on the activity (mean ±95 % CI) of its first intermediate copepod host. (**a**, **b**) Illustrate the outcome when there is potential for cooperation; two parasites (*continuous lines*) enhance each other's manipulation but only after reaching infectivity (about 11 days post infection). (**c**) Illustrates the outcome of a conflict (*red line*) between young, not yet- infective *S. solidus* (*green lines*) and older, infective ones (*blue lines*). Error bars from the treatments already presented in (a) and (b) have been omitted for better readability. *Bold numbers* on the X-axis indicate that parasites have reached infectivity. *C* unexposed control copepods, *Sing_t0* copepods singly infected with one parasite on day 0, *Sim_t0* copepods simultaneously infected with two parasites on day 0, *Sing_t7* copepods singly infected with one parasite on day 7, *Sim_t7* copepods simultaneously infected with two parasites on day 7, *Seq* copepods sequentially infected with two parasites, one each on day 0 plus day 7 (After Hafer and Milinski 2015)

Milinski 2015; LoBue and Bell 1993; Rode et al. 2013; Urdal et al. 1995). Energy drain should increase as parasite size and number increases. This might result in similar patterns (correlation between parasite number and host manipulation) as predicted by theoretical models (Poulin 1994; Brown 1999; Vickery and Poulin

2009) without fulfilling one of their assumptions, i. e. energetic costs associated with host manipulation: energy drain comes at no extra cost.

A correlation between parasite number and host manipulation might also be caused by more parasites having a larger combined volume. Dianne et al. (2012) found that experimentally infected gammarides harboring a single acanthocephalan parasite were more strongly manipulated if that parasite was larger. In parasites that can vary strongly in their mass, increased individual mass might have the same effect as increased parasite number. Only a limited number of studies has taken this possibility into consideration and found that parasite size seemed to be responsible for stronger manipulation (Seppälä et al. 2005; Benesh et al. 2009).

Benefits of manipulation will change with size and composition of the parasite community within a host. Increased parasite number also leads to increased competition. This decreases the potential gains of successful manipulation and transmission to the subsequent host (Poulin 1994; Vickery and Poulin 2009). Hence, in some cases, individual decrease in host manipulation might be so strong that even overall host manipulation decreases as parasite number increases (Vickery and Poulin 2009). This represents a bystander dilemma as studied in humans. If an emergency occurs, an increased number of bystanders do not increase the chances that at least one of them will aid the victim. Instead, the victim is less likely to receive any help at all, because from the perspective of any one bystander there are others that could provide the required help (reviewed by Fischer and Krueger 2011; Latané and Nida 1981). In gammarides, experimental double infection with an acanthocephalan parasite leads to increased phototaxis compared to single infections. Nevertheless, in infections with more than two parasites this host manipulation does not seem to increase any further (Franceschi et al. 2008). In mice infected with the nematode *Toxocara canis*, exploratory behavior is increased if parasite burdens are low but not if they are high compared to control mice (Cox and Holland 1998). Such an effect could also be caused by reduced ability of parasites to manipulate due to resource limitations or damages imposed on the host (Rigaud and Haine 2005; Franceschi et al. 2008).

Cooperation is not necessarily limited to individuals of the same species but can also occur between members of different species if they have the same aim. This hypothesis has received much less attention. Observational field evidence suggests that it can also facilitate cooperation (Lafferty and Morris 1996; Poulin et al. 2003; Santiago Bass and Weis 2009; Rode et al. 2013). For example, *Artemia* naturally infected with two microsporidian parasites are found more likely to be swarming, which is thought to enhance transmission via spores to other *Artemia*, than those infected only with one (Rode et al. 2013).

4.2.3 Free Riding

If multiple parasites with agreeing aims manipulate a host, host manipulation becomes a public good: An individual parasite that manipulates bears the costs of manipulation but all co-infecting parasites will benefit equally (Brown 1999;

Vickery and Poulin 2009). As discussed above parasites could increase their chances of encountering a suitably infected host by preferentially infecting already infected hosts. To our knowledge, the existence of free riding, *i.e.* benefits of increased transmission through co-infecting without contributing to manipulation, has not been investigated explicitly in complex life cycle parasites. Salvaudon et al. (2013) identified a potential case in vector transmitted plant viruses. Two viruses, the zucchini yellow mosaic virus and the watermelon mosaic virus infect cucurbits and are transmitted by aphids. The former virus modifies aphid-plant interaction in a way that enhances its transmission; the latter does not but probably benefits from these modifications. The existence of free-riding raises the question of how host manipulation can be maintained if it is potentially exploited by other parasites (Brown 1999). Two trematode parasites, *Acanthoparyphium* sp and *Curtuteria australis* infect cockles and require birds to prey upon them and serve as the parasites' definite host. They can enhance the likelihood of bird predation by encysting at the tip of the cockle's foot and thereby impairing its burrowing ability. However, encysting there comes at a cost: It also enhances dead end predation by fish that chew off the tip of the foot (Mouritsen and Poulin 2003). Both trematodes can also encyst in other body parts where they do not pay the cost from potential dead end predation, but cannot manipulate. *Acanthoparyphium* sp. only rarely encysts at the tip of the foot and would hence benefit from associating with *C. australis* which encysts at the tip of the foot much more often (Leung and Poulin 2010). Leung and Poulin (2010), however, found the opposite result when they exposed field collected cockles to both parasites in the lab: The stronger manipulator, *C. australis* is also the stronger competitor. It sometimes excluded *Acanthoparyphium* sp. from co-infections.

4.3 Conflict – When Parasites Disagree

4.3.1 Avoiding Conflict

Akin to seeking out suitably manipulated hosts, parasites would benefit from avoiding unsuitably manipulated hosts. This not only applies to complex life cycle parasites with different subsequent hosts but also to parasites that benefit most from a non-manipulated host, e.g. because they need to remain in it or rely on vertical transmission. There are two ways parasites can avoid co-infections. Already present parasites could protect their host from subsequent infection by unsuitably manipulating parasites. There is some evidence that vertically transmitted parasites or symbionts offer protection against pathogenic parasites (reviewed by Haine 2008; Brownlie and Johnson 2009; Feldhaar 2011). Such parasites would be fatal for the host's reproduction and fitness. Vertically transmitted parasites directly depend on their host's reproduction for transmission. Hence, any reduction in host reproduction would also result in reduced parasite fitness (reviewed by Haine 2008; Brownlie and Johnson 2009; Feldhaar 2011). Accordingly, Haine et al. (2005) tested whether a vertically transmitted parasite would succeed in protecting its gammaride host

from a manipulating trematode by recording the prevalence of single and co-infections in naturally infected hosts. They found no evidence that the vertically transmitted parasite prevented co-infections by the trematode.

If a host is already infected by an unsuitably manipulating parasite, a second parasite could avoid infecting this host. Distinguishing such avoidance from avoidance that evolved to eliminate resource competition could however proof difficult (Fauchier and Thomas 2001). Studies looking at negative associations between parasites with mutually exclusive life cycles have, to our knowledge, been limited to amphipod hosts (Dezfuli et al. 2000; Fauchier and Thomas 2001; Outreman et al. 2002; Lagrue and Poulin 2008; Haine 2008; Rauque et al. 2011). With one exception (Fauchier and Thomas 2001), they failed to find any negative association. Instead of protection or avoidance, parasites might respond to co-infections by a parasite with unsuitable manipulation by sabotaging that manipulation (Dianne et al. 2010; Hafer and Milinski 2015; Haine et al. 2005).

4.3.2 Conflict

4.3.2.1 Conflict Between Parasites with Different Definitive Hosts

Two parasites with mutually exclusive definitive hosts should be at a conflict over host manipulation. Cézilly et al. (2000) used field infected gammarides to investigate this conflict between two acanthocephalan parasites, the fish infecting *Pomphorhynchus laevis* and the bird infecting *Polymorphus minutus*. *Pomphorhynchus laevis* strongly changed the gammarids' vertical distribution in the water column while *P. minutus* infected individuals became more photophilic. Double infections seemed to result in some compromise: The host's vertical distribution was intermediate compared to singly infected hosts while their photophilia was stronger than that of only *P. minutus* infected hosts but not significantly different from that of hosts infected only by *P. laevis*. In another study using naturally infected amphipods harboring a manipulating acanthocephalan fish parasite co-infection with a non-manipulating bird infecting trematode had no significant effect on host manipulation (Rauque et al. 2011). However, since these studies used naturally infected hosts their results should be interpreted with caution (see Box 4.1). *Toxoplasma gondii* and the trematode *Toxocara canis* both change the behavior of their current rodent host to increase its susceptibility to their successive hosts, cats and dogs, respectively. Queiroz et al. (2013) and Corrêa et al. (2014a) studied their interactive effect on rats and mice using experimental infections. Since both parasites have different definitive hosts, one might expect a conflict even though this was not the focus of either study. However, even the effects of single infections with either parasite did not significantly differ from each other (Queiroz et al. 2013; Corrêa et al. 2014a) and thus the question of how such a conflict would be resolved becomes obsolete.

A conflict over which of two different definitive hosts has to be reached will only occur if manipulation is sufficiently specific (Cézilly et al. 2014). Not all mutually

exclusive life cycles might also lead to mutually exclusive manipulation. Predation enhancement seems often very unspecific. For example, three-spined sticklebacks infected by the cestode *Schistocephalus solidus* not only show a reduced fear response when presented with a simulated bird predator which presents a suitable definitive hosts to *S. solidus* (e.g. Giles 1983; Barber et al. 2004), but also when exposed to piscivorus predatory fish which would be dead-end predators (e.g Milinski 1985). Other means, e.g. spines in sticklebacks might help reduce dead-end predation (Hoogland et al. 1956). Nevertheless, such a general increase in predation susceptibility is not likely to result in any conflict over host manipulation even between parasites with very different definitive hosts. Such parasites might even benefit from each other's manipulation. Hence, in order to investigate conflict over host manipulation, significant differences between manipulation effects by different parasites should be shown in singly infected hosts as a prerequisite. Only Cézilly et al. (2000) managed to do so, though, compared to uninfected hosts, both parasites manipulated into the same direction albeit to varying extends. To proof a potential for a conflict it should ideally be shown that one behavioral alteration benefits one parasite but is costly (through a relative increase in dead-end predation) to the other. This has never been done. There is urgent need for experimental studies that investigate a clear conflict between manipulating parasites with different definitive hosts.

4.3.2.2 Conflict Between Parasites with Different Transmission Strategies

A conflict will also occur between parasites if one parasite has to remain within the host and the other has to pass to a subsequent host. Such a conflict is inevitable when a vertically transmitted parasite, or indeed any vertically transmitted organism, and a manipulating parasite co-infect the same host. There is probably no host without any vertically transmitted parasite, symbiont or commensal. Accordingly, a conflict due to different transmission strategies should be universal whenever a manipulating parasite infects a host. Nevertheless, this conflict has rarely been studied. In naturally infected gammarides co-infection by a vertically transmitted microsporidian parasite reduced manipulation by a bird infecting acanthocephalan parasite (Haine et al. 2005). In another study with naturally infected gammarides, Thomas et al. (2002) observed that hosts harboring a manipulating bird trematode were less manipulated when they also harbored a non-manipulating nematode which has to remain inside the gammaride. However, when they experimentally cured and re-infected the host with the nematodes, they were unable to reverse or reintroduce this effect. This illustrates the urgent need for experimental studies.

4.3.2.3 Conflict Between Different Developmental Stages

A conflict between two different developmental stages of the same parasite species will occur if parasites need to spend a certain time within their intermediate host before they become infective to their next host and manipulate accordingly. In this

case, predation suppression may occur before and predation enhancement after the parasite reaches infectivity. This has been predicted theoretically (Parker et al. 2009) and shown experimentally (Hammerschmidt et al. 2009; Dianne et al. 2011). In isopods, an acanthocephalan parasite induces color changes thought to enhance predation. However, only infective parasites will benefit from predation. Accordingly, color change is stronger in hosts with infective parasites but also occurs, albeit to a lesser extent, in hosts with not yet-infective ones. Unsurprisingly, hosts naturally infected by both stages seem to resemble those with infective parasites (Sparkes et al. 2004). Dianne et al. (2010) investigated the same conflict by using gammarides experimentally infected at two different time points and measuring their reaction to light. Again, the infective parasite seemed to win the conflict, but there was some indication of sabotage by the not yet-infective one. In a similar experiment, using lab bred copepods and *S. solidus*, we (Hafer and Milinski 2015) found that, as in previous studies, the infective parasite won the conflict. However, unlike in the studies discussed above, in this system, the infective and the not yet-infective parasite manipulate into opposite directions. Despite the fact that the not yet-infective parasite had a much larger effect on host behavior when each parasite was alone, the infective one completely sabotaged manipulation by the not yet-infective one in co-infections (Fig. 4.4c). This remained true even when we used two instead of one not yet-invective parasite to make up for their smaller volume (Hafer and Milinski 2015). More studies will be needed to determine whether the parasite that comes first and becomes infective first always has an advantage. Is this something that is typical of intraspecific conflict between different developmental stages? There, the more advanced parasite might have an advantage by having to mitigate any effect it had before reaching infectivity even without a co-infecting parasite. This mitigation could also act against a co-infecting parasite (Hafer and Milinski 2015).

4.4 Where to Go?

Once two parasites that disagree over host manipulation co-infect the same host, there is evidence for sabotage of host manipulation but the evidence is mostly correlational, often unclear and experimental evidence restricted to a conflict between different developmental stages (Dianne et al. 2010; Hafer and Milinski 2015). Hence we need more experimental studies, preferentially with two different parasite species between which a clear conflict over host manipulation exists. Investigating such conflict over host manipulation requires the availability of at least two suitable species and their host that can be handled in the laboratory. We should further widen the scope of the contestants we use and not only consider parasites but also commensals and symbionts as agents that could be interested in altering host behavior or at least sabotaging host manipulation. Indeed, symbiotic microbes do seem to affect host behavior (reviewed by Feldhaar 2011; Ezenwa et al. 2012). Nearly all research investigating the impact of multiple infections on host behavior has been

focused on complex life cycle parasites. They are, however, not the only parasites manipulating their hosts. For example vector transmitted parasites increase encounters between their current and subsequent hosts (Koella et al. 2006; Fereres and Moreno 2009; Mauck et al. 2012). Hence, the effect of multiple infections involving for example vector transmitted parasites deserves further attention. Vector transmitted plant viruses do seem to interact in their effect on vector behavior (Srinivasan and Alvarez 2007; Syller 2012; Salvaudon et al. 2013; Lightle and Lee 2014).

An exact understanding of the mechanisms underlying host manipulation is still largely missing, though much progress has been made in recent years (Adamo 2012; Lafferty and Shaw 2013; Helluy 2013; Hughes 2013; Perrot-Minnot and Cézilly 2013; Houte et al. 2013). Both parasites will, for example, interact with the host's immune system potentially affecting also the other parasite. The interaction with the host's immune system could be exploited by parasites for host manipulation (Adamo 2002; Lafferty and Shaw 2013; Helluy 2013). Understanding host manipulation by an individual parasite will be crucial to understand how parasites interact at a mechanistic level in multiple infections where there is potential for either cooperation or conflict. It comes down to a question that has driven studies of host manipulation for decades: Did host manipulation specifically evolve for that purpose or is it, at least originally, a side effect of infection e.g. caused by inevitable energy drain (Milinski 1990; Poulin 1995; Cézilly and Perrot-Minnot 2005; Poulin 2010; Moore 2013). When two or more parasites co-occur in the same host, do they specifically interact with each other's manipulation or do their manipulations simply add up? Revealing the mechanisms of host manipulation might also give us a better understanding of the costs of host manipulation which is a crucial assumption made when modeling cooperation with regards to host manipulation. For example, if parasites manipulate by draining energy, causing stress responses or impairing certain organs, parasite number and host manipulation are likely to correlate without cooperation having necessarily evolved.

Whether parasites will evolve specific responses to the presence of other, potentially manipulating parasites will largely depend on the underlying selection pressures which will be strongly influenced by the likelihood of such interactions to occur (Rigaud and Haine 2005). We do not know what proportion of hosts is actually manipulated by a parasite. Only a limited number of systems has been investigated and studies are biased towards traits that are easily accessible by human perception, while those that are not might be overlooked (Moore 2013). Some parasites that usually occur in high numbers within one host can always expect to encounter other conspecifics. Hence, as theoretical models predict, they should be adapted to cooperate or even free-ride on the manipulation of others and need not be able to conduct all necessary manipulation on their own (Poulin 1994; Brown 1999; Vickery and Poulin 2009). While the data is limited and often correlational, there nevertheless seems to be a pattern that in parasite species that usually occur at high parasite numbers per host, parasite number does affect host manipulation. Other parasites may not be able to adapt to encounter a particular parasite but every parasite will encounter some other parasite, commensal or symbiont. Manipulating parasites can probably expect to encounter organisms which have an interest in a

normally behaving host. Parasites would benefit from evolving general strategies to suppress any parasite with manipulation unsuitable to them – or counter manipulation. Are they likely to have the ability to do so? If not they might have to restrict themselves to deal with the most frequent parasites. We need to test the interaction of one parasite species with multiple other ones. Of course doing so, especially experimentally, will be a challenge. If such a generalist mechanism was possible it might put the manipulator at an advantage – it will always encounter other, non-manipulating organisms, but not every organism within a host might encounter a manipulating parasite.

Studying the interaction between different parasites when it comes to host manipulation might be more than just an academic enterprise. Humans too are subject to manipulating parasites. About 30 % of humans worldwide are infected by *Toxoplasma gondii* known to change various personality traits (e.g. da Silva and Langoni 2009; Flegr 2013). Are there also other parasites, pathogens, commensals or symbionts that can impact the behavior of infected human hosts? Humans are not only (accidental) intermediate hosts to manipulating parasites, they may also encounter manipulating parasites as definitive hosts. Malaria parasites manipulate their insect vector to increase transmission between human hosts (e.g. Koella et al. 2002; Lacroix et al. 2005). Could other parasites or symbionts alter the extent of that manipulation and thereby also possibly infection probabilities? If yes, they could be used to limit the impact of malaria.

References

Adamo SA (2002) Modulating the modulators: parasites, neuromodulators and host behavioral change. Brain Behav Evol 60:370–377. doi:10.1159/000067790

Adamo SA (2012) The strings of the puppet master: how parasites change host behaviour. In: Hughes DP, Brodeur J, Thomas F (eds) Host Manipulation by parasites, 1st edn. Oxford University Press, Oxford, pp 36–51

Addino M, Lomovasky BJ, Cremonte F, Iribarne O (2010) Infection by gymnophallid metacercariae enhances predation mortality of SW Atlantic stout razor clam *Tagelus plebeius*. J Sea Res 63:102–107. doi:10.1016/j.seares.2009.11.001

Barber I, Walker P, Svensson PAP (2004) Behavioural responses to simulated avian predation in female three spined sticklebacks: the effect of experimental *Schistocephalus solidus* infections. Behaviour 141:1425–1440. doi:10.1163/1568539042948231

Benesh DP, Duclos LM, Nickol BB (2005) The behavioral response of amphipods harboring *Corynosoma constrictum* (acanthocephala) to various components of light. J Parasitol 91:731–736. doi:10.1645/GE-440R.1

Benesh DP, Seppälä O, Valtonen ET (2009) Acanthocephalan size and sex affect the modification of intermediate host colouration. Parasitology 136:847–854. doi:10.1017/S0031182009006180

Brown SP (1999) Cooperation and conflict in host-manipulating parasites. Proc R Soc B 266:1899. doi:10.1098/rspb.1999.0864

Brown SP, Loot G, Grenfell B, Guégan J (2001) Host manipulation by *Ligula intestinalis*: accident or adaptation? Parasitology 123:519–529. doi:10.1017/S0031182001008678

Brownlie J, Johnson K (2009) Symbiont-mediated protection in insect hosts. Trends Microbiol 17:348–354. doi:10.1016/j.tim.2009.05.005

Cézilly F, Perrot-Minnot M-J (2005) Studying adaptive changes in the behaviour of infected hosts: a long and winding road. Behav Processes 68:223–228. doi:10.1016/j.beproc.2004.08.013

Cézilly F, Grégoire A, Bertin A (2000) Conflict between co-occurring manipulative parasites? An experimental study of the joint influence of two acanthocephalan parasites on the behaviour of *Gammarus pulex*. Parasitology 120:625–630

Cézilly F, Perrot-Minnot M-J, Rigaud T (2014) Cooperation and conflict in host manipulation: interactions among macro-parasites and micro-organisms. Front Microbiol 5:248. doi:10.3389/fmicb.2014.00248

Corrêa F, Chieffi P, Lescano SAZ, dos Santos SV (2014a) Behavioral and memory changes in *Mus musculus* coinfected by *Toxocara canis* and *Toxoplasma gondii*. Rev Inst Med Trop Sao Paulo 56:353–356. doi:10.1590/S0036-46652014000400014

Corrêa LL, Souza GTR, Takemoto RM et al (2014b) Behavioral changes caused by *Austrodiplostomum* spp. in *Hoplias malabaricus* from the São Francisco River, Brazil. Parasitol Res 113:499–503. doi:10.1007/s00436-013-3679-6

Cox DM, Holland CV (1998) The relationship between numbers of larvae recovered from the brain of *Toxocara canis*-infected mice and social behaviour and anxiety in the host. Parasitology 116:579–594

Cox DM, Holland CVC (2007) Relationship between three intensity levels of *Toxocara canis* larvae in the brain and effects on exploration, anxiety, learning and memory in the murine host. J Helminthol 75:33–41. doi:10.1079/JOH200028

Da Silva RC, Langoni H (2009) *Toxoplasma gondii*: host-parasite interaction and behavior manipulation. Parasitol Res 105:893–898. doi:10.1007/s00436-009-1526-6

De Queiroz ML, Viel TA, Papa CHG et al (2013) Behavioral changes in *Rattus norvegicus* coinfected by *Toxocara canis* and *Toxoplasma gondii*. Rev Inst Med Trop Sao Paulo 55:51–53. doi:10.1590/S0036-46652013000100009

Dezfuli BS, Giari L, Poulin R (2000) Species associations among larval helminths in an amphipod intermediate host. Int J Parasitol 30:1143–1146. doi:10.1016/S0020-7519(00)00093-X

Dianne L, Rigaud T, Léger E et al (2010) Intraspecific conflict over host manipulation between different larval stages of an acanthocephalan parasite. J Evol Biol 23:2648–2655. doi:10.1111/j.1420-9101.2010.02137.x

Dianne L, Perrot-Minnot M-J, Bauer A et al (2011) Protection first then facilitation: a manipulative parasite modulates the vulnerability to predation of its intermediate host according to its own developmental stage. Evolution 65:2692–2698. doi:10.5061/dryad.jc86t

Dianne L, Bollache L, Lagrue C et al (2012) Larval size in acanthocephalan parasites: influence of intraspecific competition and effects on intermediate host behavioural changes. Parasit Vectors 5:166. doi:10.1186/1756-3305-5-166

Dianne L, Perrot-Minnot M-J, Bauer A et al (2014) Parasite-induced alteration of plastic response to predation threat: increased refuge use but lower food intake in *Gammarus pulex* infected with the acanothocephalan *Pomphorhynchus laevis*. Int J Parasitol 44:211–216. doi:10.1016/j.ijpara.2013.11.001

Ezenwa VO, Gerardo NM, Inouye DW et al (2012) Animal behavior and the microbiome. Science 338:198–199. doi:10.1126/science.1227412

Fauchier J, Thomas F (2001) Interaction between *Gammarinema gammari* (Nematoda), *Microphallus papillorobustus* (Trematoda) and their common host *Gammarus insensibilis* (Amphipoda). J Parasitol 87:1479–1481. doi:10.1645/0022-3395(2001)087[1479:IBGGNM]2.0.CO;2

Feldhaar H (2011) Bacterial symbionts as mediators of ecologically important traits of insect hosts. Ecol Entomol 36:533–543. doi:10.1111/j.1365-2311.2011.01318.x

Fereres A, Moreno A (2009) Behavioural aspects influencing plant virus transmission by homopteran insects. Virus Res 141:158–168. doi:10.1016/j.virusres.2008.10.020

Fischer P, Krueger J (2011) The bystander-effect: a meta-analytic review on bystander intervention in dangerous and non-dangerous emergencies. Psychol Bull 13:517–537. doi:10.1037/a0023304

Flegr J (2013) How and why *Toxoplasma* makes us crazy. Trends Parasitol 29:156–163. doi:10.1016/j.pt.2013.01.007

Franceschi N, Bauer A, Bollache L, Rigaud T (2008) The effects of parasite age and intensity on variability in acanthocephalan-induced behavioural manipulation. Int J Parasitol 38:1161–1170. doi:10.1016/j.ijpara.2008.01.003

Franceschi N, Bollache L, Cornet S et al (2010) Co-variation between the intensity of behavioural manipulation and parasite development time in an acanthocephalan–amphipod system. J Evol Biol 23:2143–2150. doi:10.1111/j.1420-9101.2010.02076.x

Fredensborg BL, Longoria AN (2012) Increased surfacing behavior in longnose killifish infected by brain-encysting trematode. J Parasitol 98:899–903. doi:10.1645/GE-3170.1

Giles N (1983) Behavioural effects of the parasite *Schistocephalus solidus* (Cestoda) on an intermediate host, the three-spined stickleback, *Gasterosteus aculeatus* L. Anim Behav 31:1192–1194. doi:10.1016/S0003-3472(83)80025-6

Giles N (1987) A comparison of the behavioural responses of parasitized and non-parasitized three-spined sticklebacks, *Gasterosteus aculeatus* L., to progressive hypoxia. J Fish Biol 30:631–638. doi:10.1111/j.1095-8649.1987.tb05790.x

Hafer N, Milinski M (2015) When parasites disagree: evidence for parasite-induced sabotage of host manipulation. Evolution 69:611–620. doi:10.1111/evo.12612

Haine ER (2008) Symbiont-mediated protection. Proc Biol Sci 275:353–361. doi:10.1098/rspb.2007.1211

Haine ER, Boucansaud K, Rigaud T (2005) Conflict between parasites with different transmission strategies infecting an amphipod host. Proc R Soc B 272:2505–2510. doi:10.1098/rspb.2005.3244

Hammerschmidt K, Koch K, Milinski M et al (2009) When to go: optimization of host switching in parasites with complex life cycles. Evolution 63:1976–1986. doi:10.1111/j.1558-5646.2009.00687.x

Helluy S (2013) Parasite-induced alterations of sensorimotor pathways in gammarids: collateral damage of neuroinflammation? J Exp Biol 216:67–77. doi:10.1242/jeb.073213

Holmes JC, Bethel WM (1972) Modification of intermediate host behaviour by parasites. Zool J Linn Soc 51:123–149

Hoogland R, Morris D, Tinbergen N (1956) The spines of sticklebacks (*Gasterosteus* and *Pygosteus*) as means of defence against predators (*Perca* and *Esox*). Behaviour 10:205–236. doi:10.1163/156853956X00156

Houte S, Ros VVID, Oers M et al (2013) Walking with insects: molecular mechanisms behind parasitic manipulation of host behaviour. Mol Ecol 22:3458–3475. doi:10.1111/mec.12307

Hughes DP (2013) Pathways to understanding the extended phenotype of parasites in their hosts. J Exp Biol 216:142–147. doi:10.1242/jeb.077461

Koella JC, Rieu L, Paul REL (2002) Stage-specific manipulation of a mosquito's host-seeking behavior by the malaria parasite *Plasmodium gallinaceum*. Behav Ecol 13:816–820. doi:10.1093/beheco/13.6.816

Koella JC, Hurd H, Biron DG (2006) New prospects for research on manipulation of insect vectors by pathogens. PLoS Pathog 2:633–635. doi:10.1371/journal.ppat.0020072

Lacroix R, Mukabana W, Gouagna L, Koella JC (2005) Malaria infection increases attractiveness of humans to mosquitoes. PLoS Biol 3:1590–1593. doi:10.1371/journal.pbio.0030298

Lafferty KD (2006) Can the common brain parasite, *Toxoplasma gondii*, influence human culture? Proc Biol Sci 273:2749–2755. doi:10.1098/rspb.2006.3641

Lafferty KD, Morris AK (1996) Altered behavior of parasitized killifish increases susceptibility to predation by bird final hosts. Ecology 77:1390–1397. doi:10.2307/2265536

Lafferty KD, Shaw JC (2013) Comparing mechanisms of host manipulation across host and parasite taxa. J Exp Biol 216:56–66. doi:10.1242/jeb.073668

Lagrue C, Poulin R (2008) Intra- and interspecific competition among helminth parasites: effects on *Coitocaecum parvum* life history strategy, size and fecundity. Int J Parasitol 38:1435–1444. doi:10.1016/j.ijpara.2008.04.006

Latané B, Nida S (1981) Ten years of research on group size and helping. Psychol Bull 89:308–324. doi:10.1037/0033-2909.89.2.308

Latham ADM, Poulin R (2002) Effect of acanthocephalan parasites on hiding behaviour in two species of shore crabs. J Helminthol 76:323–326. doi:10.1079/JOH2002139

Lefèvre T, Lebarbenchon C, Gauthier-Clerc M et al (2009) The ecological significance of manipulative parasites. Trends Ecol Evol 24:41–48. doi:10.1016/j.tree.2008.08.007

Leung TLF, Poulin R (2007) Interactions between parasites of the cockle *Austrovenus stutchburyi*: hitch-hikers, resident-cleaners, and habitat-facilitators. Parasitology 134:247–255. doi:10.1017/S0031182006001478

Leung TLF, Poulin R (2010) Intra-host competition between co-infecting digeneans within a bivalve second intermediate host: dominance by priority-effect or taking advantage of others? Int J Parasitol 41:449–454. doi:10.1016/j.ijpara.2010.11.004

Lightle D, Lee J (2014) Raspberry viruses affect the behavior and performance of A*mphorophora agathonica* in single and mixed infections. Entomol Exp Appl 151:57–64. doi:10.1111/eea.12170

LoBue CCP, Bell M (1993) Phenotypic manipulation by the cestode parasite *Schistocephalus solidus* of its intermediate host, *Gasterosteus aculeatus*, the threespine stickleback. Am Nat 142:725–735. doi:10.1086/285568

Luong LT, Hudson PJ, Braithwaite VA (2011) Parasite-induced changes in the anti-predator behavior of a cricket intermediate host. Ethology 117:1019–1026. doi:10.1111/j.1439-0310.2011.01951.x

Mauck K, Bosque-Pérez NA, Eigenbrode SD et al (2012) Transmission mechanisms shape pathogen effects on host-vector interactions: evidence from plant viruses. Funct Ecol 26:1162–1175. doi:10.1111/j.1365-2435.2012.02026.x

Maure F, Brodeur J, Ponlet N et al (2011) The cost of a bodyguard. Biol Lett 7:843–846. doi:10.1098/rsbl.2011.0415

Milinski M (1985) Risk of predation of parasitized sticklebacks (*Gasterosteus aculeatus* L.) under competition for food. Behaviour 93:203–216. doi:10.1163/156853986X00883

Milinski M (1990) Parasites and host decision-making. In: Barnard CJ, Behnke JM (eds) Parasitism and host behaviour. Taylor & Francis Group, London, pp 95–116

Milinski M (1997) How to avoid seven deadly sins in the study of behavior. Adv Stud Behav 26:159–180. doi: 10.1016/S0065-3454(08)60379-4

Milinski M (2014) The past and the future of behavioral ecology. Behav Ecol 25:680–684. doi:10.1093/beheco/aru079

Moore J (2002) Parasites and the behavior of animals. Oxford University Press, New York

Moore J (2013) An overview of parasite-induced behavioral alterations – and some lessons from bats. J Exp Biol 216:11–17. doi:10.1242/jeb.074088

Mouritsen KN (2002) The parasite-induced surfacing behaviour in the cockle *Austrovenus stutchburyi*: a test of an alternative hypothesis and identification of potential mechanisms. Parasitology 124:521–528. doi:10.1017/S0031182002001427

Mouritsen KN, Poulin R (2003) Parasite-induced trophic facilitation exploited by a non-host predator: a manipulator's nightmare. Int J Parasitol 33:1043–1050. doi:10.1016/S0020-7519(03)00178-4

Outreman Y, Bollache L, Plaistow S, Cézilly F (2002) Patterns of intermediate host use and levels of association between two conflicting manipulative parasites. Int J Parasitol 32:15–20. doi:10.1016/S0020-7519(01)00304-6

Parker GA, Ball MA, Chubb JC et al (2009) When should a trophically transmitted parasite manipulate its host? Evolution 63:448–458. doi:10.1111/j.1558-5646.2008.00565.x

Perrot-Minnot M-J, Cézilly F (2013) Investigating candidate neuromodulatory systems underlying parasitic manipulation: concepts, limitations and prospects. J Exp Biol 216:134–141. doi:10.1242/jeb.074146

Petney T, Andrews R (1998) Multiparasite communities in animals and humans: frequency, structure and pathogenic significance. Int J Parasitol 28:377–393. doi:10.1016/S0020-7519(97)00189-6

Poulin R (1994) The evolution of parasite manipulation of host behaviour: a theoretical analysis. Parasitology 109:109–118

Poulin R (1995) "Adaptive" parasitized changes in the behaviour of animals: a critical review. Int J Parasitol 25:1371–1383. doi:10.1016/0020-7519(95)00100-X

Poulin R (2010) Parasite manipulation of host behavior: an update and frequently asked questions. Adv Study Behav 41:151–186. doi:10.1016/S0065-3454(10)41005-0

Poulin R, Thomas F (1999) Phenotypic variability induced by parasites: extent and evolutionary implications. Parasitol Today 15:28–32. doi:10.1016/S0169-4758(98)01357-X

Poulin R, Valtonen ET (2001) Interspecific associations among larval helminths in fish. Int J Parasitol 31:1589–1596. doi:10.1016/S0020-7519(01)00276-4

Poulin R, Curtis M, Rau M (1992) Effects of *Eubothrium salvelini* (Cestoda) on the behaviour of *Cyclops vernalis* (Copepoda) and its susceptibility to fish predators. Parasitology 105:265–271. doi:10.1017/S0031182000074199

Poulin R, Nichol K, Latham ADM (2003) Host sharing and host manipulation by larval helminths in shore crabs: cooperation or conflict? Int J Parasitol 33:425–433. doi:10.1016/S0020-7519(03)00002-X

Rauque CA, Paterson RA, Poulin R, Tompkins DM (2011) Do different parasite species interact in their effects on host fitness? A case study on parasites of the amphipod *Paracalliope fluviatilis*. Parasitology 138:1176–1182. doi:10.1017/S0031182011000928

Rigaud T, Haine ER (2005) Conflict between co-occurring parasites as a confounding factor in manipulation studies? Behav Processes 68:259–262. doi:10.1016/j.beproc.2004.09.005

Rode NO, Lievens EJP, Flaven E et al (2013) Why join groups? Lessons from parasite-manipulated Artemia. Ecol Lett 16:493–501. doi:10.1111/ele.12074

Salvaudon L, De Moraes CM, Mescher MC (2013) Outcomes of co-infection by two potyviruses: implications for the evolution of manipulative strategies. Proc R Soc B. doi:10.1098/rspb.2012.2959

Santiago Bass C, Weis JS (2009) Conspicuous behaviour of *Fundulus heteroclitus* associated with high digenean metacercariae gill abundances. J Fish Biol 74:763–772. doi:10.1111/j.1095-8649.2008.02148.x

Santos EGN, Santos CP (2013) Parasite-induced and parasite development-dependent alteration of the swimming behavior of fish hosts. Acta Trop 127:56–62. doi:10.1016/j.actatropica.2013.03.008

Santos EGN, Cunha RA, Santos CP (2011) Behavioral responses of *Poecilia vivipara* (Osteichthyies: Cyprinodontiformes) to experimental infections of *Acanthocollaritrema umbilicatum* (Digenea: Cryptogonimidae). Exp Parasitol 127:522–526. doi:10.1016/j.exppara.2010.10.018

Seppälä O, Karvonen A, Valtonen ET (2005) Manipulation of fish host by eye flukes in relation to cataract formation and parasite infectivity. Anim Behav 70:889–894. doi:10.1016/j.anbehav.2005.01.020

Seppälä O, Karvonen A, Valtonen ET (2011) Eye fluke-induced cataracts in natural fish populations: is there potential for host manipulation? Parasitology 138:209–214. doi:10.1017/S0031182010001228

Sparkes TC, Wright VM, Renwick DT (2004) Intra-specific host sharing in the manipulative parasite *Acanthocephalus dirus*: does conflict occur over host modification? Parasitology 129:335–340. doi:10.1017/S0031182004005564

Srinivasan R, Alvarez JM (2007) Effect of mixed viral infections (Potato virus Y-Potato leafroll virus) on biology and preference of vectors *Myzus persicae* and *Macrosiphum euphorbiae* (Hemiptera: Aphididae). J Econ Entomol 100:646–655. doi:10.1603/0022-0493(2007)100[646:EOMVIP]2.0.CO;2

Syller J (2012) Facilitative and antagonistic interactions between plant viruses in. Mol Plant Pathol 13:204–216. doi:10.1111/J.1364-3703.2011.00734.X

Thomas F, Mete K, Helluy S et al (1997) Hitch-hiker parasites or how to benefit from the strategy of another parasite. Evolution (NY) 51:1316–1318

Thomas F, Poulin R, Renaud F (1998a) Nonmanipulative parasites in manipulated hosts: 'hitch-hikers' or simply 'lucky passengers'? J Parasitol 84:1059–1061

Thomas F, Renaud F, Poulin R (1998b) Exploitation of manipulators: "hitch-hiking" as a parasite transmission strategy. Anim Behav 56:199–206. doi:10.1006/anbe.1998.0758

Thomas F, Fauchier J, Lafferty KD (2002) Conflict of interest between a nematode and a trematode in an amphipod host: test of the "sabotage" hypothesis. Behav Ecol Sociobiol 51:296–301. doi:10.1007/s00265-001-0442-2

Thomas F, Poulin R, Brodeur J (2010) Host manipulation by parasites: a multidimensional phenomenon. Oikos 119:1217–1223. doi:10.1111/j.1600-0706.2009.18077.x

Thomas F, Brodeur J, Maure F et al (2011) Intraspecific variability in host manipulation by parasites. Infect Genet Evol 11:262–269. doi:10.1016/j.meegid.2010.12.013

Urdal K, Tierney JF, Jakobsen PJ (1995) The tapeworm *Schistocephalus solidus* alters the activity and response, but not the predation susceptibility of infected copepods. J Parasitol 81:330–333

Vickery WL, Poulin R (2009) The evolution of host manipulation by parasites: a game theory analysis. Evol Ecol 24:773–788. doi:10.1007/s10682-009-9334-0

Wedekind C, Milinski M (1996) Do three-spined sticklebacks avoid consuming copepods, the first intermediate host of *Schistocephalus solidus*?—An experimental analysis of behavioural resistance. Parasitology 112:371–383. doi:10.1017/S0031182000066609

Weinreich F, Benesh DP, Milinski M (2013) Suppression of predation on the intermediate host by two trophically-transmitted parasites when uninfective. Parasitology 140:129–135. doi:10.1017/S0031182012001266

Wisenden BD, Martinez-Marquez JY, Gracia ES, McEwen DC (2012) High intensity and prevalence of two species of trematode metacercariae in the fathead minnow (*Pimephales promelas*) with no compromise of minnow anti-predator competence. J Parasitol 98:722–727. doi:10.1645/GE-2454.1

Chapter 5
Can Parasites Change Thermal Preferences of Hosts?

Elżbieta Żbikowska and Anna Cichy

5.1 Introduction

The notion that temperature is a master variable controlling animal biochemistry, physiology, and behavior needs no explanation. In the physiological range elevated temperature accelerates biochemical changes and increases cellular metabolic rate, leading to accelerated growth, early sexual maturity and ability to reproduce (Thomas and Blanford 2003). All organisms have thermal optimum at which their biological processes reach maximum potential, and slow down below and above this limit (Gutierrez et al. 2003). Whereas at temperatures below the optimum the effects of the blocked progress are usually reversible, at temperatures above the optimum they are permanent, as a consequence of protein denaturation. Literature provides many examples of how temperature affects the growth and fertility of organisms (Aziz and Raut 1996; Gilbert and Raworth 1996; Gillooly et al. 2002; Aggiletta et al. 2004; Żuo et al. 2012).

Free living and parasitic ectotherms, whose body temperature depends mainly on the temperature of the surroundings, constitute a particularly valuable source of information about the relationship between temperature and physiology (Jonhston and Bennett 1996; Portner 2002; Żippay et al. 2004; Muñoz et al. 2005). Thus ectothermic hosts of parasites posing a threat to humans and animals have always inspired research. Referred to as vectors of malaria, Anopheles mosquitoes transmitting *Plasmodium* sp., develop more rapidly at elevated temperatures (Bayoh and Lindsay 2003). Similarly, *Biomphalaria glabrata* snails, the source of cercariae of human schistosomes, significantly accelerate egg hatching at temperatures raised by 10–15 °C (Sturrock and Sturrock 1972). A rise in temperature affects the development of micro- and macroparasites in ectothermic hosts (Lv et al. 2006; Harvell

E. Żbikowska (✉) • A. Cichy
Department of Invertebrate Zoology, Faculty of Biology and Environment Protection, Nicolaus Copernicus University in Toruń, Toruń, Poland
e-mail: ezbikow@umk.pl; Anna.Cichy@umk.pl

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et al. 1999, 2002): it accelerates the multiplication of polyhedrosis virus in *Bombyx mori* (Kobayashi et al. 1981), significantly shortens the development of different *Plasmodium* sp. in definitive hosts (Fialho and Schall 1995; Craig et al. 1999) as well as the development of tapeworm larvae (Macnab and Barber 2011) and trematodes (Studer et al. 2010) in intermediate hosts.

Beside geological factors, temperature, distinguishing climate zones, has greatly contributed to the present species distribution in the world. In the animal kingdom adaptations to low temperatures are extremely important for free living endotherms and ectotherms. Moreover, the geographical range limits of parasites transmitted in both groups of hosts are determined indirectly or directly by thermal conditions. Temperature, affecting the distribution of endothermic hosts, indirectly determines the range limits of their parasites. Host migrations as well as human activity leading to the introduction (whether conscious or not) of certain species to new areas are responsible for expanding the range limits of parasites. The direct correlation between temperature and parasite transmission in different climate zones results from the parasite ability to produce resting forms (cysts or eggs resistant to frost penetration) aiding the propagation of the species, as well as from incorporating ectothermic hosts in parasite lifecycles. Since the body temperature of ectotherms is usually the same as that of the surroundings, parasitic lifecycle stages in ectothermic hosts are directly affected by this factor (Marcgoliese 2008; Blanar et al. 2009). The increased prevalence of parasitic forms in thermally polluted water bodies located in cold climate zones may serve as an example (Eure 1976; Hoglund and Thulin 1990; Żbikowska et al. 2014). In addition, the direct effect of temperature on parasites is well illustrated by area prevail of endemic malaria in human populations: it is much smaller than what would be expected from the range limits of endothermic and ectothermic hosts (i.e. people and malarial mosquitos) participating in the transmission (Howes et al. 2013).

The topic of how temperature determines the boundaries of parasitic human and animal invasions has been frequently discussed in view of the forthcoming global warming (Harvell et al. 2002; Brooks and Hoberg 2007; Mas-Coma et al. 2008; Marcgoliese 2008; Meerburg and Kijlstra 2009; Dobson 2009; Lafferty 2009; Adamo and Lovett 2011; Paull and Johnson 2011; Studer and Poulin 2014). Remarkably, arguments accentuating the threat of "global warming" draw attention to numerous research projects including the investigation into thermal behavior of ectotherms. The ability of ectotherms to select thermal conditions in the environment has already been analyzed in numerous pioneering studies (Reynolds and Casterlin 1976; Reynolds 1977a, b; Casterlin and Reynolds 1979a; Reynolds 1979; Reynolds and Casterlin 1979a, b; Richards et al. 1977; Casterlin and Reynolds 1980a, b; Kingsolver and Watt 1983). While in some ectothermic species thermoreceptive organs have already been identified (Sullivan 1954; Murray 1959; Bailey 1969; Ploomi et al. 2004), in other (molluscs) the existence of such organs is presumed, based solely on the observations of thermal behavior of these animals (Sokolova et al. 2000).

The majority of studies on thermal behavior of ectotherms focuses on behavioral fever, a defensive reaction of organisms invaded by pathogens (viruses, bacteria,

fungi) or parasites (protists, metazoa), (Kluger 1979; Bernheim and Kluger 1976; Bronstein and Conner 1984; Myhre et al. 1997; Kalsbeek 2001; Ouedraogo et al. 2003, 2004). Behavioral fever in response to the infection by pathogens was reported in reptiles (Vaughn et al. 1974), bony fish (Reynolds et al. 1976), amphibians (Casterlin and Reynolds 1977), and numerous invertebrates (Casterlin and Reynolds 1979b, 1980b; Louis et al. 1986; Watson et al. 1993; Lefcort and Eiger 1993; Inglis et al. 1996; Adamo 1998; Blanford et al. 1998; Blanford and Thomas 1999, 2000; Starks et al. 2000; Elliot et al. 2002; Roode and Lefevre 2012). The temptation to find parallels between the mechanisms of fever in ectotherms and endotherms triggered search for similar elements involved in the induced increase in body temperature in the representatives of both groups (Stanley 2006; Nakamura 2011; Boltaña et al. 2013). The investigation provided some interesting results, which, if treated with due care, may enable researchers to expand the knowledge of the mechanisms of thermal behavior of ectotherms.

Owing to the monoxenic lifecycle and a very short ontogenesis, the impact of pathogens on their hosts is usually limited to provoking a defensive reaction, including a fever response. On the other hand, created through co-evolution, long-lasting host-parasite relationships seem to be more complex; defense reactions of hosts are considerably limited or even used for the propagation of parasites (Dobson and Carper 1992). In this case, responses to parasitic invasion can include not only behavioral fever but also behavioral anapyrexia, i.e. reverse fever, ensuring the stability of the relationship on the specimen level (Muller and Schmid-Hempel 1993; Adamo 1998; Moore and Freehling 2002; Macnab and Barber 2011; Żbikowska 2011).

In long-lasting relationships changes in the body temperature of ectothermic hosts can benefit the following: (i) the host (ii) the parasite, (iii) the host and the parasite (Fialho and Schall 1995; Lefèvre et al. 2008). Behavioral fever, though exhausting for hosts (Boorstein and Ewald 1987) leads to the mobilization of phagocytes and the production of defense humoral factors (Boltaña et al. 2013). However, increased body temperature of hosts resulting from their migration to warmer microenvironments accelerates parasitic growth (Eling et al. 2001; Paull and Johnson 2011), increases the number of parasitic offspring (Koprivnikar and Poulin 2009), and boost the invasive potential of parasitic larvae released into the environment (Thieltges and Rick 2006). For this reason, it is difficult to classify an increase in the host body temperature as a reaction aimed at exterminating intruders, considering that the thermal tolerance of the parasite is often higher than that of the host (Moore 2002). On the other hand, lowering thermal preferendum extends the life of the infected host but extends the production of parasite propagules (Żbikowska 2006), also contributing to the success of the latter.

Moreover, literature provides numerous examples of how parasites manipulate thermal preferences of their hosts and describes cases in which host thermal behavior helps parasites reach successive stages in their heteroxenic life cycle (see review by Dawkins 2012). The “manipulation hypothesis”, however, is still the subject of controversy in the scientific community. Although there is abundant evidence that behavioral changes observed in infected hosts enhance parasite propagation (see

review by Thomas et al. 2005), conflicting interpretations abound (Kavaliers and Colwell 1992; Campbell et al. 2010). Minchella (1985) maintains that changes of this kind have no adaptive value for parasites and can only be viewed as mere coincidences. Moore and Gotelli (1990) believe that the fact that a parasite invade the host nervous system is never caused by its "desire" to control host behavior but by the wish to avoid host defense. Host altered behavior, beneficial for the parasite, seems "fortuitous payoff". Finally, Poulin (1995), a keen supporter of the hypothesis of manipulation, emphasizes the fact that parasites transmitted in food chains benefit coincidentally when the infected parasite donor feeds intensively thus exposing itself for the consumption by parasite recipient. The author mentions certain conditions that must be met so that behavioral changes of infected hosts can be considered the signs of manipulation: (i) they must be complex, (ii) they must show symptoms of purpose, (iii) they should occur independently in different lineages of parasites, (iv), they should significantly increase the fitness of one of the counterparts.

It is not always possible to analyze cases considered parasite-induced changes in host thermal preferences according to Poulin's guidelines. The key to determine whether parasites manipulate hosts or not is to understand the mechanism of the observed modifications. The majority of available publications focus on speculations only and fail to explain the molecular background. Despite this drawback, presented evidence of parasite impact on host thermal behavior provides good basis for further analysis. A variety of host-parasite relationships allows for an assessment of thermobehavioral adaptations in different lineages.

Due to their medical or economic importance, three groups of ectothermic hosts, i.e. molluscs, arthropods, and fish are subject to investigation on parasite-induced changes in thermal behavior. Molluscs, and snails in particular, are key hosts in lifecycle of Digenea. In arthropods, insects serve as vectors of malaria and filariasis, but also as pollinators which determine agricultural production. Interest in their thermal preferences results from both the advances of biological control of vectors of parasitosis and veterinary care over beneficial insects. Finally, the economic importance of fish and possible losses in fish farms caused by parasites encourage research on various aspects of host-parasite interactions, including those related to thermal preferences.

5.2 Example 1: Snails and Parasites

Digenean trematodes are strongly associated with snails. Remarkably, over 85 % of these parasites use gastropods as their first intermediate hosts – they develop their early larval stages in several hundred species of Gastropoda (Combes et al. 1980; Faltýnková et al. 2007, 2008; Żbikowska and Nowak 2009; Cichy et al. 2011). The influence of ambient temperature on snail physiology has been studied by many authors (Hylleberg 1975; Costil 1994; Navarro et al. 2002; Britton and McMahon 2004). Kavaliers (1992) and Sokolova et al. (2000) suggest that snails have

thermodetecting organs and can choose or avoid some thermal microhabitats in the environment. This fact may indicate that the migration of snails in the thermally diversified environment is not accidental. Aware of the healing effect of behavioral fever, Leffcort and Bayne (1991) studied thermal preferences of *Biomphalaria glabrata* infected with *Schistosoma mansoni*, determined to assess whether parasite invasion will affect host thermal behavior. The failure to obtain symptoms of behavioral fever in *Biomphalaria* and an unyielding attitude of Cabanac and Rossetti (1987) regarding the phylogeny of fever and mollusc inability to display this defense response, led to the stagnation in the research into parasite impact on snail thermal behavior.

Over 10 years ago, while we were investigating the prevalence of larval Digenea in populations of freshwater snails, we observed that the fitness of *Lymnaea stagnalis* hosts kept in different thermal conditions depended on the parasite species (Żbikowska 2004). Since available literature failed to provide any data on thermal preferences of *L. stagnalis* infected with trematodes, we decided to investigate whether gastropods have the ability to generate a behavioral fever response. Although the initial results indicated that the mean daily value calculated of the temperatures selected in thermal gradient (Fig. 5.1) by *L. stagnalis* infected with immature sporocysts of *Plagiorchis elegans* or *Diplostomum pseudospathaceum* was slightly higher than the mean daily calculated for control snails (free of infection), the difference was only around 1 °C ($P=0.0499$). Surprisingly, the results of our research showed that snails releasing fully formed cercaria (i.e. snails with a patent invasion) of certain trematode species selected significantly lower (5 °C difference, $P<0.001$) temperature than control snails. Further research established that *L. stagnalis* with a patent invasion of *Trichobilharzia szidati* (Żbikowska 2005), *Plagiorchis elegans*, *Diplostomum pseudospathaceum* (Żbikowska 2011), or *Notocotylus attenuatus* (Żbikowska and Żbikowski 2015), as well as *Planorbarius corneus* with a patent invasion of *Notocotylus ephemera*, showed signs of behavioral anapyrexia (Żbikowska and Cichy 2012) (Fig. 5.2). In spite of many attempts

Fig. 5.1 A set for automatic registration of snail thermal preferences. Snails move in a chamber with an oblong thermal gradient (temperature range: +8 to +38 °C). The position is recorded by the infrared sensors connected to thermocouples. The data are transferred to a computer and stored by GRAD software

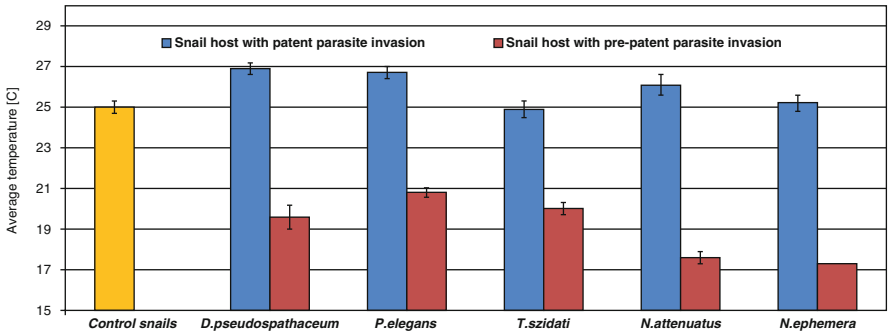

Fig. 5.2 Mean daily values calculated of temperatures selected by *Lymnaea stagnalis* (infected with *Diplostomum pseudospathaceum*, *Plagiorchis elegans*, *Trichobilharzia szidati* or *Notocotylus attenuatus*) and *Planorbarius corneus* (infected with *Notocotylus ephemera*). Only the preferences of snails with a patent invasion were statistically significantly different from the preferences of uninfected snails (control snails) and from the preferences of snails with a pre-patent invasion ($p < 0.001$)

to analyze reversed fever in endotherms, the mechanism of this process is still poorly understood (Clemmer et al. 1992; Steiner and Branco 2003). Observations indicate that it is a response to the injection of high doses of pyrogens (Amaral et al. 2002). However, it has not yet been determined whether the fact that snails with a patent trematode invasion select cooler places can be considered behavioral anapyrexia. Taking into account that a metabolic rate and oxygen consumption decrease at low temperatures, and that weakened snails have a higher survival probability (Torsten 2005), it can be concluded that the observed thermobehavioral reaction of hosts releasing cercariae ensured a longer lifetime for parasites. Our laboratory experiment conducted at constant temperatures demonstrated that snails infected with the majority of parasites mentioned above lived longer at a lower (<20 °C) than at a higher temperature (>25 °C). This suggests that the symptoms of behavioral anapyrexia displayed by infected snails extended the duration of their interaction with parasites. Not only does this behavior prolong host survival but it also increases chances for parasite success by allowing more parasite larvae within a single infected host (Żbikowska 2005; Żbikowska and Cichy 2012; Żbikowska and Żbikowski 2015).

We continued the research on thermal preferences of snails with a patent trematode invasion (releasing cercariae) and with a pre-patent invasion (before releasing cercariae, developing sporocysts and/or redia). All investigated specimens of the latter group selected a relatively high temperature of 25 + 1 °C in the thermal gradient, which seems interesting in view of the fact that these animals normally inhabit lakes in the temperate climate zone. In the majority of cases the temperature was similar to that selected by non-infected snails (Fig. 5.2). Our laboratory experiments indicate that at elevated temperatures the metabolic rate of snails increased, causing accelerated reproduction and improved egg production in non-infected specimens (Żbikowska 2006), and leading to accelerated parasite growth in infected specimens, unable to breed because of the invasion. As previously mentioned, keeping

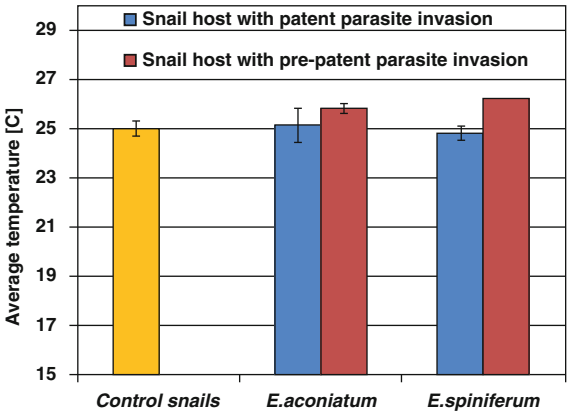

Fig. 5.3 The mean daily values of temperatures selected by *P. corneus* and *L. stagnalis* with echinostomes invasion. There were no statistically significant differences between thermal preferences of snails under study

infected individuals at a constant elevated temperature shortened their life but, according to Hechinger et al. (2009), trematodes castrating snails affect host thermal preferences to ensure their own success, not host fitness. In addition, under natural conditions snails had the opportunity to adjust the body temperature to, for example, the specific stage of parasite development (Bates et al. 2011), which was not possible in the laboratory.

L. stagnalis infected with *Echinoparyphium aconiatum* and *P. corneus* infected with *Echinostoma spiniferum* constituted a particularly interesting experimental group. Similarly to snails with a pre-patent invasion of other species and to uninfected snails, specimens with a pre-patent invasion of the above echinostomes tended to move to the warmer end of the thermal gradient (Fig. 5.3). However, increased temperature proved fatal: under these conditions infected snails lived for the shortest period of time (Żbikowska 2006; Żbikowska and Żbikowski 2015). Moreover, unlike hosts of other trematode species, snails releasing echinocercariae in the thermal gradient showed no symptoms of behavioral anapyrexia (Żbikowska 2005; Żbikowska and Cichy 2012; Żbikowska and Żbikowski 2015). In a series of additional tests we made several interesting discoveries. Unlike other trematode species, echinostomes use snails as second intermediate hosts. Moreover, they frequently choose the same snail species which served as their first intermediate hosts. However, due to the high mortality of the previously infected hosts, the transmission of echinocercariae to snails already releasing cercariae is rarely successful (Sorensen and Minchella 1998). Similar thermal preferences of infected and uninfected snails provide an opportunity for parasites to be successfully transmitted, supposing that the preferences are the same in the natural environment.

It should be noted, however, that the accelerated death of the first intermediate hosts of echinostomes at an elevated temperature shortens the time when parasites can shed cercariae. In order to establish how this affects parasite transmission we investigated the rate of echinocercariae emission in different thermal conditions. We discovered that at a temperature of 25 ± 1 °C the rate of cercariae emission from first hosts is twice as high as at 19 ± 1 °C. In addition, echinocercariae invasiveness

towards second intermediate hosts increases in direct proportion to temperature (Żbikowska 2006; Żbikowski and Żbikowska 2009). Thus the fact that first hosts of echinostomes remain at elevated temperatures increases their mortality, but promotes parasite transmission.

Based on the understanding of lifecycles of all investigated parasites and on the monitoring of seasonal changes in their prevalence in snails populating lakes of northern Poland (Fig. 5.4) we made an assumption that *E. spiniferum*, and *E. aconiatum* winter in snails in the form of metacercariae, not sporocysts, as is the case with *D. pseudospathaceum* and *P. elegans*. The presence of snails with a patent invasion of echinostomes in the coastal zone in the warmest months (July-August) facilitates parasite transmission, leading to the exhaustion of first intermediate hosts (Żbikowska 2006; Cichy 2013). The development strategy of the investigated echinostomes involves a short but intensive exploitation of first intermediate hosts because easy transmission to second intermediate hosts (snails) guarantees their extended survival in the environment in the form of metacercariae, relatively harmless for hosts (Fried and Graczyk 2000). The consumption of metacercariae by birds completes the parasitic lifecycle. The comparison of reproductive strategies of the investigated echinostomes and other trematode species shows that the presence or absence of the symptoms of behavioral anapyrexia is a decisive factor in parasite transmission (Fig. 5.5). *D. seudospathaceum* cercariae leave a snail to penetrate a host fish (Valtonen and Gibson 1997). Extending the relationship with the snail extends the emission of invasive larvae. The cercariae of bird schistosomes *T. szidati* leave a snail to find a final host (Meuleman et al. 1983). Also in this case, cercariae emission, extended for many weeks, increases the likelihood of parasite reproductive success. Finally, in the strategy developed by the two studied species of notocotylids, the released cercariae quickly transform into metacercariae, which wait to be ingested by definitive hosts (Żdarska 1964). It can be assumed that again an extended interaction with intermediate hosts increases the likelihood of parasite success by extending their availability to definitive hosts.

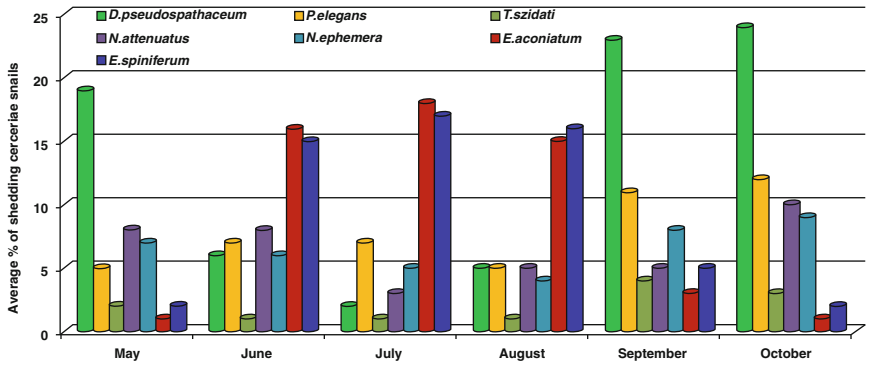

Fig. 5.4 Seasonal dynamics of the prevalence of patent invasions of 7 trematode species in snails collected in the coastal zone of lakes

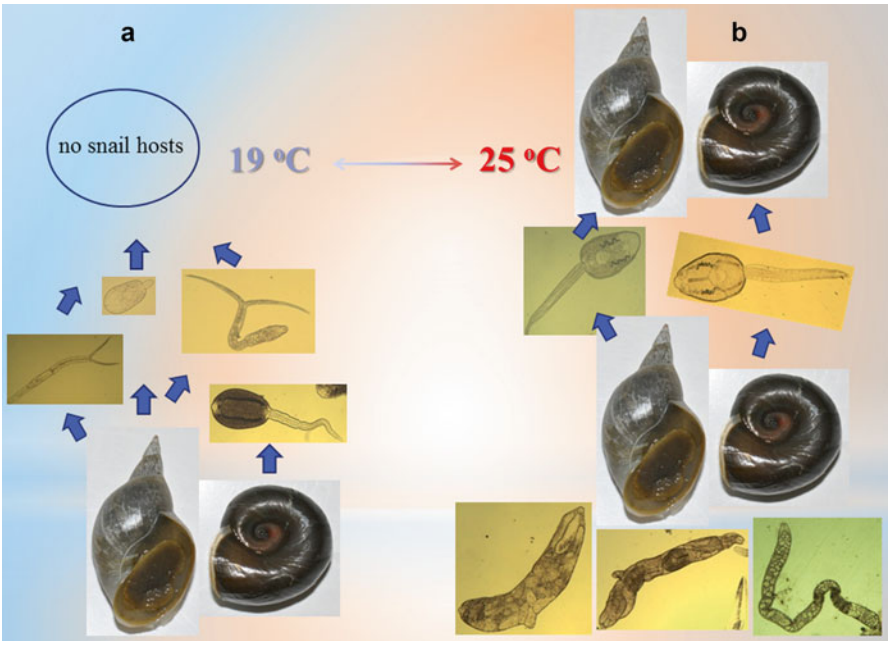

Fig. 5.5 Snail thermal preferences in view of Digenea lifecycles. (**a**) At lower temperatures host snails for a long time release cercariae: *Diplostomum pseudospathaceum* (target: fish), *Plagiorchis elegans* (target: insect larvae), *Trichobilharzia szidati* (target: water birds), and larvae encysting into metacercariae: *Notocotylus attenuatus* and *N. ephemera*. Extended larval shedding and increased survival of both host-seeking cercariae and encysted metacercariae improves chances for parasite reproductive success (Żbikowska 2006). (**b**) At elevated temperatures uninfected snails accelerate their development (Hodasi 1976); in snails with a pre-patent invasion of *Diplostomum pseudospathaceum*, *Plagiorchis elegans*, *Trichobilharzia szidati*, *Notocotylus attenuatus*, *N. ephemera*, *Echinoparyphium aconiatum*, *Echinostoma spiniferum* parasite larvae develop faster, and echinocercariae released from snails (i) find more effectively and (ii) invade sooner second intermediate hosts (Żbikowski and Żbikowska 2009) (Author of photographs: Anna Cichy)

The above examples of the correlation between snail thermal behavior and parasite invasion do not confirm host manipulation. However, it is worth emphasizing that various trematode species can take advantage of thermal preferences of even the same host species. This observation may indicate that host thermal behavior is a response to the presence of parasitic larvae.

Diverse parasite-induced changes in thermal biology of the first intermediate host *Zeacumantus subcarinatus* infected with two castrating trematodes, *Maritrema novaezealandesis* and *Philophthalamus* sp. as well as an interesting analysis of the manipulation of host thermal behavior were presented by Bates et al. (2011). The authors discovered that the animals acclimated to high temperatures (35 and 40 °C) for a short period of time (1 h) became more resistant to these temperatures in the environment. The tolerance of specimens infected with *M. novaezealandesis* was significantly higher than the tolerance of specimens infected with *Philophthalamus* sp. According to the authors, high tolerance to heat

observed in the hosts of *M. novaezealandesis* constitutes an important element of their adaptation to high temperature in their habitat. In the experiment larvae of *M. novaezealandesis* survived a one-hour exposure to 40 °C whereas larvae of *Philophthalamus* sp. failed to survive. Although a higher number of *Philophthalamus* sp. cercariae were released at temperatures above 25 °C, parasite rediae responded badly to increased temperature. The authors also accentuated that the hosts of double invasions (with *M. novaezealandesis* and *Philophthalamus* sp.) were more tolerant to a rise in temperature than individuals infected only with *Philophthalamus* sp. They interpreted this as a possible effect of some substances (hormone-like compounds and regulatory peptides) secreted by *M. novaezealandesis*. The authors' suggestion make it clear why snails infected with this parasite selected warmer places in the thermal gradient. The influence of a hypothetical *Maritrema*-derived substance on snail behavior would make parasites more effective at competing for space in the environment. In these circumstances, the reduced fitness of hosts may be viewed as a problem of secondary importance and a side effect of "manipulation". This is consistent with the results obtained by Fredensborg et al. (2005), who maintained that regardless of thermal conditions, the development of infected individuals carries higher costs.

To sum up the observations of *Z. subcarinatus* infected with two trematode species, Bates et al. (2011) suggested four possible explanations of the observed changes in thermal biology of parasitized snails: (i) the impact of different parasites on thermal responses of the same host may vary but generally depends on "the spatial segregation or pathy distribution of conspecific hosts harboring different parasite species as they seek microhabitats with contrasting thermal properties", (ii) the effect of temperature on infected hosts can change over a long period of time, (iii) in certain conditions a co-infection can enhance chances for parasite success, (iv) parasites may manipulate host thermal preferences.

It is hard to resist the logic of the above arguments suggesting the impact of trematodes on thermal biology of their first intermediate hosts. However, we firmly believe that only when the effect of "hormone-like compounds and regulatory peptides" (or any other substance) on the mechanism of the observed thermoregulatory reactions is sufficiently recognized, will the real causes of this phenomenon be revealed. We have already initiated research on behavioral fever in *P. corneus*. In a series of experiments using a thermal gradient we have established that the snails exhibit symptoms of behavioral fever in response to injections of bacterial, fungal (Żbikowska et al. 2013a), and viral (Żbikowska et al. 2013b) pyrogens. Inoculating snails with pyrogens normally used to trigger sterile inflammation in endotherms was aimed at determining whether these animals respond to substances used effectively in comparative thermal biology of different endo- and ectothermic species. Positive effects of the experiments encouraged us to investigate the impact of antipyretics on behavioral fever induced by pyrogens. We are convinced that the results of our research as well as the discovery that *P. corneus* can produce substances involved in fever reactions in endotherms (see review by Coyne 2011) will enable us to understand the mechanism of snail thermal behavior controlled (?) by parasites.

5.3 Example 2: Insects and Parasites

Research on thermal behavior of insects focuses on both behavioral fever and the relationship between host thermal preferences and parasite success. An interesting analysis of the interactions between honeybees and monoxenic *Nosema ceranae* was delivered by Campbell et al. (2010). In their experiment bees infected with microsporidia selected higher temperatures than uninfected specimens. Pointing out that *N. ceranae* shows increased fertility at elevated temperatures (Martin-Hernandez et al. 2009), the authors concluded that observed differences between thermal preferences of infected and uninfected insects are induced by parasites, the main beneficiaries of the changes.

It must be accentuated that the choice of honeybees was not random. *N. ceranae*, originally known as a parasite of Asian *Apis cerana*, has recently been identified in other pollinators such as *Apis mellifera* in Taiwan (Huang et al. 2007), bumblebee in South America (Plischuk et al. 2009), China (Li et al. 2012) and Europe (Graystock et al. 2013) and is now considered a serious threat to bumblebee and bee colonies around the world. The authors are convinced that the parasite's leap into new areas and its effective competition with *N. apis* may be associated with an increased reproduction of this species in bees, which select a higher temperature under the influence of microsporidia. Regardless of whether the changes in thermal preferences of infected bees can be considered an example of manipulating host thermal behavior or only a side effect of parasite invasion, the natural selection in parasite genes aimed at exploiting the host raised thermal preferendum considerably increases the success of the former, thus fulfilling one of Poulin's conditions (1995).

Not only monoxenic parasites benefit from altered thermal preferences of infected insect hosts. Heteroxenic parasites, including *Plasmodium* sp., can also increase their chances for successful transmission. Many species of these etiological vectors of malaria divide their lifecycle between ectothermic definitive and endothermic intermediate hosts (Collins and Jeffery 2007). This fact encourages reflection on parasite possibility to control thermal behavior of ectothermic hosts in order to (i) find endothermic hosts more effectively (ii) adapt insect preferences to the temperature optimal for parasite development. The results of the research on thermoreception and its contribution to helping infected mosquitoes find endothermic hosts indicate that temperature plays a role in this process (Maekawa et al. 2011). However, there are more examples indicating the possibility of manipulating thermal preferences of insect hosts during intra-insect parasite development, i.e. from gametocyte to sporozoite stage.

Interesting observations were made by Fialho and Schall (1995), who studied the transmission of *Plasmodium mexicanum* by flies of the *Lutzomyia vexator*. Analyzing the behavior of flies infected with *P. mexicanum*, the authors concluded that the parasites were able to manipulate their hosts and that the manipulation shortened parasite development in definitive hosts. Given the high mortality rate of infected vectors (only 2 % survive two meals, vital for parasite reproductive success), temperature-dependent acceleration of parasite growth within the insect

significantly facilitates parasite propagation. The experiment was conducted in the temperature range well tolerated by both hosts and parasites, i.e. 16–32 °C. The authors established that once flies consumed vertebrate blood, they moved to warmer environments to raise their body temperature. This improved their digestion and accelerated egg laying. However, the temperature selected by flies which consumed blood contaminated with parasites was higher than that preferred by uninfected specimens. The observation that at temperatures above 22 °C parasite growth in the insect was significantly accelerated justified the hypothesis of parasite manipulation of host thermal behavior. The authors, analyzing the curves of "parasite development" (sporozoites traveling from mature oocysts to sandfly salivary glands) and "sandfly feeding schedule" (sandfly finds a suitable oviposition site, lays eggs and is ready for another blood meal) emphasize the fact that a temperature rise has a more significant influence on the development of parasite oocysts than on host reproduction. This complies with Poulin's criterion (1995) of host manipulation by a parasite.

The experiment showed that not all insect-*Plasmodium* sp. relationships can be regarded as cases of parasite manipulation of host thermal behavior. Blanford et al. (2009) studying *Anopheles stephensi* mosquitoes infected with *Plasmodium yoelii* found no differences between the thermal preferences of experimental and control specimens. However, they made an important observation that in the thermal gradient both the control and experimental insects selected temperature ranging between 24 and 28 °C, which had a favorable effect on both the insect reproduction and early stages of parasite development (Noden et al. 1995; Kirby and Lindsay 2004). We believe that this temperature range was sufficient to fulfill lifecycles of both counterparts in *A. stephensi – P. yoelli* relationship.

These two examples prove that a categorical evaluation of thermal preferences in a host-parasite relationship, cannot be provided. The fact that thermal optima of the counterparts overlap, seriously hampers the interpretation. We believe that the comparison of mean temperatures calculated for time intervals shorter than 24 h would make it possible to see the differences between control and experimental insects. Parasite development may depend not only on mean daily temperatures, but also on temperature fluctuations recorded over shorter periods of time. It should be accentuated that since temperature regulates physiological processes of both counterparts, their mutual influence may escape arbitrary statistical analysis.

The presence of parasites in insects may lead to increasing or lowering the host thermopreferendum, compared to the control group. As was demonstrated in the subchapter on snails and trematodes, ectotherms are capable of generating symptoms of behavioral anapyrexia, i.e. selecting lower temperatures in response to parasite invasion. The therapeutic effect of low temperatures has already been recorded in insects infected with parasitoids (Muller and Schmid-Hempel 1993) and in certain parasitic infections.

Moore and Freehling (2002) studied the effect of temperature-sensitive acanthocephalan *Moniliformis moniliformis* on thermal behavior of two species of cockroaches. Although mean temperatures calculated of the values selected by infected and uninfected insects were similar, they observed inhibited parasite development

in both host species when the cockroaches had the possibility to choose thermal conditions (compared to hosts kept at a constant, relatively high temperature of 28 or 30 °C). The authors concluded that reduced temperature might have a healing effect on infected hosts, which had been already emphasized in the earlier publication by Moore (2002). Nevertheless, it cannot be excluded that selecting colder microenvironments by infected insects can also benefit parasites, offering more time to synchronize the presence of donor and recipient hosts in the environment (Combes 1999). The authors do not analyze the results of their laboratory experiment in relation to the natural habitat of infected insects. As is well-known, the delayed development of parasites, correlated with phenological conditions, facilitates their transmission (Mackauer and Sequeira 1993).

The selected examples of parasite-induced modifications of insect thermal behavior show different types of these changes: increased thermopreferendum, reduced thermopreferendum or no reaction. However, changes in thermal biology of hosts always bring real or potential benefits for parasites. These profits result either from accelerated parasite transmission to a subsequent host (for monoxenic *N. ceranae* or heteroxenic *Plasmodium* sp. whose survival depends on the ability of the insect to consume two meals) or extended interaction with the host (cockroach-*M. moniliformis* relationship).

These examples demonstrate that arbitrary statistical analysis restricts the interpretation of the results. When thermal tolerance ranges of the host and parasite overlap, the possible impact of the latter on the thermal behavior of the first can be difficult to identify, especially when the comparison is based on the mean value of the temperatures selected in 24 h (*A. stephensi* – *P. yoelli* example). We appreciate the significance of the analysis of the cockroach – *M. moniliformis* relaltionship, in which the authors used a more sophisticated method of comparing the impact of the constant temperature versus the temperature selected by insects in the thermal gradient.

5.4 Example 3: Fish and Parasites

A great number of parasite invasions in fish is temperature-related. It is generally known that too low temperature of water is responsible for fungal infections and a higher mortality rate in aquarium fish. On the other hand, an elevated temperature mobilizes hosts' immune system and increases their ability to eliminate pathogens (Butler et al. 2013).

Similarly to the previously examined examples of invertebrate hosts, in vertebrates more complex temperature-related responses accompany parasitic invasions. The complexity again results from the host-parasite co-evolution, by which parasites, through mimicry (Hurford and Day 2013), the suppression of host defense mechanisms (Christensen and LaFond 1986) or location in areas inaccessible for host digestive enzymes (Fischer and Freeman 1973), are able to survive within hosts and produce propagules as well as use host physiology and behavior for the

transmission. Numerous examples of temperature-dependent parasitic invasions in fish were presented by Khan (2012).

Macnab and Barber (2011) tested the hypothesis that an increase in temperature aggravates the conflict between the tapeworm *Schistocephalus solidus* and *Gasterosteus aculeatus* fish species. Maintained at 20 °C for 8 weeks the tapeworm larvae (plerocercoids) reached an invasive size in experimentally infected fish. In contrast, kept at 15 °C for the same amount of time they failed to do so. In addition, the authors used a set of interconnected aquariums with different water temperature, in which they observed thermal preferences of fish infected with young or mature (ready for transmission) plerocercoids. Fish infected with young larvae selected significantly lower temperatures than the hosts of the invasive parasite stages. Since the dose of parasitic material was comparable to the dose of parasitic fungi that causes behavioral fever, it was expected that the infected fish would increase rather than reduce their thermopreferendum. However, assuming that the host reaction bearing the symptoms of behavioral anapyrexia (which, as previously mentioned, in endotherms is generated in response to high doses of pyrogen) is typical of *S. solidus* invasion, it must be considered a surprise that *G. aculeatus* invaded by large (older) plerocercoids, ready for further invasion, chose the aquarium with the warmest water.

Thermal behavior of fish infected with plerocercoids cannot be explained by energy deficiency resulting from parasite invasion. It is obvious that this energy shortage was more severe in specimens infected with older larvae and that a higher degree of host exhaustion would justify their selecting colder environments. Although this analysis is largely speculative, it must be accentuated that in both host groups it was the parasite that was the beneficiary of the altered thermal behavior of the host. The migration of the fish infected with young plerocecoids to colder places (in the natural environment to the deeper parts of a water body) protected larvae incapable of further transmission from premature ingestion by definitive hosts (birds). At the same time fish infected with mature, invasive plerocercoids migrated to warmer places (in the natural environment to the surface of a water body) and became easier prey for final hosts, thus increasing the likelihood of parasite transmission. Not knowing the mechanism of the observed thermobehavioral reactions, the authors do not reject the possibility that they are a by-product of parasite invasion. However, it is obvious that fish behavior contributes to the reproductive success of parasite.

The above example indicates that regardless of the systematic position, ectothermic hosts can respond to the presence of parasites by altering their thermal preferences. That complies with Poulin's requirement (1995) of an independent emergence of similar reactions to parasite invasion in different evolutionary lineages of hosts. A trophic link between fish and fish-eating birds creates a convenient route of transmission for many parasitic species. In life cycles of these parasites fish act as intermediate hosts, and birds, as final (Loot et al. 2001; Pérez-del-Olmo et al. 2014). Numerous studies focus on increased availability of infected fish for bird hosts as a consequence of alterations in fish behavior or appearance caused by the invasion of parasitic larvae (see review by Mikheev 2011). Such spectacular changes as

blindness (Crowden and Broom 1980), reduced ability to escape (shifted center of mass, blocked fins) (Maillard 1976) and impaired mimicry (Bullard and Overstreet 2008), indicate beyond all doubt that the problems are caused by parasites trying to improve their transmission. Nevertheless, the theory that parasite-induced changes in thermal biology of fish hosts facilitate parasite transmission is difficult to prove and requires detailed research into the physiology and metabolism of these animals.

5.5 Conclusions

The above examples of changes in host thermal biology present a range of host-parasite interactions shaped by evolution. Repeated in different evolutionary lineages, the responses of ectothermic hosts to parasite invasions, based on the selection of higher or lower temperatures than uninfected animals, seem particularly interesting. It is obvious that thermobehavioral reactions alone, so difficult to interpret in terms of statistical analysis, fail to prove definitively parasite contribution to manipulating host behavior. However, the results of numerous studies lead to the conclusion that parasite transmission is always facilitated by altered thermal preferences of hosts. Falsifying the hypothesis of the parasite impact on host thermal behavior, it can be assumed that differences between thermal biology of infected and uninfected specimens result from the mobilization of their immune system due to the increased thermopreferendum. On the other hand, lowering the body temperature is connected with the depletion of the host's energy resources. However, the results obtained by the authors mentioned in this chapter indicate that host reactions depend on parasite species. Different thermobehavioral reactions of the same host species to two different parasite species (albeit invading the same body tissues) are particularly useful to prove that the observed changes are not random. Regardless of whether thermal biology of infected hosts can be regarded as a sign of manipulation, the fact that the parasites use their host thermal preferences to improve their transmission is a remarkable feature. Hence the assumption that a possibility to modify parasite-induced changes in thermal biology of hosts is determined by a parasite lifecycle. Here too, as in the case of snails-echinostomes versus snails-other trematodes, two types of relationships are possible: (i) a short, but intense, highly pathogenic for the host, or (ii) extended on the specimen level, less pathogenic for the host. The combination of thermal experiments and studies on various aspects of the physiology of host-parasite interactions would provide additional evidence for the still speculative analysis.

In our opinion, at present it is not possible to determine whether the observed parasite-induced changes in host thermal biology can be considered the manipulation of host physiology. This topic requires a detailed investigation into the mechanism of thermobehavioral reactions. We believe that exploring the issue using methods generally applied in the research on fever and anapyrexia in endotherms will provide an insight into the nature of thermal behavior of ectothermic hosts.

References

Adamo SA (1998) The specificity of behavioral fever in the cricket *Acheta domesticus*. J Parasitol 84:529–533

Adamo SA, Lovett MME (2011) Some like it hot: the effects of climate change on reproduction, immune function and disease resistance in the cricket *Gryllus texensis*. J Exp Biol 214:1997–2004

Aggiletta MJ Jr, Steury TD, Sears MW (2004) Temperature, growth rate, and body size in Ectotherms: fitting pieces of a life-history puzzle. Integr Comp Biol 44:498–509

Amaral JPS, Marvin GA, Hutchison VH (2002) The influence of bacterial lipopolysaccharide on the thermoregulation of the box turtle *Terrapene carolina*. Phys Biol Zool 75:273–282

Aziz MD, Raut SK (1996) Thermal effect on the life-cycle parameters of the medically important freshwater snail species Lymnaea (Radix) luteola (Lamarck). Mem Inst Oswaldo Cruz 91:119–128

Bailey SER (1969) The responses of sensory receptors in the skin of the green lizard, *Lacerta viridis*, to mechanical and thermal stimulation. Comp Biochem Physiol 29:161–172

Bates AE, Leiterer F, Wiedeback ML, Poulin R (2011) Parasitized snails take the heat: a case of host manipulation? Oecologia 167:613–621

Bayoh MN, Lindsay SW (2003) Effect of temperature on the development of the aquatic stages of *Anopheles gambiae* sensu stricto (Diptera: Culicidae). Bull Entomol Res 93:375–381

Bernheim HA, Kluger MJ (1976) Fever and antypyresis in the lizard *Dipsosaurus dorsalis*. Am J Physiol 231:198–203

Blanar CA, Munkittrick KR, Houlahan J, Maclatchy DL, Marcogliese DJ (2009) Pollution and parasitism in aquatic animals: a meta-analysis of effect size. Aquat Toxicol 93:18–28

Blanford S, Thomas MB (1999) Host-thermal biology: the key to understanding host-pathogen interactions and microbial pest control? Agr Forest Entomol 1:195–202

Blanford S, Thomas MB (2000) Thermal behavior of two acridid species: effects of habitat and season on body temperature and the potential impact on biocontrol with pathogens. Environ Entomol 29:1060–1069

Blanford S, Read AF, Thomas MB (2009) Thermal behaviour of *Anopheles stephensi* in response to infection with malaria and fungal entomopathogens. Malar J 8:72, DOI:10.1186/1475-2875-8-72

Blanford S, Thomas MB, Langewald J (1998) Behavioural fever in the Senegalense grasshopper, *Oedaleus senegalensis*, and its implications for biological control using pathogens. Ecol Entomol 23:9–14

Boltaña S, Rey S, Roher N, Vargas R, Huerta M, Huntingford FA, Goets WF, Moore J, Garcia-Valtanen P, Estepa A, MacKenzie S (2013) Behavioural fever is asynergic signal amplifying the innate immune response. Proc R Soc B 280:2013 1381, http://dx.doi.org/10.1098/rspb.2013.1381

Boorstein SM, Ewald PW (1987) Costs and benefits of behavioural fever in *Melanoplus sanguinipes* infected by *Nosema acridophagus*. Physiol Zool 60:586–595

Britton DK, McMahon RF (2004) Seasonal and artificially elevated temperatures influence bioenergetic allocation patterns in the common pond snail, *Physella virgata*. Physiol Biochem Zool 77:187–196

Bronstein SM, Conner WE (1984) Endotoxin-induced behavioural fever in the Madagascar cockroach. Gromphadorhina portentosa. J Ins Physiol 30:327–330

Brooks DR, Hoberg EP (2007) How will global climate change affect parasite–host assemblages? Trends Parasitol 23:571–574

Bullard SA, Overstreet RM (2008) Digeneans as enemies of fishes. In: Eiras J, Segner H, Wahil T, Kapoor BG (eds) Fish diseases. Science Publishers, Enfield, New Hampshire, pp 817–976

Butler MW, Stahlschmidt ZR, Ardia DR, Davis S, Davis J, Guillette LJ Jr, Johnson N, McCormick SD, McGraw KJ, DeNardo DF (2013) Thermal sensitivity of immune function: evidence against a generalist-specialist trade-off among endothermic and ectothermic vertebrates. Am Nat 181:761–774

Cabanac M, Rossetti Y (1987) Fever in snails, reflection on a negative result. Comp Biochem Physiol A 87:1017–1020
Campbell J, Kessler B, Mayack C, Naug D (2010) Behavioural fever in infected honeybees: parasitic manipulation or coincidental benefit? Parasitology 137:1487–1496
Casterlin ME, Reynolds WW (1977) Behavioral fever in anuran amphibian larvae. Life Sci 20:593–596
Casterlin ME, Reynolds WW (1979a) Behavioral thermoregulation in the grass shrimp, *Palaemonetes vulgaris* (Say). Rev Can Biol 38:45–46
Casterlin ME, Reynolds WW (1979b) Fever induced in marine arthropods by prostaglandin E1. Life Sci 25:1601–1603
Casterlin ME, Reynolds WW (1980a) Behavioral response of the New England dog whelk, *Nassarius trivittatus*, to a temperature gradient. Hydrobiologia 69:79–81
Casterlin ME, Reynolds WW (1980b) Fever and antipyresis in the crayfish *Cambarus bartoni*. J Physiol (Lond) 303:417–421
Christensen BM, LaFond MM (1986) Parasite-induced suppression of the immune response in *Aedes aegypti* by *Brugia pahangi*. J Parasitol 72:216–219
Cichy A (2013) Rozprzestrzenienie i różnorodność przywr digenicznych (Trematoda: Digenea) w populacjach wodnych gatunków ślimaków (Mollusca: Gastropoda) z terenu Pojezierza Brodnickiego. PhD thesis, Nicolaus Copernicus University
Cichy A, Faltynkova A, Żbikowska E (2011) Cercariae (Trematoda, Digenea) in European freshwater snails a checklist of records from over one hundred years. Folia Malacol 19:165–189
Clemmer TP, Fisher CJ, Bone RC, Slotman GJ, Metz CA, Thomas FO (1992) Hypothermia in the sepsis syndrome and clinical outcome. Crit Care Med 20:1395–1401
Collins WE, Jeffery GM (2007) *Plasmodium malariae*: parasite and disease. Clin Microbiol Rev 20:579–592
Combes C (1999) Ekologia i ewolucja pasożytnictwa. Długotrwałe wzajemne oddziaływania. Wydawnictwo Naukowe PWN, Warszawa, 628pp
Combes C, Albaret JL, Arvy L, Bartoli P, Bayssade–Dufour C, Deblom S, Durette-Desset MC, Gabrion C, Jourdane J, Lambert A, Leger N, Maillerd C, Matricon M, Nassi H, Prevost G, Richard J, Theron A (1980) Atlas Mondiale des Cercaires. Museum National d'Histoire Naturelle, Paris, 235pp
Costil K (1994) Influence of temperature on survival and growth of two freshwater planorbid species, *Planorbarius corneus* and *Planorbis planorbis*. J Moll Stud 60:223–235
Coyne VC (2011) The importance of ATP in the immune system of molluscs. Inv Surv J 8:48–55
Craig MH, Snow RW, Sueur D (1999) A climate based distribution model of malaria transmission in sub-Saharan Africa. Parasitol Today 15:105–111
Crowden AE, Broom DM (1980) Effects of eye-fluke, *Diplostomum spathaceum*, on the behavior of dace (*Leuciscus leuciscus*). Anim Behav 28:287–294
Dawkins R (2012) Host manipulation by parasites. Oxford University Press, Oxford, 240pp
Dobson AP (2009) Climate variability, global change, immunity, and the dynamics of infectious diseases. Ecology 90:920–927
Dobson A, Carper R (1992) Global warming and potential changes in host-parasite and disease-vector relationships. In: Peters RL, Lovejoy TE (eds) Global warming and biodiversity. Yale University Press, New Haven, pp 201–207
Eling W, Hooghof J, van de Vegte-Bolmer M, Sauerwein R, Van Gemert G (2001) Tropical temperatures can inhibit development of the human malaria parasite Plasmodium falciparum in the mosquito. In: Proceedings of the Section Experimental and Applied Entomology. Netherlands Entomological Society, Amsterdam, pp 151–156
Elliot SL, Blanford S, Thomas MB (2002) Host-pathogen interactions in a varying environment: temperature, behavioural fever and fitness. Proc R Soc Lond 269:1599–1607
Eure H (1976) Seasonal abundance of *Neoechinorhynchus cylindratus* taken from largemouth bass (*Micropterus salmoides*) in a heated reservoir. Parasitology 73:355–370

Faltýnková A, Našincová V, Kablasková L (2007) Larval trematodes (Digenea) of great pond snails, *Lymnaea stagnalis* (L.), (Gastropoda, Pulmonata) in Central Europe: a survey of species and key to their identification. Parasite 14:39–51

Faltýnková A, Našincová V, Kablasková L (2008) Larval trematodes (Digenea) of planorbid snails (Gastropoda:Pulmonata) in Central Europe: a survey of species and key to their identification. Syst Parasitol 69:155–178

Fialho RG, Schall JJ (1995) Thermal ecology of a malarial parasite and its insect vector: consequences for the parasite's transmission success. J Anim Ecol 64:553–562

Fischer H, Freeman RS (1973) The role of plerocercoids in the biology of *Proteocephalus ambloplitis* (Cestoda) maturing in smallmouth bass. Can J Zool 51:133–141

Fredensborg BL, Mouritsen KN, Poulin R (2005) Impact of trematodes on host survival and population density in the intertidal gastropod *Zeacumantus subcarinatus*. Mar Ecol Prog Ser 290:109–117

Fried B, Graczyk TK (2000) Echinostomes as experimental models for biological research. Kluwer Academic Publishers, Dordrecht/Boston, p 273

Gilbert N, Raworth DA (1996) Insects and temperature: a general theory. Can Entomol 128:1–13

Gillooly J, Charnov EL, West GB, Savage VM, Brown JH (2002) Effects of size and temperature on developmental time. Nature 417:70–73

Graystock P, Yates K, Darvill B, Goulson D, Hughes WHO (2013) Emerging dangers: deadly effects of an emergent parasite in a new pollinator host. Int J Parasitol 114:114–119

Gutierrez A, Pointer JP, Yong M, Sanchez J, Theron A (2003) Evidence of phenotypic differences between resistant and susceptible isolates of *Pseudosuccinea columella* (Gastropoda: Lymnaeidae) to *Fasciola hepatica* (Trematoda: Digenea) in Cuba. Parasitol Res 90:129–134

Harvell CD, Kim K, Burkholder JM, Colwell RR, Epstein PR, Grimes DJ, Hofman EE, Lip EK, Osterhaus ADME, Overstreet RM, Porter JW, Smith GW, Vasta GR (1999) Emerging marine diseases-climate links and anthropogenic factors. Science 285:1505–1510

Harvell CD, Mitchell CE, Ward JR, Altizer S, Dobson AP, Ostfeld RS, Samuel MD (2002) Ecology – climate warming and disease risks for terrestrial and marine biota. Science 296:2158–2162

Hechinger RF, Laffarty KD, Mancini FT, Warner RR, Kuris AM (2009) How large is the hand in the puppet? Ecological and evolutionary factors affecting the body mass of 15 trematode parasitic castrators in their snail host. Evol Ecol 23:651–667

Hodasi JK (1976) The effects of low temperature on *Lymnaea truncatula*. Z Parasitenkd 48:281–286

Hoglund J, Thulin J (1990) The epidemiology of the metacercariae of *Diplostomum baeri* and *Diplostomum spathaceum* in perch (*Perca fluviatilis*) from the warm water effluent on a nuclear-power station. J Helminthol 64:139–150

Howes RE, Dewi M, Piel FB, Monteiro WM, Battle KE, Messina JP, Sakuntabhai A, Satyagraha AW, Williams TN, Baird JK, Hay SJ (2013) Spatial distribution of G6PD deficiency variants across malaria-endemic regions. Malar J 12:418–433

Huang W-F, Jiang J-H, ChenY-W, Wang Ch-H (2007) A *Nosema ceranae* isolate from the honeybee *Apis mellifera*. Apidologie 38:30–37

Hurford A, Day T (2013) Immune evasion and the evolution of molecular mimicry in parasites. Evolution 67:2889–2904

Hylleberg J (1975) The effect of salinity and temperature on egestion in mud snails (Gastropoda: Hydrobiidae). Oecologia 21:279–289

Inglis GD, Johnson DL, Goettel MS (1996) Effects of temperature on thermoregulation on mycosis by *Beauveria bassiana* in grasshoppers. Biol Contr 7:131–139

Jonhston LA, Bennett AF (1996) Animals and temperature: phenotypic and evolutionary adaptation. Society of Experimental Biology. Seminar Series. Cambridge Univ Press, Cambridge/ New York, 419pp

Kalsbeek V (2001) Field studies of Entomophthora (Zygomycetes: Entomophthorales) – induced behavioral fever in *Musca domestica* (Diptera: Muscidae) in Denmark. Biol Contr 21:264–273

Kavaliers M (1992) Opioid systems, behavioral regulation and shell polymorphism in the land snail, *Cepaea nemoralis*. J Comp Physiol 162:172–178
Kavaliers M, Colwell DD (1992) Parasitism, opioid systems and host behaviour. Adv Neuroimmunol 2:287–295
Khan RA (2012) Host-parasite interactions in some fish species. J Parasitol Res. doi:10.1155/2012/237280
Kingsolver J, Watt W (1983) Thermoregulatory strategies in Colias Butterflies: thermal stress and the limits of adaptation in temporally varying environments. Am Nat 121:32–55
Kirby MJ, Lindsay SW (2004) Responses of adult mosquitoes of two sibling species, *Anopheles arabiensis* and *A. gambiae* s.s. (Diptera: Culicidae) to high temperatures. Bull Entomol Res 94:441–448
Kluger MJ (1979) Fever in ectotherms: evolutionary implications. Am Zool 19:295–304
Kobayashi M, Inagaki S, Kawase S (1981) Effect of high temperature on the development of nuclear polyhedrosis virus in the silkworm, *Bombyx mori*. J Invertebr Pathol 38:386–394
Koprivnikar J, Poulin R (2009) Effects of temperature, salinity, and water level on the emergence of marine cercariae. Parasitol Res 105:957–965
Lafferty KD (2009) The ecology of climate change and infectious diseases. Ecology 90:888–900
Lefcort H, Bayne CJ (1991) Thermal preferences of resistant and susceptible strains of Biomphalaria glabrata (Gastropoda) exposed to Schistosoma mansoni (Trematoda). Parasitology 103:357–362
Lefcort H, Eiger SM (1993) Antipredatory behaviuor of feverish tadpoles: implications for pathogen transmission. Behaviour 126:13–27
Lefèvre T, Roche B, Poulin R, Hurd H, Renaud F, Thomas F (2008) Exploitation of host compensatory responses: the "must" of manipulation? Trends Parasitol 24:435–439
Li J, Chen W, Wu J, Peng W, An J, Schmid-Hempel P, Schmid-Hempel R (2012) Diversity of Nosema associated with bumblebees (*Bombus* spp.) from China. Int J Parasitol 42:49–61
Loot G, Francisco P, Santoull F, Lek S, Guegan JF (2001) The three hosts of the *Ligula intestinalis* (Cestoda) life cycle in Lavernose-Lacasse gravel pit, France. Arch Hydrobiol 152:511–525
Louis C, Jourdan M, Cabanac M (1986) Behavioral fever and therapy in a rickettsia-infected Orthoptera. Am J Physiol 250:R991–R995
Lv S, Zhou XN, Zhang Y, Liu HX, Zhu D, Yin WG, Steinmann P, Wang XH, Jia TW (2006) The effect of temperature on the development of *Angiostrongylus cantonensis* (Chen 1935) in *Pomacea canaliculata* (Lamarck 1822). Parasitol Res 99:583–587
Mackauer M, Sequeira R (1993) Patterns of development in insect parasites. In: Beckage NE, Thompson SN, Federici BA (eds) Parasites and pathogens of insects, vol 1. Academic, New York, pp 1–23
Macnab V, Barber I (2011) Some (worms) like it hot: fish parasites grow faster in warmer water, and alter host thermal preferences. Global Change Biol 18:1540–1548. doi: 10.1111/j.1365-2486.2011.02595.x
Maekawa E, Aonuma H, Nelson B, Yoshimura A, Tokunaga F, Fukumoto S, Kanuka H (2011) The role of proboscis of the malaria vector mosquito *Anopheles stephensi* in host-seeking behavior. Parasit Vectors 4:10. doi:10.1186/1756-3305-4-10
Maillard C (1976) Distomatoses de poissons en milieu lagunaire. PhD thesis, Universite des Sciences et Techniques du Languedoc, Montpellier, 383pp
Marcgoliese DJ (2008) The impact of climate change on the parasites and infectious diseases of aquatic animals. Rev Sci Tech OIE 27:467–484
Martin-Hernandez R, Meana A, Garcia-Palencia P, Marin P, Botias C, Garrido-Bailon E, Barrios L, Higes M (2009) Effect of temperature on the biotic potential of honeybee microsporidia. Appl Environ Microbiol 75:2554–2557
Mas-Coma S, Valero MA, Bargues MD (2008) Effects of climate change on animal and zoonotic helminthiases. Rev Sci Tech Off Int Epiz 27:443–452
Meerburg BG, Kijlstra A (2009) Changing climate-changing pathogens: *Toxoplasma gondii* in North-Western Europe. Parasitol Res 105:17–24

Meuleman EA, Huyer AR, Mooij JH (1983) Maintenance of the life cycle of *Trichobilharzia ocellata* via the duck *Anas platyrhynchos* and the pond snail *Lymnaea stagnalis*. Neth J Zool 34:414–417

Mikheev VN (2011) Monoxenous and heteroxenous fish parasites manipulate the behavior of their hosts in different ways. Zh Obshch Biol 72:183–197

Minchella DJ (1985) Host life-history variation in response to parasitism. Parasitology 90:205–216

Moore J (2002) Parasites and the behavior of animals. Oxford University Press, New York, 338pp

Moore J, Freehling M (2002) Cockroach hosts in thermal gradients suppress parasite development. Oecologia 133:261–266

Moore J, Gotelli NJ (1990) A phylogenetic perspective on the evolution of altered host behaviours: a critical look at the manipulation hypothesis. In: Behnke JM, Bernard CJ (eds) Parasitism and host behaviour. Taylor and Francis, London, pp 193–203

Muller CB, Schmid-Hempel P (1993) Exploitation of cold temperature as defence against parasitoids in bumblebees. Nature 363:65–67

Muñoz JPL, Finke GR, Camus PA, Bozinovic F (2005) Thermoregulatory behavior, heat gain and thermal tolerance in the periwinkle *Echinolittorina peruviana* in central Chile. Comp Bioch Physiol A 142:92–98

Murray RW (1959) The response of the ampullae of Lorenzini to combined stimulation by temperature change and weak direct currents. J Physiol 145:1–13

Myhre K, Cabanac M, Myhre G (1997) Fever and behavioural temperature regulation in the frog *Rana esculenta*. Acta Physiol Scand 101:219–229

Nakamura K (2011) Central circuitries for body temperature regulation and fever. Am J Physiol Regul Integr Comp Physiol 301:R1207–R1228

Navarro JM, Leiva GE, Gallardo CS, Varela C (2002) Influence of diet and temperature on physiological energetics of *Chorus giganteus* (Gastropoda: Muricidae) during reproductive conditioning. N Z J Mar Freshw Res 36:321–332

Noden BH, Kent MD, Beier JC (1995) The impact of variationsin temperature on early *Plasmodium falciparum* development in *Anopheles stephensi*. Parasitology 5:539–545

Ouedraogo RM, Cusson M, Goettel MS, Brodeur J (2003) Inhibition of fungal growth in thermoregulating locusts, *Locusta migratoria*, infected by the fungus *Metarhizium anisopliae* var *acridum*. J Invertebr Pathol 82:103–109

Ouedraogo RM, Goettel MS, Brodeur J (2004) Behavioral thermoregulation in the migratory locust: a therapy to overcome fungal infection. Oecologia 138:312–319

Paull SH, Johnson PTJ (2011) High temperature enhances host pathology in a snail–trematode system: possible consequences of climate change for the emergence of disease. Freshwater Biol 56:767–778

Pérez-del-Olmo A, Georgieva S, Pula HJ, Kostadinova A (2014) Molecular and morphological evidence for three species of Diplostomum (Digenea: Diplostomidae), parasites of fishes and fish-eating birds in Spain. Parasit Vectors 7:502. doi:10.1186/s13071-014-0502-x

Plischuk S, Martín-Hernández R, Prieto L, Lucía M, Botías C, Meana A, Abrahamovich AH, Lange C, Higes M (2009) South American native bumblebees (Hymenoptera:Apidae) infected by *Nosema ceranae* (Microsporidia), an emerging pathogen of honeybees (*Apis mellifera*). Environ Microbiol Rep 1:131–135

Ploomi A, Must A, Merivee E, Luik A, Mänd M (2004) Electrophysiological characterization of the cold receptors in the ground beetle *Pterostichus oblongopunctatus*. Agr Res 2:99–106

Portner HO (2002) Climate variations and the physiological basis of temperature dependent biogeography: systemic to molecular hierarchy of thermal tolerance in animals. Comp Biochem Physiol A 132:739–761

Poulin R (1995) "Adaptive" change in the behavior of parasitized animals: a critical review. Int J Parasitol 25:1371–1383

Reynolds WW (1977a) Temperature as a proximate factor in orientation behavior. J Fish Res Board Can 34:734–739

Reynolds WW (1977b) Fish orientation behavior: an electronic device for studying simultaneous responses to two variables. J Fish Res Board Can 34:300–304
Reynolds WW (1979) Perspective and introduction to the symposium: thermoregulation in ectotherms. Am Zool 19:193–194
Reynolds WW, Casterlin ME (1976) Thermal preferenda and behavioral thermoregulation in three centrarchid fishes. In: Esch GW, McFarlane RW (eds) Thermal ecology II. Technical Information Service, Springfield, pp 185–190
Reynolds WW, Casterlin ME (1979a) Behavioral thermoregulation and the "final preferendum" paradigm. Am Zool 19:211–224
Reynolds WW, Casterlin ME (1979b) Thermoregulatory behavior of the primitive arthropod *Limulus polyphemus* in an electronic shuttlebox. J Thermal Biol 4:165–166
Reynolds WW, Casterlin ME, Covert JB (1976) Behavioural fever in teleost fishes. Nature 259:41–42
Richards FP, Reynolds WW, McCauley RW, Crawshaw LI, Coutant CC, Gift JJ (1977) Temperature preference studies in environmental impact assessments: an overview with procedural recommendations. J Fish Res Board Can 34:728–761
Roode JC, Lefevre T (2012) Behavioral immunity in insects. Insects 3:789–820
Sokolova IM, Granovitch AI, Berger VJ, Johannesson K (2000) Intraspecific physiological variability of the gastropod *Littorina saxatilis* related to the vertical shore gradient in White and North Seas. Mar Biol 137:297–308
Sorensen RE, Minchella DJ (1998) Parasite influences on host life history: *Echinostoma revolutum* parasitism of *Lymnaea elodes* snails. Oecologia 115:188–195
Stanley D (2006) Prostaglandins and other eicosanoids in insects: biological significance. Annu Rev Entomol 51:25–44
Starks PT, Blackie CA, Seeley TD (2000) Fever in honeybee colonies. Naturwissenschaften 87:229–231
Steiner AA, Branco LGS (2003) Fever and anapyrexia in systemic inflammation: intracellular signaling by cyclic nucleotides. Front Biosci 8:1398–1408
Studer A, Poulin R (2014) Analysis of trait mean and variability versus temperature in trematode cercariae: is there scope for adaptation to global warming? Int J Parasitol 44:403–413
Studer A, Thieltges DW, Poulin R (2010) Parasites and global warming: net effects of temperature on an intertidal host-parasite system. Mar Ecol Prog Ser 415:11–22
Sturrock RF, Sturrock BM (1972) The influence of temperature on the biology of *Biomphalaria glabrata* (Say), intermediate host of *Schistosoma mansoni* on St. Lucia, West Indies. Ann Trop Med Parasitol 66:385–390
Sullivan CM (1954) Temperature reception and responses in fish. J Fish Res Board Can 11:153–170
Thieltges DW, Rick J (2006) Effect of temperature on emergence, survival, and infectivity of cercariae of the marine trematode *Renicola roscovita* (Digenea: Renicolidae). Dis Aquat Organ 73:63–68
Thomas MB, Blanford S (2003) Thermal biology in insect-parasite interactions. Trends Ecol Evol 18:344–350
Thomas F, Adamo S, Moore J (2005) Parasitic manipulation: where are we and where should we go? Behav Proc 68:185–199
Torsten H (2005) Respiration rate in *Bithynia tentaculata* (L.) (Gastropoda: Bithynidae) in response to acclimation and acute temperature change. J Moll Stud 71:127–131
Valtonen ET, Gibson DI (1997) Aspects of the biology of diplostomid metacercarial (Digenea) populations occurring in fishes in different localities of northern Finland. Ann Zool Fennici 34:47–59
Vaughn LK, Brenheim H, Kluger MJ (1974) Fever in the lizard *Dipsosaurus dorsalis*. Nature 252:473–474
Watson DW, Mullens BZ, Petersen JJ (1993) Behavioral fever response of *Musca domestica* (Diptera: Muscidae) to infection by *Entomophthora muscae* (Zygomycetes: Entomophthorales). J Invert Pathol 61:10–16

Żbikowska E (2004) Does behavioral fever occur in snails parasitized with trematode larvae? J Thermal Biol 29:675–679

Żbikowska E (2005) Do larvae of *Trichobilharzia szidat*i and *Echinostoma revolutum* generate behavioral fever in *Lymnaea stagnalis* ? Parasitol Res 97:68–72

Żbikowska (2006) Interakcje w układzie żywiciel-pasożyt między błotniarkami *Lymnaea stagnalis* i przywrami z gatunków: *Diplostomum pseudospathaceum*, *Echinoparyphium aconiatum*, *Plagiorchis elegens*. Wydawnictwo UMK, Toruń, 134pp

Żbikowska E (2011) One snail-three Digenea species, different strategies in host-parasite interaction. Anim Biol 61:1–19

Żbikowska E, Cichy A (2012) Symptoms of behavioural anapyrexia-reverse fever as a defence response of snails to fluke invasion. J Invertebr Pathol 109:269–273

Żbikowska E, Nowak A (2009) One hundred years of research on the natural infection of freshwater snails by trematode larvae in Europe. Parasitol Res 105:301–311

Żbikowska E, Żbikowski J (2015) Digenean larvae—the cause and beneficiaries of the changes in host snails' thermal behavior. Parasitol Res. doi:10.1007/s00436-014-4276-z

Żbikowska E, Wrotek S, Cichy A, Kozak W (2013a) Thermal preferences of wintering snails *Planorbarius corneus* (L.) exposed to lipopolysaccharide and zymosan. J Invertebr Pathol 112:57–61

Żbikowska E, Cichy A, Papierkiewicz D (2013b) Viral pyrogen affects thermoregulatory behavior of wintering *Planorbarius corneus* (L.) snails (Mollusca: Gastropoda). J Therm Biol 38:543–547

Żbikowska E, Kletkiewicz H, Walczak M, Burkowska A (2014) Coexistence of *Legionella pneumophila* bacteria and free-living amoebae in lakes serving as a cooling system of a power plant. Water Air Soil Poll 225:2066. doi:10.1007/s11270-014-2066-y

Żbikowski J, Żbikowska E (2009) Invaders of an invader-trematodes in *Potamopyrgus antipodarum* in Poland. J Invertebr Pathol 101:67–70

Żdarska Z (1964) Contribution to the development and species independence of *Notocotylus ephemera* (Nitzsch, 1807) (syn. *N. thienemanni* Szidat L et Szidat Y, 1933) Cs. Parasitology 11:309–318

Żippay ML, Place SP, Hofman GE (2004) The molecular chaperone Hsc70 from eurythermal marine goby exhibits temperature sensitivity during luciferase refolding assays. Comp Biochem Physiol A 138:1–7

Żuo W, Moses ME, West GB, Hou C, Brown JH (2012) A general model for effects of temperature on ectotherm ontogenetic growth and development. Proc Biol Sci 279:1840–1846

Chapter 6
Host Manipulation by *Toxoplasma gondii*

Jaroslav Flegr

The first indices of manipulation activity of *Toxoplasma* appeared in 60–70s of the twentieth century. Hutchison and his coworkers and successors published about 20 papers showing that congenital, acute and even chronic toxoplasmosis have specific impacts on the behavior of infected mice. The infection was associated with hyperactivity in an open field (Hay et al. 1984b, 1983), increased voluntary wheel running (Hay et al. 1985), decreased ability to discriminate between familiar and novel stimuli (Hay et al. 1984a), impairment of motor performance and coordination (Hutchison et al. 1980a), and impairment of memory resulting in learning deficits (Piekarski et al. 1978; Witting 1979), for review see (Hutchison et al. 1980b; Skallová et al. 2006). In nineties, the manipulation activity of *Toxoplasma* started to be systematically studied by Joanne Webster in Oxford on a more suitable animal model, the rat (*Rattus norvegicus*). In contrast to short-lived and toxoplasmosis sensitive mice, in this toxoplasmosis tolerant animal, acute toxoplasmosis quickly proceeds into its latent stage (as usually occurs in humans) in which all clinical symptoms of disease disappear but some specific behavioral symptoms of the parasite manipulation remain apparent for a long time. Infected rats express deficits in learning (Piekarski et al. 1978; Witting 1979), decreased neophobia and increased trappability (Webster et al. 1994), hyperactivity in a familiar environment (Webster 1994) and an increased exploration of a novel object (Berdoy et al. 1995). The most impressive product of manipulation activity described on this stage of research in rats, which was later confirmed also in mice and humans, is the so called Fatal attraction phenomenon, i.e. change their native, inborn fear of the odor of cats into an attraction to this odor (Berdoy et al. 2000). The infected mice and rats visit more often and stay longer in places containing the odor of cat urine. Conversely, they are not attracted by the odor of urine of other species (Vyas et al. 2007).

J. Flegr
Section of Biology, Faculty of Science, Charles University in Prague,
Vinicna 7, 128 44, Prague 204004, Czech Republic
e-mail: Flegr@cesnet.cz

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Some of the toxoplasmosis-associated behavioral changes weaken or even disappear with time from the infection and differ depending on strain of *Toxoplasma* and the species or strain of host. For example, the maximum reduction of mouse activity and maximum impairment of reaction times of infected mice were observed at the peak of pathological symptoms and disappeared before 12 weeks post infection (Hrdá et al. 2000). The fatal attraction phenomenon that was observed in mice 2 months after infection with two Type II strains of *Toxoplasma* (Prugniaud and ME49) did not exist in ME49 after another 5 months; on the other hand, only this strain experienced impaired spatial working memory (Kannan et al. 2010). The *Toxoplasma* infection very often has different, frequently even contrasting, effect on behavior of males and females (Xiao et al. 2012). The Fatal attraction phenomenon was observed only in females of Balb/c mice while a decrease in preference for novel food was observed only in male mice. Infected female mice expressed higher activity in open field test while infected males lower activity. A gene expression study revealed that *Toxoplasma* infection altered the expression of genes involved in the development of the forebrain, neurogenesis, and sensory and motor coordination in females, while in male mice, infection led mainly to modulation of genes associated with olfactory function (Xiao et al. 2012). Large *Toxoplasma* strain specific differences were also observed in the concentration of various neurotransmitters in the brains of artificially infected animals, suggesting that Type I strains of *Toxoplasma* probably express the strongest manipulative activity (Abdoli 2013; Xiao et al. 2013). It is not clear yet, which of the *Toxoplasma*-associated behavioral changes are products of manipulative activity of the parasite aimed to increase the probability of the transmission in latent phase of infection (Holmes and Bethel, 1972), and which are the product of other manipulative activities of parasite, e.g. of the down-regulation of the host immune functions, and which are just transient side-effects of passed acute infection. The most convincing evidence for the manipulative nature of some of the observed toxoplasmosis-associated changes was obtained on other experimental model, namely on humans (Flegr 2013b).

The study of *Toxoplasma* manipulation of human behavior started at early 90s of the past century. The first studies showed that personality profiles of subjects with latent toxoplasmosis (about one third of humans worldwide) specifically differ from personality profile of *Toxoplasma*-free subjects (Flegr and Hrdý 1994). The intensity of changes in some personality factors increases with time since the infection or with decreases in anti-*Toxoplasma* antibodies. This suggests that these changes represent results of the cumulative effects of latent toxoplasmosis rather than transient after effects of passed acute infection. Some changes in personality are in the same direction in men and women, e.g., a decreased tendency for novelty seeking or decreased consciousness, while some are in the opposite direction in men and women, e.g., an increased Cattell's factor of pretension in men and decreased in women, increased Cattells' factor of superego strength in women and decreased in men (Flegr 2010). The changes in personality profile are associated with corresponding changes in infected subjects' behavior. For example, *Toxoplasma*-infected men scored lower in tidiness of their clothes than uninfected men, whereas infected women scored higher than uninfected women (Lindová et al. 2006). In experimental

games (Dictator game and Ultimatum game) the infected male students expressed less altruism while infected women more than their non-infected pears (Lindová et al. 2010). Latent toxoplasmosis may even be responsible for differences in some cultural traits between countries. For example, the prevalence of toxoplasmosis explains a significant portion of the variance in aggregate neuroticism among populations, in the 'neurotic' cultural dimensions of sex roles and uncertainty avoidance (Lafferty 2006) as well as the variance in the incidence of suicides (Lester 2010).

An analogous version of the Fatal attraction phenomenon and the decreased psychomotor performance that were described originally in experimentally infected rodents were later observed in *Toxoplasma*-infected humans. In a double blind experiment, infected men rated the smell of highly diluted cat urine (but not urine of other four animals) as more pleasant and infected women as less pleasant than *Toxoplasma*-free subjects (Flegr et al. 2011). Both infected men and women have impaired reaction times (Havlíček et al. 2001) and express many specific defects in cognitive performance (Beste et al. 2014; Flegr et al. 2013; Pearce et al. 2013, 2014; Priplatova et al. 2014; Stock et al. 2013), including in school achievements (Ferreira et al. 2013; Flegr et al. 2012b). Again, the impairment in reaction times increases with the time since infection when the age of subjects is statistically controlled. It is highly probable that observed changes in reaction times (and also decreased capacity of long term concentration) are responsible for the observed about 2.6 times higher probability of traffic accidents and work place accidents observed in *Toxoplasma*-infected subjects in about 6 independent studies in past ten years (Flegr et al. 2002; Kocazeybek et al. 2009; Yereli et al. 2006). The subjects with Rh positive blood group are fully (heterozygotes) or at least partly (homozygotes) protected against deterioration of reaction times (Novotná et al. 2008), risk of traffic accidents (Flegr et al. 2009) and many other effects of latent toxoplasmosis as well as against other detrimental factors as smoking, aging and fatigue, as demonstrated in subsequent studies (Flegr et al. 2012a). This byproduct of *Toxoplasma* manipulation activity research not only solved an old enigma surrounding the existence of the Rh polymorphism, but could become important in many fields of human physiology and for clinical practices in the future.

The studies published mainly at the beginning of twenty-first century shed some light on the physiological mechanisms of *Toxoplasma* manipulation. *T. gondii* possesses two unique genes for key enzymes that catalyze the synthesis of the important neurotransmitter dopamine (Gaskell et al. 2009). These genes are expressed in *Toxoplasma* bradyzoites in tissue cysts in the brains of infected animals; a large amount of dopamine is produced there and is exported to the surrounding neural tissue (Prandovszky et al. 2011). The level of dopamine in the brain is known to negatively correlate with the personality trait of novelty seeking, one the traits that is significantly lower in *Toxoplasma*-infected subjects. The increased level of dopamine, or rather resulting imbalance in concentration of dopamine between different parts of brain could also explain the tight connection between schizophrenia and toxoplasmosis, a phenomenon studied for more than 50 years (Willner 1997). It is known that the imbalance in dopamine concentration plays a key proximal role in schizophrenia. Nearly all modern antipsychotic drugs either decrease the level of

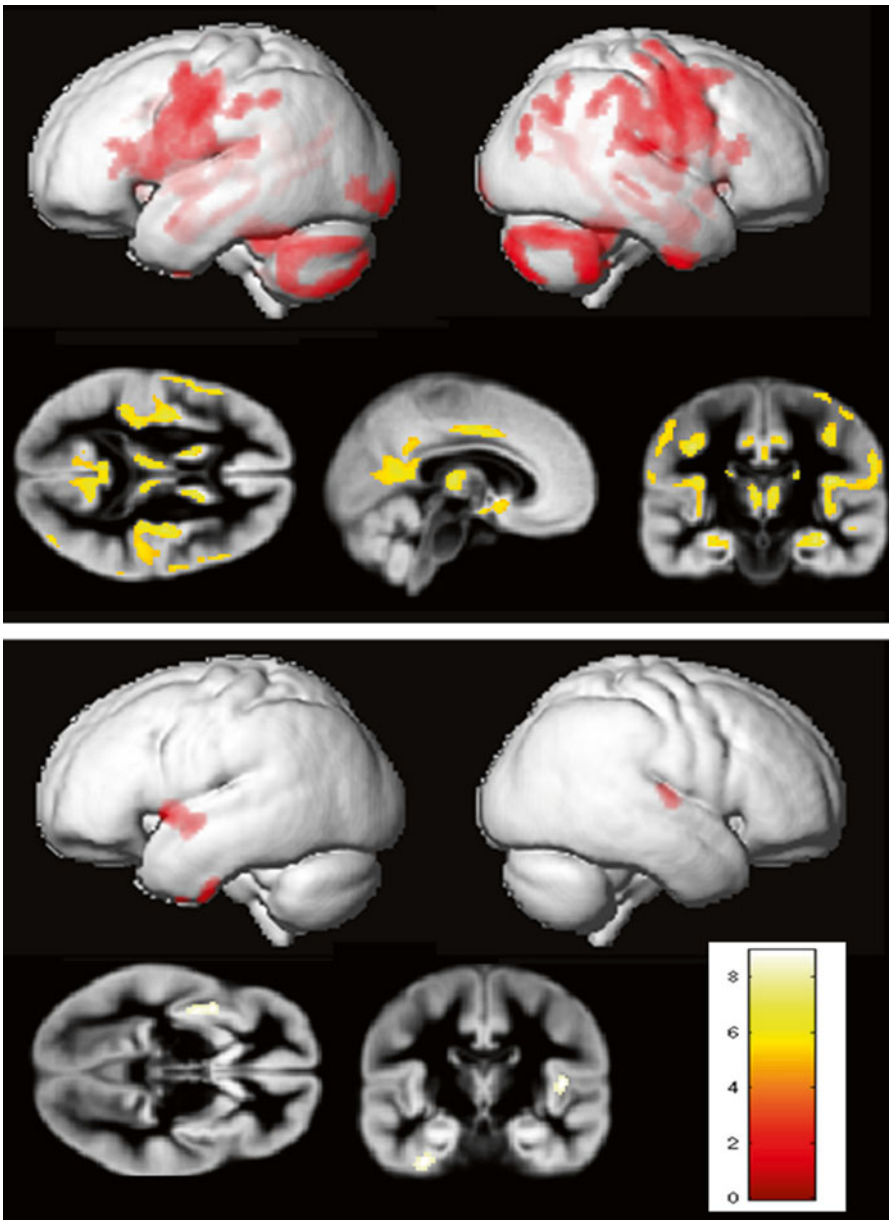

Fig. 6.1 The regional gray matter volume reduction in schizophrenia for *Toxoplasma*-infected subjects (*upper image*), and *Toxoplasma*-free (*lower image*) subjects. Significant results ($P<0.05$, FWE, cluster ≥ 50 voxels) are displayed on study specific 3D template and mean image slices. L or R, left or right hemisphere; the intensity of color reflects difference in gray matter density between schizophrenia and control subjects, the bar in the lower left corner represents T value for slices. *Toxoplasma*-infected patients but not *Toxoplasma*-free patients had reduced grey matter density in specific regions of a brain in comparison with corresponding controls (Horacek et al. 2012)

dopamine in brain of schizophrenic patients or inhibit binding of this neurotransmitter to its receptors (Nikam and Awasthi 2008). Results of recent studies suggest that toxoplasmosis plays an important role in the onset of schizophrenia in a significant portion of genetically predisposed patients. Moreover, the clinical picture of schizophrenia in *Toxoplasma*-infected patients differs from that of *Toxoplasma*-free patients. For example, the decrease in gray matter density in the brain occurs only in *Toxoplasma*-infected patients (Horacek et al. 2012), Fig. 6.1 and the same is true for gender differences in the onset of schizophrenia – on average, a 3-year delay of the onset of the disease in women exists only in *Toxoplasma*-infected subjects (Holub et al. 2013). *Toxoplasma*-infected schizophrenia patients express more severe positive symptoms of the psychiatric disease (more frequent or intense hallucinations, delusions) than *Toxoplasma*-free subjects (Holub et al. 2013; Wang et al. 2006).

Men with latent toxoplasmosis have increased levels of free testosterone while women have decreased levels (Flegr et al. 2008). It has been observed in a rodent model that *Toxoplasma* induces synthesis of this steroid hormones in the testes of infected males (Lim et al. 2013). Increased levels of testosterone could explain why *Toxoplasma* infected men are in average 3 cm taller than their *Toxoplasma*-free peers and their photos are also rated as more masculine and dominant by female raters (Flegr et al. 2005). It is possible that the increased level of testosterone results in higher competiveness, which may also at least partly explain the higher risk of traffic accidents (however, this was observed also in female drivers) or the increased probability of birthing sons in women and in mice females with relatively recent *Toxoplasma* infection (Kaňková et al. 2007a, b). It is also not clear whether increased levels of testosterone are a symptom of manipulation activity by *Toxoplasma* aimed to increase its chance for successful transmission, or a part of its struggle with the host immune system (testosterone is known to have a potent immunosuppressive activity), or whether it is just some nonadaptive side effect of the parasitic infection. In *Toxoplasma*-infected rats, however, the Fatal attraction phenomenon (loss of the fear response to cat odor and its change into an attraction) can be observed only in intact, not castrated males (Lim et al. 2013). It can be also speculated that increased levels of testosterone in males, resulting in increased sexual activity, could result in increased efficiency of sexual transmission of *Toxoplasma*. Viable parasites were frequently observed in seminal fluid of infected males and sexual transmission of toxoplasmosis from infected male to female during sexual intercourse was observed in many animal species. In humans, only indirect evidence for sexual transmission of toxoplasmosis exists (Flegr 2013a; Flegr et al. 2014a). It can probably occur only in acute or post-acute phase of the infection and therefore the unprotected sex is probably only a marginal risk factor of toxoplasmosis. However, it can play an extremely important role in acquiring the most devastating form of toxoplasmosis, congenital toxoplasmosis, i.e., in transmission of the parasite from mother in acute phase of the infection to a developing embryo. It is indicative that about two thirds of *Toxoplasma* infections in pregnant women cannot be explained by the known risk factors.

Clinical Relevance

Research of manipulation activity by *Toxoplasma* started as typical basic research in the field of evolutionary parasitology. Results obtained during past 20 years, however, showed that this activity of the parasite could have an important effect on human wellbeing and that latent toxoplasmosis could have an even larger public health and economic impact than other forms of toxoplasmosis put together. For example, just the increased risk of traffic and work place accidents could be together responsible for a similar number of deaths as malaria. Schizophrenia, which affects about 1 % humans, represents huge economic burden. The prevalence of toxoplasmosis also explains large part of between-countries differences in the incidence of other serious psychiatric and nonpsychiatric diseases, including obsessive–compulsive disorder, epilepsy, suicides, and cardiovascular diseases (Flegr et al. 2014b), see Fig. 6.2. At least some of the observed associations between these diseases and toxoplasmosis can be caused by manipulation activity of the

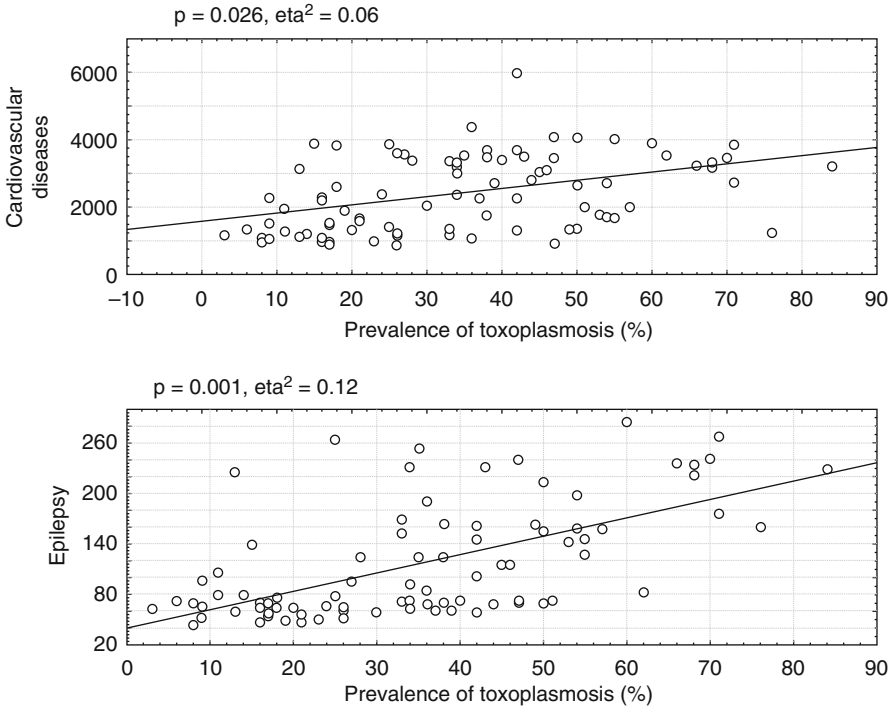

Fig. 6.2 Correlation of prevalence of toxoplasmosis with and cardiovascular diseases and epilepsy-attributed morbidity for 88 WHO-member countries. The axes show prevalence of toxoplasmosis (%) in women of childbearing age and y-axes the number years of 'healthy' life lost by virtue of being in a state of poor health or disability due to particular disease per 100,000 inhabitants in 2004 (Flegr et al. 2014b)

parasite. Presently, no effective method of treatment of, or vaccination against, toxoplasmosis exists. However, the results of manipulation activity studies suggest that more effort should be focused not only on prevention and treatment of *Toxoplasma* infection, but also to prevention of manipulative activity of this common parasite in future.

References

Abdoli A (2013) *Toxoplasma gondii* and neuropsychiatric diseases: strain hypothesis. Neurol Sci 34(9):1697–1698. doi:10.1007/s10072-012-1264-x

Berdoy M, Webster JP, Macdonald DW (1995) Parasite-altered behaviour: is the effect of *Toxoplasma gondii* on *Rattus norvegicus* specific? Parasitology 111:403–409

Berdoy M, Webster JP, Macdonald DW (2000) Fatal attraction in rats infected with *Toxoplasma gondii*. Proc R Soc Biol Sci Ser B 267(1452):1591–1594

Beste C, Getzmann S, Gajewski PD, Golka K, Falkenstein M (2014) Latent *Toxoplasma gondii* infection leads to deficits in goal-directed behavior in healthy elderly. Neurobiol Aging 35(5):1037–1044. doi:10.1016/j.neurobiolaging.2013.11.012

Ferreira EC, Marchioro AA, Guedes TA, Mota D, Guilherme ALF, de Araujo SM (2013) Association between seropositivity for *Toxoplasma gondii*, scholastic development of children and risk factors for *T. gondii* infection. Trans R Soc Trop Med Hyg 107(6):390–396. doi:10.1093/trstmh/trt026

Flegr J (2010) Influence of latent toxoplasmosis on the phenotype of intermediate hosts. Folia Parasitol 57:81–87

Flegr J (2013a) How and why *Toxoplasma* makes us crazy. Trends Parasitol 29(4):156–163

Flegr J (2013b) Influence of latent *Toxoplasma* infection on human personality, physiology and morphology: pros and cons of the *Toxoplasma*-human model in studying the manipulation hypothesis. J Exp Biol 216(1):127–133. doi:10.1242/jeb.073635

Flegr J, Hrdý I (1994) Influence of chronic toxoplasmosis on some human personality factors. Folia Parasitol 41:122–126

Flegr J, Havlíček J, Kodym P, Malý M, Šmahel Z (2002) Increased risk of traffic accidents in subjects with latent toxoplasmosis: a retrospective case-control study. BMC Infect Dis 2:art-11

Flegr J, Hrušková M, Hodný Z, Novotná M, Hanušová J (2005) Body height, body mass index, waist-hip ratio, fluctuating asymmetry and second to fourth digit ratio in subjects with latent toxoplasmosis. Parasitology 130:621–628

Flegr J, Lindová J, Kodym P (2008) Sex-dependent toxoplasmosis-associated differences in testosterone concentration in humans. Parasitology 135:427–431

Flegr J, Klose J, Novotná M, Berenreitterová M, Havlíček J (2009) Increased incidence of traffic accidents in *Toxoplasma*-infected military drivers and protective effect RhD molecule revealed by a large-scale prospective cohort study. BMC Infect Dis 9:art. 72

Flegr J, Lenochová P, Hodný Z, Vondrová M (2011) Fatal attraction phenomenon in humans: cat odour attractiveness increased for *Toxoplasma*-infected men while decreased for infected women. PLoS Neglect Trop D 5(11), e1389. doi:10.1371/journal.pntd.0001389

Flegr J, Geryk J, Volny J, Klose J, Cernochova D (2012a) Rhesus factor modulation of effects of smoking and age on psychomotor performance, intelligence, personality profile, and health in Czech soldiers. PLoS One 7(11), e49478. doi:10.1371/journal.pone.0049478

Flegr J, Guenter W, Bielinski M (2012b) *Toxoplasma gondii* infection affects cognitive function – corrigendum. Folia Parasitol 59:253–254

Flegr J, Preiss M, Klose J (2013) Toxoplasmosis-associated difference in intelligence and personality in men depends on their Rhesus blood group but not ABO blood group. PLoS One 8(4):e61272. doi:10.1371/journal.pone.0061272

Flegr J, Klapilová K, Kaňková Š (2014a) Toxoplasmosis can be a sexually transmitted infection with serious clinical consequences. Not all routes of infection are created equal. Med Hypotheses 83:286–289

Flegr J, Prandota J, Sovickova M, Israili ZH (2014b) Toxoplasmosis – a global threat. Correlation of latent toxoplasmosis with specific disease burden in a set of 88 countries. PLoS One 9(3):e90203. doi:10.1371/journal.pone.0090203

Gaskell EA, Smith JE, Pinney JW, Westhead DR, McConkey GA (2009) A unique dual activity amino acid hydroxylase in *Toxoplasma gondii*. PLoS One 4, e4801

Havlíček J, Gašová Z, Smith AP, Zvára K, Flegr J (2001) Decrease of psychomotor performance in subjects with latent 'asymptomatic' toxoplasmosis. Parasitology 122:515–520

Hay J, Hutchison WM, Aitken PP, Graham DI (1983) The effect of congenital and adult-acquired *Toxoplasma* infections on activity and responsiveness to novel stimulation in mice. Ann Trop Med Parasitol 77:483–495

Hay J, Aitken PP, Graham DI (1984a) *Toxoplasma* infection and response to novelty in mice. Z Parasitenkd 70:575–588

Hay J, Aitken PP, Hair DM, Hutchison WM, Graham DI (1984b) The effect of congenital *Toxoplasma* infection on mouse activity and relative preference for exposed areas over a series of trials. Ann Trop Med Parasitol 78:611–618

Hay J, Aitken PP, Arnott MA (1985) The influence of *Toxoplasma* infection on the spontaneous running activity of mice. Z Parasitenkd 71:459–462

Holmes J, Bethel WM (1972) Modification of intermidiate host behaviour by parasites. In: Canning EU, Wright CA (eds) Behavioural aspects of parasite transmission. Academic, New York, pp 123–149

Holub D et al (2013) Differences in onset of disease and severity of psychopathology between toxoplasmosis-related and toxoplasmosis-unrelated schizophrenia. Acta Psychiatr Scand 127:227–238. doi:10.1111/acps.12031

Horacek J et al (2012) Latent toxoplasmosis reduces gray matter density in schizophrenia but not in controls: Voxel-based-morphometry (VBM) study. World J Biol Psychiatry 13(7):501–509. doi:10.3109/15622975.2011.573809

Hrdá Š, Votýpka J, Kodym P, Flegr J (2000) Transient nature of *Toxoplasma gondii*-induced behavioral changes in mice. J Parasitol 86(4):657–663

Hutchison WM, Aitken PP, Wells BW (1980a) Chronic *Toxoplasma* infections and motor performance in the mouse. Ann Trop Med Parasitol 74:507–510

Hutchison WM, Bradley M, Cheyne WM, Wells BWP, Hay J (1980b) Behavioural abnormalities in *Toxoplasma* -infected mice. Ann Trop Med Parasitol 74:337–345

Kaňková Š, Kodym P, Frynta D, Vavřinová R, Kuběna A, Flegr J (2007a) Influence of latent toxoplasmosis on the secondary sex ratio in mice. Parasitology 134:1709–1717

Kaňková Š, Šulc J, Nouzová K, Fajfrlik K, Frynta D, Flegr J (2007b) Women infected with parasite *Toxoplasma* have more sons. Naturwissenschaften 94:122–127

Kannan G, Moldovan K, Xiao JC, Yolken RH, Jones-Brando L, Pletnikov MV (2010) *Toxoplasma gondii* strain-dependent effects on mouse behaviour. Folia Parasitol 57:151–155

Kocazeybek B et al (2009) Higher prevalence of toxoplasmosis in victims of traffic accidents suggest increased risk of traffic accident in *Toxoplasma*-infected inhabitants of Istanbul and its suburbs. Forensic Sci Int 187:103–108

Lafferty KD (2006) Can the common brain parasite, *Toxoplasma gondii*, influence human culture? Proc R Soc Biol Sci Ser B 273:2749–2755

Lester D (2010) Predicting European suicide rates with physiological indices. Psychol Rep 107:713–714

Lim A, Kumar V, Hari Dass SA, Vyas A (2013) *Toxoplasma gondii* infection enhances testicular steroidogenesis in rats. Mol Ecol 22(1):102–110. doi:10.1111/mec.12042

Lindová J et al (2006) Gender differences in behavioural changes induced by latent toxoplasmosis. Int J Parasitol 36:1485–1492

Lindová J et al (2010) Pattern of money allocation in experimental games supports the stress hypothesis of gender differences in *Toxoplasma gondii*-induced behavioural changes. Folia Parasitol 57:136–142

Nikam SS, Awasthi AK (2008) Evolution of schizophrenia drugs: a focus on dopaminergic systems. Curr Opin Invest Drugs 9:37–46

Novotná M et al (2008) *Toxoplasma* and reaction time: role of toxoplasmosis in the origin, preservation and geographical distribution of Rh blood group polymorphism. Parasitology 135:1253–1261

Pearce BD et al (2013) Toxoplasma gondii exposure affects neural processing speed as measured by acoustic startle latency in schizophrenia and controls. Schizophr Res 150:258–261

Pearce BD, Kruszon-Moran D, Jones JL (2014) The association of *Toxoplasma gondii* infection with neurocognitive deficits in a population-based analysis. Soc Psychiatry Psychiatr Epidemiol 49(6):1001–1010. doi:10.1007/s00127-014-0820-5

Piekarski G, Zippelius HM, Witting PA (1978) Auswirkungen einer latenten *Toxoplasma* -Infektion auf das Lernvermogen von weissen Laboratoriumsratten and Mausen. Z Parasitenkd 57:1–15

Prandovszky E, Gaskell E, Martin H, Dubey JP, Webster JP, McConkey GA (2011) The neurotropic parasite *Toxoplasma gondii* increases dopamine metabolism. PLoS One 6(9), e23866

Priplatova L, Sebankova B, Flegr J (2014) Contrasting effect of prepulse signals on performance of *Toxoplasma*-infected and *Toxoplasma*-free subjects in an acoustic reaction times test. PLoS One 9(11):e112771. doi:10.1371/journal.pone.0112771

Skallová A, Kodym P, Frynta D, Flegr J (2006) The role of dopamine in *Toxoplasma*-induced behavioural alterations in mice: an ethological and ethopharmacological study. Parasitology 133:525–535

Stock AK, Heintschel von Heinegg E, Kohling HL, Beste C (2013) Latent *Toxoplasma gondii* infection leads to improved action control. Brain Behav Immun. doi:10.1016/j.bbi.2013.11.004

Vyas A, Kim SK, Giacomini N, Boothroyd JC, Sapolsky RM (2007) Behavioral changes induced by *Toxoplasma* infection of rodents are highly specific to aversion of cat odors. Proc Natl Acad Sci U S A 104:6442–6447

Wang HL, Wang GH, Li QY, Shu C, Jiang MS, Guo Y (2006) Prevalence of *Toxoplasma* infection in first-episode schizophrenia and comparison between *Toxoplasma*-seropositive and *Toxoplasma*-seronegative schizophrenia. Acta Psychiatr Scand 114:40–48

Webster JP (1994) The effect of *Toxoplasma gondii* and other parasites on activity levels in wild and hybrid *Rattus norvegicus*. Parasitology 109:583–589

Webster JP, Brunton CFA, Macdonald DW (1994) Effect of *Toxoplasma gondii* upon neophobic behaviour in wild brown rats, *Rattus norvegicus*. Parasitology 109:37–43

Willner P (1997) The dopamine hypothesis of schizophrenia: current status, future prospects. Int Clin Psychopharmacol 12(6):297–308

Witting PA (1979) Learning capacity and memory of normal and *Toxoplasma* -infected laboratory rats and mice. Z Parasitenkd 61:29–51

Xiao J et al (2012) Sex-specific changes in gene expression and behavior induced by chronic *Toxoplasma* infection in mice. Neuroscience 206:39–48. doi:10.1016/j.neuroscience.2011.12.051

Xiao JC, Li Y, Jones-Brando L, Yolken RH (2013) Abnormalities of neurotransmitter and neuropeptide systems in human neuroepithelioma cells infected by three *Toxoplasma* strains. J Neural Transm 120(12):1631–1639. doi:10.1007/s00702-013-1064-3

Yereli K, Balcioglu IC, Ozbilgin A (2006) Is *Toxoplasma gondii* a potential risk for traffic accidents in Turkey? Forensic Sci Int 163:34–37

Chapter 7
The Brain Worm Story

Heinz Mehlhorn

7.1 Introduction

Although the so-called small liver fluke, the trematode *Dicrocoelium dendriticum*, which as adult worm infects the bile ducts of a broad spectrum of ruminants but also those of horses, camels, donkeys, guinea pigs and humans, is known since 1819 (Rudolphi 1819, Loos 1899 cited by Krull and Mapes 1952). However, its most important feature = the ability to induce a significant behavioral change of infected intermediate hosts (ants) is only known since the middle of the last century (Lämmler 1962; Hohorst and Graefe 1961; Hohorst and Lämmler 1962; Romig et al. 1980). Similar changes of behaviour were seen in ants (*Camponotus compressiscapus*) infected by the African liver fluke *Dicrocoelium hospes* (Lucius 1980; Lucius et al. 1980). In the evening both species the infected ants climb on plants and fix themselves there with their mandibles. This fixation is released, when temperatures increase next morning. But since the most important final hosts (ruminants) feed in the meadow early in the morning, ingestion rates of attached ants increase and thus many adult worms may develop (Manga-Gonzalez et al. 2001).

H. Mehlhorn
Department of Zoomorphology, Cell Biology and Parasitology,
Heinrich Heine University, Universitätsstr. 1, 40225 Düsseldorf, Germany
e-mail: mehlhorn@uni-duesseldorf.de

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7.2 The Worms

7.2.1 Species and Names

- *Dicrocoelium dendriticum* (syn. *D. lanceolatum*): occurs in Europe, Asia, America and North Africa,
- *Dicrocoelium hospes*: occurs in Africa South of the Sahara,
- *Dicrocoelium sinensis*: occurs in some Chinese regions.

7.2.2 Origin of Names

Greek: *dikroos* = double; *koilos* = furcated; *dendron* = empty; **Latin**: *lanceola* = lance; *hospes* = host; *chinensis* = from China.

7.2.3 Morphology

The adult hermaphroditic and contractile worms (flukes) of these species are highly stretchable and reach a length of up to 12 mm and a width of up to 3 mm (Figs. 7.1, 7.2, and 7.3). They are found in the bile ducts and in the gall bladder of their hosts where they disturb severely the spreading of bile and thus minimize food digestion and growth of infected hosts. Huge numbers of worms may lead even to anemia. Infected livers of slaughtered animals cannot be used for human consumption. (Piekarski 1963; Lucius and Frank 1978; Romig 1980; Hinaidy 1983; Spindler et al. 1986; Schuster and Neumann 1986; Mehlhorn 2012, 2016)

7.2.4 Life Cycle

Adult worms excrete huge numbers of brownish thick-walled eggs (40 µm × 25 µm) already containing a miracidium (Figs. 7.1 and 7.4). The posterior region of this miracidium contains two dense regions which represent the so-called germ balls.

Fig. 7.1 Diagrammatic representation of life cycle stages of *Dicrocoelium dendriticum*. **A** Final host: chiefly sheep and cattle; humans are incidental ("accidental hosts"). *1* Sexually mature liver fluke (see under *III*). *1 a* Egg with a fully formed miracidium. **B** Intermediate host: land snails (*Helicella*, *Zebrina*). *2* Miracidium which has emerged from a snail. *3 a* The youngest sprorocyst. *b* The oldest sporocyst stage (mother sporocyst). *c* Daughter sporocyst. *d* A single cercaria (the so-called *Cercaria vitrina*). *e* Shell of *Helicella ericetorum*. *f* Shell of *Zebrina dendrita*. **C** *2*. Intermediate hosts: ants. *4 a* Slime balls laid by the snail on grass stem. *4 b* An isolated (single) slime ball laid by the snail. *5 a* An ant eating slime balls. *5 b* Mature metacercariae from ants. (*I*) A miracidium emerging. (*II*) "Cercaria vitrina". (*III*) A sexually mature liver fluke (From: Piekarski 1963)

When xerophilic snails (land pulmonates: Stylommatophora; e.g. *Zebrina* species, *Helicella* species, *Cochlicopa* species, *Limicolaria* species) ingest such eggs, the miracidia hatch (being provided with a bore spike) and migrate into the snail "liver"

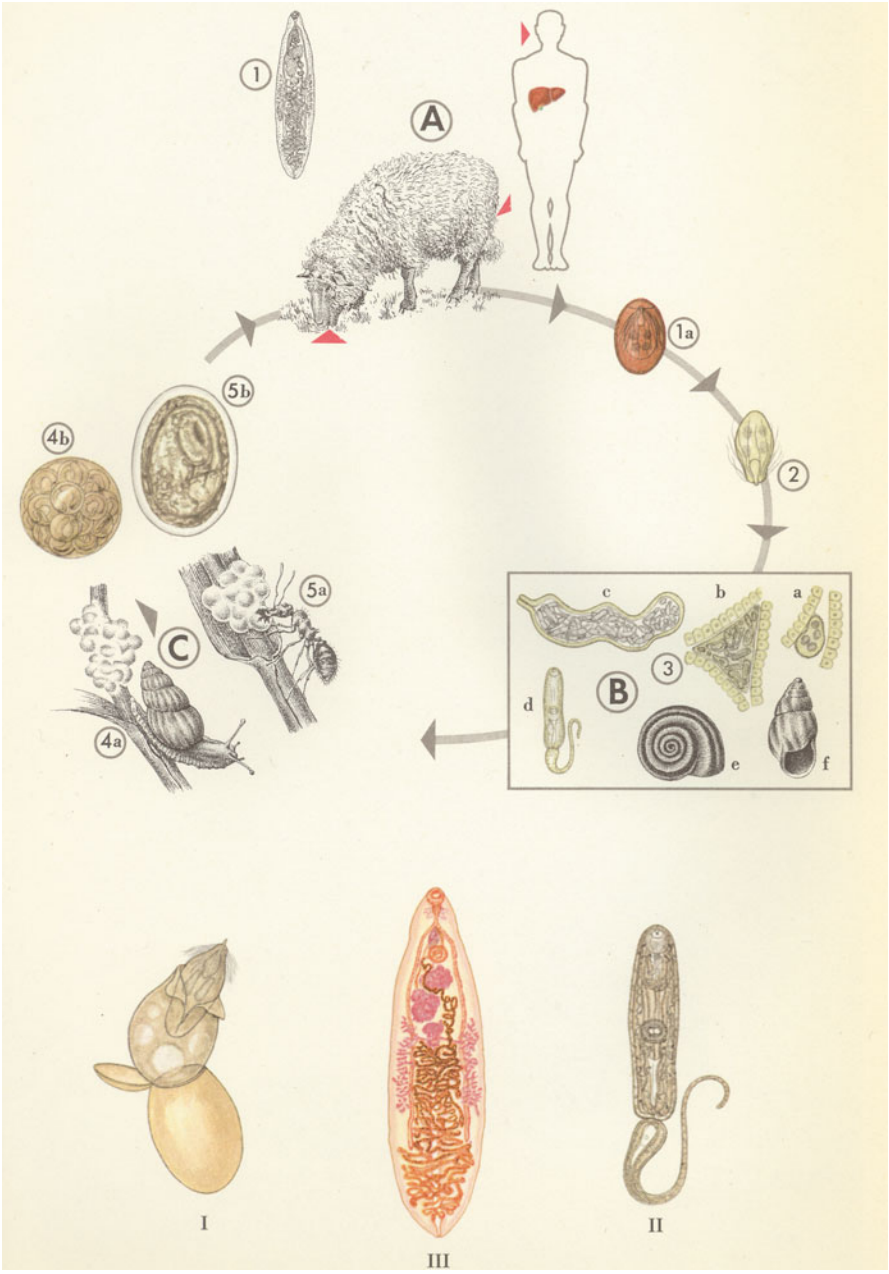

Fig. 7.2 Light micrograph of an coloured adult worm of *Dicrocoelium dendriticum*

(digestion gland), where they settle and develop into mother sporocysts. Inside the latter daughter sporocysts are formed asexually from germ balls. Inside these daughter sporocysts mostly 10–40 cercariae are developed. They also possess an anterior bore spike, two suckers and a single tail, which is used for pulling movements. The development inside the snail takes 3–5 months. After this the cercariae leave the sporocysts via an opening and migrate into the breathing hollow of the snail, where they are included into 1 mm sized slime balls, which protect the cercariae from drying. Aggregation of such slime balls may reach 1–5 cm in diameter and then may contain hundreds of infectious cercariae. As soon as second intermediate hosts (= ants mainly of the genus *Formica*) ingest such slime balls, the cercariae penetrate into the stomach wall of the ant and pass by help of their stiletto-like bore spike leaving their tail behind. Having reached the haemocoel of the ant, the cercariae wander from there into the head of the ant, where in general one (rarely 2 or 3) cercaria penetrates into the subesophageal ganglion (brain), while the rest of the cercariae return into the haemocoel of the hind body, where they encyst themselves to

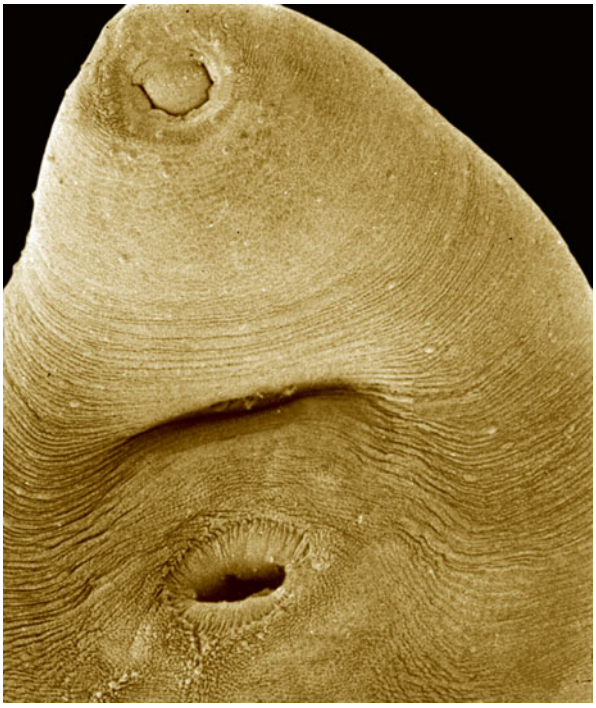

Fig. 7.3 Scanning electron micrograph of the anterior end of an adult worm of *Dicrocoelium dendriticum* showing that the surface is smooth = not covered by scales like it is the case in the large liver fluke *Fasciola hepatica*

so-called metacercariae. The cercaria inside the ganglion, however, does not become firmly encysted, but is covered only by a smooth layer and thus remains unable to develop further into an adult worm, when ingested by a final host as has been shown by experimental transmissions (Hohorst and Graefe 1961; Hohorst 1962; Lämmler 1962). In the case of *D. dendriticum* the brain of infected ants contains mostly only one single metacercaria, while in the case of infections with *D. hospes* in general two are found in the *Camponotus* ants.

These unsheated so-called "brain-worms" introduce a peculiar change in the behaviour of the infected ants. While uninfected worker ants enter their nest as soon as temperatures decrease (e.g. in the evening), infected ones bite firmly and undetachable into leaves of grass – apparently induced by a permanent cramp/spasm of the muscles of the mouthparts. This fixed attachment is only released on next morning, when temperatures increase. Since many final hosts such as sheep start their feeding early in the morning, they have higher chances to ingest larger numbers of such attached = infected ants compared to a situation with free running ants during daytime.

The location of the so-called "Hirnwurm" (German Hirn = brain; wurm = worm) stages in the brain of infected ant specimens is different in *D. dendriticum* and

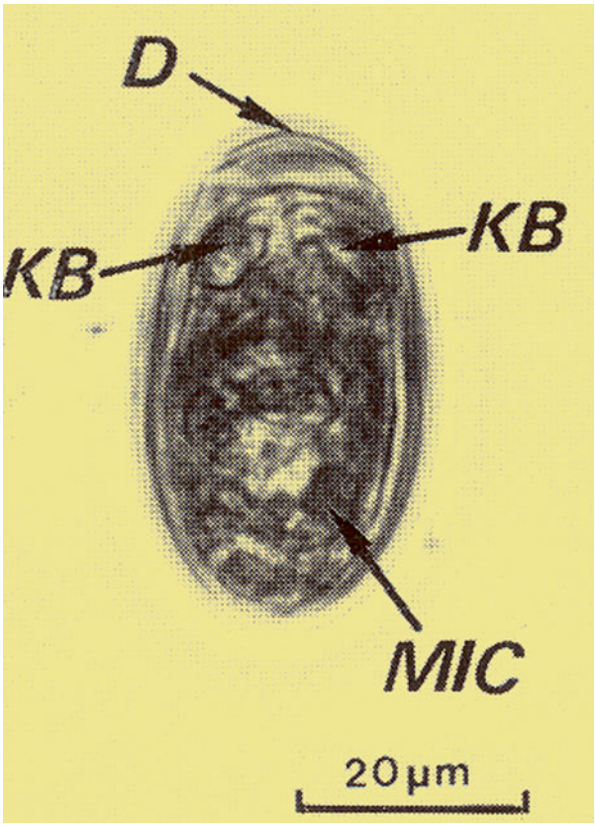

Fig. 7.4 Light micrograph of an egg of *Dicrocoelium dendriticum* showing the included miracidium. *D* operculum, *KB* germ ball, *MIC* miracidium larva

D. hospes. The "Hirnwurm" of *D. dendriticum* was mostly (90 %) situated in the ventral part of the subesophageal ganglion in close contact to the origin of the mandible nerves, while those of *D. hospes* have a definite preference for the antennal lobes, where mostly both lobes contain each such a stage. Since they are mostly found in the dorsal part of this lobe, contacts with the origin of the antennal nerve are common (Romig et al. 1980).

The pure presence of such "Hirnwurm" stages, however, cannot explain alone the attachment behaviour of infected ants, since the presence of metacercariae of the bird trematode *Brachylecithum mosquensis* inside the second intermediate host (*Camponotus* species) leads to other behavioural changes of infected ants than attachment to plants. These changes, however, also likewise enhance the probability that ants and with them the metacercariae become ingested by the final host (birds) (Carney 1969; Carpenter 1970). However, the localization of the metacercariae of B. *mosquensis* in the "brain" of the ants is different, since one or two deviating metacercariae are seen mostly only in the proximity of the **supraesophageal ganglion**, while the "Hirnwurm" of *D. dendriticus* mostly develops in the **subesophageal ganglion**.

However, it needs more physiological and molecular biological studies to find out the triggering of the behavioural changes of trematode-infected ants. The pure presence of a "Hirnwurm" in the brain of an ant cannot explain the observed effects. This is underlined by findings that parasite stages (cysticercoids) of the tapeworm *Choanotaenia* sp., which do not enter the central nervous system of their intermediate hosts (ants of the genus *Leptothorax nylanderi*), induce similar behavioural changes: they rest in groups on the ground without feeding = just increasing the chance to become ingested (Plateaux 1972).

Furthermore nearly identical reactions of ants (=climbing and fixing themselves on plants) were also found in ants being infected with the fungus species of the genus *Entomophthora* (Loos-Frank and Zimmermann 1976; Wilson 1977).

Thus the functional origin and steering of the described behavioural changes are far from being understood. Such a peculiar behaviour is surely not explained by the meaning of term altruism, which describes a behaviour (of humans) when one individual spends his life to save that of others.

References

Carney WP (1969) Behavioral and morphological changes in carpenter ants harbouring dicrocoeliid metacercariae. Am Midl Nat 82:605–611

Carpenter WP (1970) *Brachylecithum mosquensis*: infection in the vertebrate, molluscan and arthropod hosts. Trans Am Microsc Soc 89:233–250

Hinaidy HK (1983) In German: *Dicrocoelium supperi* nomen novum (syn. *D. orientalis* Sudarikov et Ryjikov 1951), a new trematode for the parasitic fauna of Austria. Zentralbl Veterinarmed B 30:576–589

Hohorst W (1962) In German: The role of ants in the developmental cycle of the lancet fluke *Dicrocoelium dendriticum*. Parasitol Res 22:105–106

Hohorst W, Graefe G (1961) In German: Ants – obligate intermediate hosts of the lancet fluke *Dicrocoelium dendriticum*. Naturwissenschaften 48:229–235

Hohorst W, Lämmler G (1962) In German: Experimental studies on dicrocoeliosis. Tropenmed Parasitol 13:377–397

Krull WH, Mapes CR (1952) Studies on the biology of *Dicrocoelium dendriticum* including the relation to the intermediate host *Cionella lubrica*. Cornell Vet 42:603–605

Lämmler G (1962) In German: The experimental infection of final hosts of *Dicrocoelium dendriticum*. Parasitol Res 22:106–107

Loos-Frank B, Zimmermann G (1976) In German: About a behavioral change analogous to an infestation with *Dicrocoelium* of ants of the genus *Formica* by a fungus of the genus *Entomophthora*. Parasitol Res 49:281–289

Lucius R (1980) Further contributions to the biology of *Dicrocoelium hospes* Looss, 1907, in West Africa (Ivory Coast). Zentralbl Bakteriol Hyg 1. Abt Ref 267:306

Lucius R, Frank W (1978) In German: Contributions to the biology of *Dicrocoelium hospes* Looss, 1907 (Trematodes, Dicrocoeliidae). Acta Trop 35:161–181

Lucius R, Romig T, Frank W (1980) *Camponotus compressiscapus* André (Hymenoptera, Formicidae), an experimental second intermediate host of *Dicrocoelium hospes* Looss, 1907 (Trematodes, Dicrocoeliidae). Parasitol Res 63:271–275

Manga-Gonzalez MY, Gonzalez-Lanza C, Cabanas E, Campo R (2001) Contributions to and review of dicrocoeliosis, with special reference to the intermediate hosts of *Dicrocoelium dendriticum*. Parasitology 123:S91–S114

Mehlhorn H (2012) In German: The parasites of animals, 7th edn. Springer, New York/Heidelberg
Mehlhorn H (ed) (2016) Encyclopedia of parasitology, 4th edn. Springer, New York
Piekarski G (1963) Medical parasitology. Springer, Berlin/New York
Plateaux L (1972) Sur les modifications produites chez une fourmi par la présence d'un parasite cestode. Ann Sci Nat Zool 14:203–220
Romig T (1980) Studies on the "Hirnwurm" of *Dicrocoelium hospes* and *Dicrocoelium dendriticum*. Zentralbl Bakteriol Hyg I Abt Ref 267:307
Romig T, Lucius R, Frank W (1980) Cerebral larvae in the second intermediate host of *Dicrocoelium dendriticum* (Rudolphi, 1819) and *Dicrocoelium hospes* Looss, 1907 (Trematodes, Dicrocoeliidae). Parasitol Res 63:277–286
Schuster R, Neumann B (1988) In German: On the seasonal occurrence of *Dicrocoelium dendritium* in intermediate hosts. Angewandte Parasitol 29:31–36
Spindler EM, Zahler M, Loos-Frank B (1986) Behavioral aspects of ants as second intermediate hosts of *Dicrocoelium dendritium*. Parasitol Res 72:689–692
Wilson DS (1977) How nepotistic is the brain worm? Behav Ecol Sociobiol 2:421–425

Chapter 8
The Bodyguard Phenomenon

Heinz Mehlhorn

8.1 Introduction

Parasites, that change host behavior, are diverse and comprise viruses, bacteria and a wide range of eukaryotes including fungi, protozoans, worms and parasitoids (insects). The existing host-parasite/parasitoid relationships can be defined either narrowly, where the parasite is physically and metabolically dependent on the host, or more broadly as it is the case in ecological-evolutionary systems comprising more or less obligate partnerships. The bodyguard phenomenon belongs to the latter group (Horwitz and Wilcox 2005; Thomas et al. 2010a, b).

Bodyguards are commonly known as trained, armed and (hopefully) well paid persons, who should protect important personalities from aggressions of envious contemporaries. Before this background the term has been transformed to the mostly non-voluntary protection activities of animals that are forced by a parasite or a parasitoid to act in this way, whereby often sophisticated methods have been developed by protection searchers. Such a forced protection may be initiated by injection of paralyzing compounds – or even more sophisticated – by various modes of manipulations (Hart 1990), which according to Poulin (2010) and Maure et al. (2013) alter significantly the normal behavior of the protection givers in such a way, that they set back their own life and offer perfect protection to the "client", when guaranteeing the survival during its larval development and/or phases of any vulnerability or weakness. This type of bodyguard protection, which will be presented here more in detail, is one of in total four categories established by Maure et al. (2013) to cover and describe host manipulations by

H. Mehlhorn
Department of Zoomorphology, Cell Biology and Parasitology,
Heinrich Heine University, Universitätsstr. 1, 40225 Düsseldorf, Germany
e-mail: mehlhorn@uni-duesseldorf.de

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various parasites. The second type of common manipulations besides the bodyguard phenomenon occurs e.g. when gammarid crustaceans infected with trematode larvae stay close to the air-water interface even when these sites are dangerous due to activities of potential final hosts (waterfowls) of the trematodes instead of escaping into deeper water regions, what is done by uninfected specimens of the same species of crustaceans (Helluy 1984; Bethel and Holmes 1977). As third type of host manipulations is considered when hosts that normally avoid water contact such as crickets (e.g. *Nemobius sylvestris*) jump into water and thus give parasitizing larval nematomorph stages (e.g. *Paragordius tricuspidatus*) the chance to leave its host and to find potential mating partners in the water (Thomas et al. 2002a, b). The fourth and last of the Maure et al. (2013) types of host manipulations is seen in the group of parasites using a so-called vector-borne transmissions. This type of manipulation occurs, when parasites such as the agents of malaria (*Plasmodium* species) induce their vectors (mosquitoes of the genus *Anopheles*) to reduce the amount of blood ingested at a donor and to visit more hosts for further food uptake. This changed behavior would increase the chance that infectious *Plasmodium* stages (sporozoites) that are transmitted potentially during each sucking act become distributed to significantly more hosts thus increasing the general survival chance for these vector-dependent parasites (Jensen and Mehlhorn 2009).

Examples for bodyguard manipulations and for so-called released bodyguard dimensions are presented in the review of Maure et al. (2013). Some selected examples are considered here more in detail.

8.2 True Bodyguards

8.2.1 Ladybird Beetle and Parasitic Wasp

In this case the wasp injects a fertilized egg into the body cavity of such a ladybird beetle. As soon as the prepupal stage of the wasp is able to hatch from the body cavity, it produces a cocoon at which the partially paralyzed ladybird beetle becomes attached and then starts by displaying heavy twitches to defend the cocoon of the wasp against aggressive predators (Maure et al. 2011).

8.2.2 Caterpillar (Butterfly Larva) and Parasitic Wasp

The larva of the butterfly *Pieris brassicae* defends by heavy web spinning and aggressive movements the included larva of the parasitic wasp *Cotesia glomerata* from predation and hyperparasitism (Harvey et al. 2011).

8.2.3 *Spider Hosts and Parasitic Wasp*

The orb-webweaving spider *Allocyclosa bifurca* builds under the control of the parasitoid wasp *Polysphincta gutfreundi* a highly stable orb web, within which the larva of the parasitic wasp places its pupal cocoon, which is then additionally covered by silk threads, which increase considerably the intended camouflage (Eberhard 2001; 2010a, b).

8.2.4 *Bumble Bee and Endoparasitic Fly*

When bumble bees (*Bombus terrestris*) are parasitized by a copoid fly larva, the bee workers start unusual digging activities. Within these pit-like hollows the fly pupa has better hibernation chances than on plain ground.

8.3 Predation Suppressions and Bodyguard Dimension

These terms are introduced and subsequently used by Parker et al. (2009) and Maure et al. (2013). Parker et al. (2009) use "predation suppression" in a way, that this term should cover the evolutionary stable strategy of parasites to switch from predation suppression during the non-infective phase of their life cycle to a considerable predation enhancement as soon as the infective stage is reached and thus can be transmitted. Maure et al. (2013) claim the existence of such examples being close to their "bodyguard dimension" group and present the following examples:

(a) Medoc et al. (2009) demonstrated that the amphipod crustacean *Gammarus roseli*, when infected with the acanthocephalan worm *Polymorphus minutus* (Fig. 8.1), showed better swimming abilities in the presence of non-host predators, spent more time at the surface of the water and remained significantly longer hidden, when exposed to non-host predators compared to non-infected stages of *Gammarus* specimens. These apparent multiple manipulations by the acanthocephalan worm larva help that infected stages of its intermediate host (*Gammarus*) are less common ingested by non-host predators but remain high enough in number to produce a significant infection rate among effective predators (birds such as ducks, chicken, seagulls = final hosts), which are essential to propagate the species, since they contain the sexual stages (for life cycle of *P. minutus* see Taraschewski and Sures in: Mehlhorn 2016; Fig. 8.1).

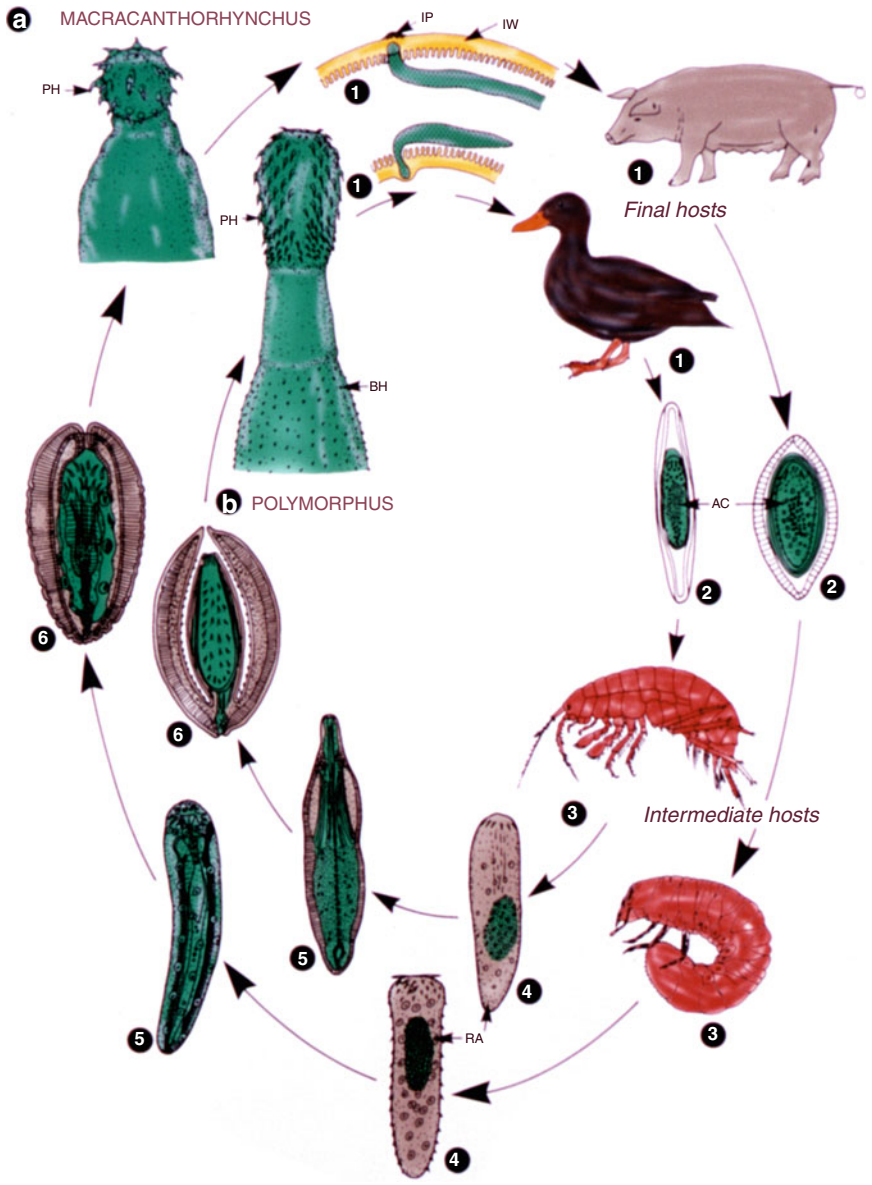

Fig. 8.1 Life cycle of common acanthocephalan species. (**a**) *Macracanthorhynchus hirudinaceus*; (**b**) *Polymorphus minutus. 1* The adults live in the intestine of their final hosts, being attached by their hooked proboscis. The penetration of the intestinal wall leads to inflamed protrusions (*IP*) appearing along the outer side. *2* After copulation the adult females excrete eggs for several months (patent period). These eggs are passed fully embryonated (i.e. they contain the hooked acanthor larva) with the feces of the host. *3–6* Intermediate hosts (*Gammarus* spp. or beetle larvae) become infected by ingesting infective eggs. Inside the intestine the acanthor is released from the egg (*4*), enters the body cavity, and is transformed into an acanthella larva (*5*). The latter grows up within 60–95 days (in *M. hirudinaceus*) and is described as infective larva (cystacanth). Infection of the final host occurs when they swallow infected intermediate hosts. The young worms reach sexual maturity within 60–90 days in *M. hirudinaceus* (after 20 days in *P. minutus*) and start egg production (=end of prepatent period). *AC* acanthor, *BH* body hooks, *IP* inflamed protrusion of IW, *IW* intestinal wall, *PH* proboscis hooks, *RA* released acanthor

(b) Hammerschmidt et al. (2009) showed a similar type of manipulation that also decreases the possibility that copepods containing as first intermediate hosts the procercoid larva of the fish tapeworm *Triaenophorus crassus* are ingested by non-competent fish species, which cannot act as a second intermediate host (developing the plerocercoid larva) as it becomes possible by some other especially adapted fish species. Final hosts of this pseudophyllidean species are fish, which belong to the raptor group (Mehlhorn 2016; Wiesner and Ribbeck 1978).

(c) Another more simple type of "bodyguard dimension" is described by Milinski (1985). The specimens of the stickleback species *Gasterosteus aculeatus* avoid any predator when infected by microsporidian cysts of the species *Glugea anomala* thus giving higher chances to this protozoan parasites to produce of much more infective spores, which would not be set free in case of an early killing of the host fish by a predator (Fig. 8.2a, b).

(d) Again another type of "bodyguard dimension" is found in the transmission cycle of the bird malaria species *Plasmodium gallinaceum*. These protozoan parasites stimulate their insect vector (the mosquito *Aedes aegypti*) twice in a sequential manner. During the phase when the sporozoites of the protozoan parasites are not yet produced or not yet infectious, the female mosquito shows a reduced blood feeding activity. However, the total number of bites and the

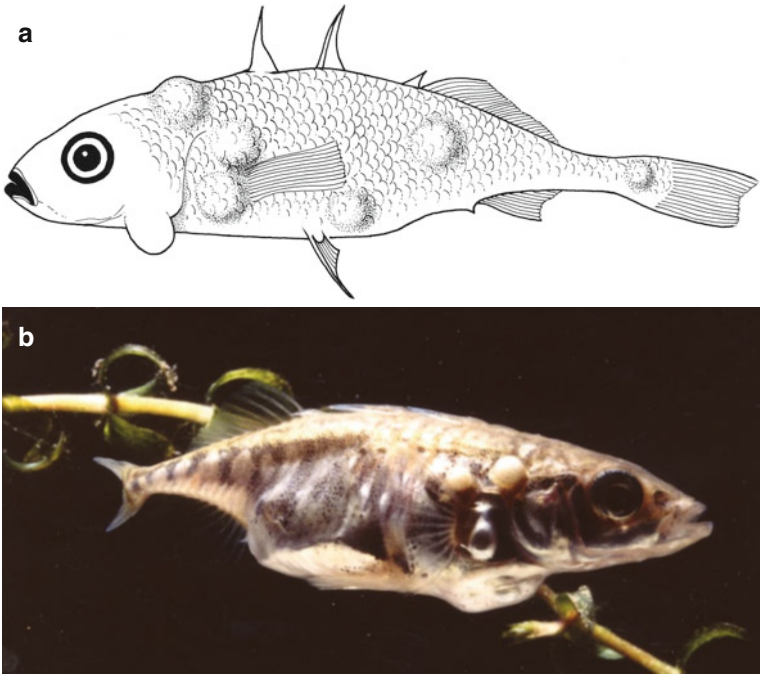

Fig. 8.2 Macroscopic (**b**) and diagrammatic (**a**) representations of a 2-spine-stickleback (*Gasterosteus aculeatus*), which show whitish protruding cysts of a microsporidian species

number of hosts attacked for blood meals becomes considerably increased as soon as the sporozoites have entered the salivary glands of the mosquito and have reached there full infectivity (by producing the typical protecting surface coat) (Koella et al. 2002). Then exist considerable higher chances of the infectious stage of the parasite (sporozoite) to reach a maximum number of their bird hosts.

(e) A simultaneous and multifactorial bodyguard activity was described in the case of the intermediate host *Gammarus insensibilis* infected by the trematode *Microphallus pupillorobustus*. There the infected crustacean shows several bodyguard-like behavioural changes that protect the included worm stage from being ingested by the wrong host (e.g. non-patent predators). Among these peculiar modifications occur: changing to a positive phototactism, negative geotactism, a different evasive behaviour, longer intermolt periods, reduced pairing activity and thus reduced fecundity and finally an increase of its glycogen contents being surely supporting the enclosed parasite (Helluy 1984; Ponton et al. 2005; Thomas et al. 1995; Maure et al. 2013).

8.4 Conclusions

The above described systems of bodyguard protection or related host-parasite combinations are probably only the tip of the iceberg of the true amount of such interactions. Rarely and unsufficiently investigated are also the different steering systems and types of physiological interactions between the partners in a bodyguard system. Thus research in this field is urgently needed.

Literature

Bethel WM, Holmes JC (1977) Increased vulnerability of amphipods to predation owing to an altered behaviour induced by larval acanthocephalans. Can J Zool 55:110–115

Eberhard WG (2001) Under the influence: webs and building behavior of *Plesiometa argyra* (Araneae, Tetragnathidae) when parasitized by *Hymenoepimecis argyraphaga* (Hymenoptera, Ichneumonidae). J Arachnol 29:354–366

Eberhard WG (2010a) Recovery of spiders from the effects of parasitic wasps: implications for fine-tuned mechanisms of manipulation. Anim Behav 79:375–383

Eberhard WG (2010b) New types of behavioral manipulation of host spiders by a parasitoid wasp. Psyche 2010, Article ID 950614, doi:10.1155/2010/950614

Hammerschmidt K, Koch K, Milinski M, Chubb JC, Parker GA (2009) When to go: optimization of host switching in parasites with complex life cycles. Evolution 63:1976–1986

Hart BL (1990) Behavioural adaptations to pathogens and parasites: five strategies. Neuroscience and Behavioural Rev 14:273–294

Harvey JA, Tanaka T, Kruidhof M, Vet LEM, Gols R (2011) The 'usurpation hypothesis' revisited: dying caterpillar repels attack from a hyperparasitoid wasp. Anim Behav 81:1281–1287

Helluy S (1984) Relations hôtes-parasites du trématode *Microphallus papillorobustus* (Rankin, 1940) III – facteurs impliqués dans les modifications du comportement des *Gammarus*, hôtes intermédiaires et tests de prédation. Ann Parasitol Hum Comp 59:41–56

Horwitz P, Wilcox BA (2005) Parasites, ecosystems and sustainability: an ecological and complex system perspective. Int J Parasitol 35:725–732
Jensen M, Mehlhorn H (2009) 75 years of Resochin in the fight against malaria. Düsseldorf University Press, Düsseldorf
Koella JC, Rieu L, Paul REL (2002) Stage-specific manipulation of a mosquito's host-seeking behavior by the malaria parasite *Plasmodium gallinaceum*. Behav Ecol 13:816–820
Maure F, Brodeur J, Ponlet N, Doyon J, Firlej A, Elguero É, Thomas F (2011) The cost of a bodyguard. Biol Lett 7:843–846
Maure F, Daoust SP, Brodeur J, Mitta G, Thomas F (2013) Diversity and evolution of bodyguard manipulation. J Exp Biol 216:36–42
Médoc V, Rigaud T, Bollache L, Beisel JN (2009) A manipulative parasite increasing an antipredator response decreases its vulnerability to a nonhost predator. Anim Behav 77:1235–1241
Mehlhorn H (ed) (2016) Encyclopedia of parasitology, 4th edn. Springer, New York/Berlin
Milinski M (1985) Risk of predation of parasitized sticklebacks (*Gasterosteus aculeatus* L.) under competition for food. Behaviour 93:203–216
Parker GA, Ball MA, Chubb JC, Hammerschmidt K, Milinski M (2009) When should a trophically transmitted parasite manipulate its host? Evolution 63:448–458
Ponton F, Biron DG, Joly C, Helluy S, Duneau D, Thomas F (2005) Ecology of parasitically modified populations: a case study from a gammarid trematode system. Mar Ecol Prog Ser 299:205–215
Poulin R (2010) Parasite manipulation of host behavior: an update and frequently asked questions. Adv Stud Behav 41:151–186
Taraschewski H, Sures B (2016) Acanthocephala. In: Mehlhorn H (ed) Encyclopedia of parasitology, 4th edn. Springer, New York/Berlin
Thomas F, Renaud F, Derothe JM, Lambert A, Meeüs T, Cézilly F (1995) Assortative pairing in *Gammarus insensibilis* (Amphipoda) infected by a trematode parasite. Oecologia 104:259–264
Thomas F, Fauchier J, Lafferty KD (2002a) Conflict of interest between a nematode and a trematode in an amphipod host: test of the 'sabotage' hypothesis. Behav Ecol Sociobiol 51:296–301
Thomas F, Schmidt Rhaesa A, Martin G, Manu C, Durand P, Renaud F (2002b) Do hairworms (Nematomorpha) manipulate the water seeking behaviour of their terrestrial hosts? J Evol Biol 15:356–361
Thomas F, Poulin R, Brodeur J (2010a) Host manipulation by parasites: a multidimensional phenomenon. Oikos 119:1217–1223
Thomas F, Poulin R, Brodeur J (2010b) Infection syndrome and multidimensionality: two terms for two different issues. Oikos 119:1230
Wiesner E, Ribbeck R (1978) Wörterbuch der Veterinärmedizin. G. Fischer, Jena

Chapter 9
Remote Control: Parasite Induced Phenotypic Changes in Fish

Thomas Kuhn, Regina Klapper, Julian Münster, Dorian D. Dörge, Judith Kochmann, and Sven Klimpel

9.1 Introduction

According to the concepts of evolution and adaptation, the entire biology of all animal species, whether free-living or parasitic, is a result of and geared towards its survival and reproduction. By definition, a parasite is an organism that lives on or in another organism (host) exploiting the resources necessary for their own survival and causing it harm. Although probably one of the most successful life strategies in nature (in fact, it is generally believed that parasites outnumber free-living species in food webs), limiting determinant is doubtlessly the need of the parasite to encounter an appropriate host at each stage of its life cycle (e.g. Windsor 1998; MacKenzie 1999; Poulin and Morand 2004; Rossiter 2013). The life-cycle of fish parasites can either be direct or indirect, i.e. involving one or a trophic transmission via several host species, respectively. Fish parasites with a complex life cycle are faced with a particular challenge in large volume aquatic environments where densities of hosts are generally low. Under such circumstances, the emergence of specific strategies to increase frequencies of encounters of parasites and hosts seems inevitable (Cézilly et al. 2010). Parasites have evolved strategies to increase the probability of a successful transmission, i.e. either by increasing random encounters simply by disseminating vast amounts of propagules, or by producing specified propagules that will reduce the randomness of host encounters (Combes 1991; Sasal and Thomas 2005).

Among these strategies, the (targeted) alteration of the host's phenotype is certainly the most impressive and spectacular way of a parasite to improve its odds in the transmission process. Although it has generated a lot of attention among

T. Kuhn (✉) • R. Klapper • J. Münster • D.D. Dörge • J. Kochmann • S. Klimpel
Institute for Ecology, Evolution and Diversity, Senckenberg Biodiversity and Climate Research Centre, Senckenberg Gesellschaft für Naturforschung, Goethe-University, Max-von-Laue-Str. 13, Frankfurt/Main D-60439, Germany
e-mail: t.kuhn@bio.uni-frankfurt.de

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scientists who put massive efforts into the documentation and exploration of these phenomena, the basic mechanisms behind these alterations remain largely unknown. Those who have thoroughly studied and reviewed the facilitation of parasite transmission and demographic effects, (physiological) mechanisms, adaptive nature, population biology, and phenotypic alterations in hosts in the context of parasite induced changes in host behaviour are, to name but a few, Barber (2007), Barber et al. (2000), Combes (1991), Dobson (1988), Hurd (1990), Lafferty (1999), Moore (1984, 2002, 2013), Moore and Gotelli (1990), Poulin (1994), Poulin and Thomas (1999).

Combes (1991) analysed the elementary ethological mechanisms that may have been the object of selection in a parasite's life cycle and coined the term "favorization" which describes an adaptive ethological process modifying the spatio-temporal positions of the parasite and its target in a way that increases the probability of their encounter. Kuris (1997) introduced the more specific term "parasite increased susceptibility to predation" to represent the manipulation by a parasite that increases predation on its intermediate hosts. Lafferty (1999) refined this later as "parasite increased trophic transmission (PITT)" under the assumption that an increased predation is not necessarily adaptive (cf. Combes 1991).

In this context, Poulin (1995) pointed out that phenotypic changes can only be considered adaptive if certain prerequisites apply and proposed four criteria to distinguish between adaptive and non-adaptive alterations: (1) complexity of alterations, (2) degrees of purposive design, (3) independent evolution among lineages, and most importantly, (4) an increase of the fitness of the host. However, the question whether phenotypic host alterations are of adaptive origin or rather side effects or "by products" of an infection, is still controversially discussed (e.g. Cézilly et al. 2010; Thomas et al. 2012).

An impressive number of publications exist that have compiled and categorised parasitic infections and the correlated occurrence of changes in phenotypic traits (e.g. behaviour, morphology, physiology) of their hosts. Among those, many studies on fish parasites have documented an impact on almost every aspect of fish behaviour (Barber et al. 2000). The aim of this short communication is to provide a quick and basic overview over the forms and diversity of parasite induced behavioural changes in marine and freshwater fish species. Most frequently reported parasites and fish behaviour alterations were compiled and presented in a table. Additionally, some parasite specific forms of behaviour are exemplified in the text. As this overview study does not claim to be exhaustive, we refer the reader to more detailed and in depth reviews by e.g. Barber (2007), Barber et al. (2000), Dobson (1988), Moore (2002).

9.2 Forms of Host Manipulation

Host manipulation, best studied and known from parasites with indirect life cycles, seems to enhance probabilities of transmission and vulnerability to predatory definitive hosts (Moore 2002; Thomas et al. 2005). Poulin (2010) defined host

manipulation as any alteration in host phenotype induced by a parasite that has fitness benefits for the parasite. As such, typical phenotypic changes in hosts comprise behavioural alterations alongside changes in host morphology and/or physiology. As described by Thomas et al. (2005) there are two ways of how parasites can alter host behaviour. Direct mechanisms involve interactions with nervous system or muscle, e.g. neuroactive substances may be secreted by the parasite resulting in a behavioural change of the host. Indirect effects can occur when the presence of the parasite affects host development, intermediate metabolism and/or immunity, leading secondarily to changes in behaviour (host-mediated). By the same token it is assumed that a direct manipulation of the host's behaviour requires the parasite to expend energy, whilst indirect manipulations do not pose additional energetic costs for the parasite. However, a differentiation of manipulative behavioural changes (direct and indirect) as well as the isolation of specific mechanisms has proven to be difficult. Another problem is that many results on parasite induced behavioural changes in hosts have been obtained in laboratory experiments. Thus, they might only be valid under controlled conditions and their relevance in the field needs to be considered carefully. In conclusion, changes in host behaviour are most likely a mix of direct and indirect effects and it is believed that the basic mechanisms behind host manipulation involve four physiological systems, which are to a large extent interconnected: neural, endocrine, neuromodulatory, and immunomodulatory (Lafferty and Shaw 2013).

Various alterations in behaviour of hosts infected by parasites are known and have been extensively described by Moore (2002). In fish hosts, they are frequently reported from host individuals carrying very heavy parasite burden (Barber et al. 2000). In this section, a general overview of the most common behavioural changes in fish hosts will be given: foraging behaviour (Fig. 9.1), implications on motility (Fig. 9.2), altered sexual behaviour (reproduction) (Fig. 9.3), anti-predator behaviour (predator avoidance) (Fig. 9.4), and habitat selection (Fig. 9.5). For a more extensive review see Barber et al. (2000).

9.2.1 Foraging Behaviour (Fig. 9.1)

Alterations of foraging behaviour may either be directly caused by the physical presence of the parasite that restricts the capacity of the stomach (Wright et al. 2006), or a response of the host to compensate for the physiological disadvantages by the infection (e.g. Godin and Sproul 1988). One of the disadvantages is that parasites utilize the host's energy reserves for their own growth and development. Thus, energetic drain is one of the major physiological implications of parasite infections leading to nutritional stress in the host. However, nutritional stress can also be a consequence of infections that reduce the competitive ability or act on the foraging success (Barber and Wright 2005). Hence, one way to counteract the energetic limitation is to avoid food competition through alterations in prey choice and diet composition (e.g. Milinski 1984). Another way for compensation is to increase time for

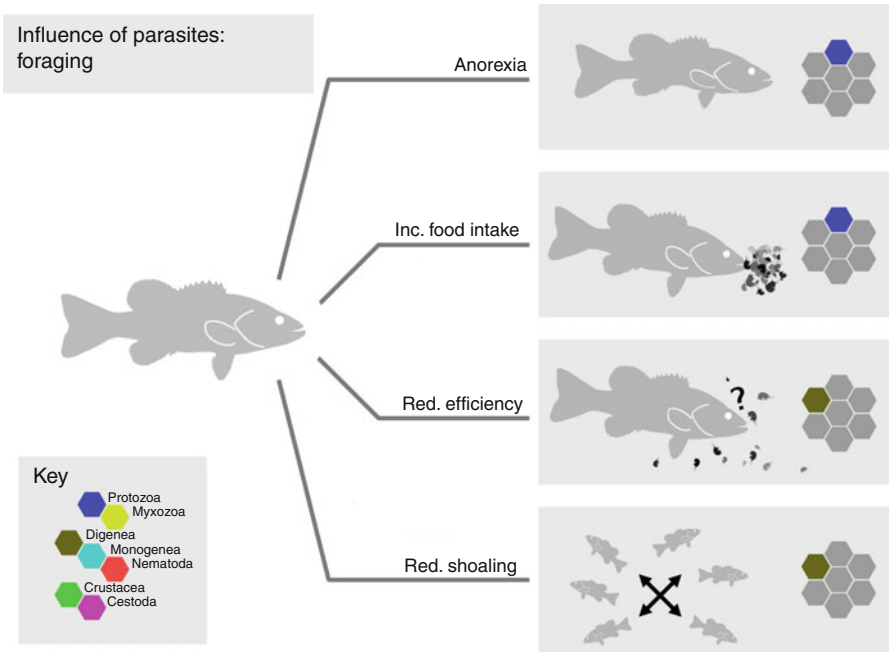

Fig. 9.1 Influence of parasites on foraging behaviour of fish host

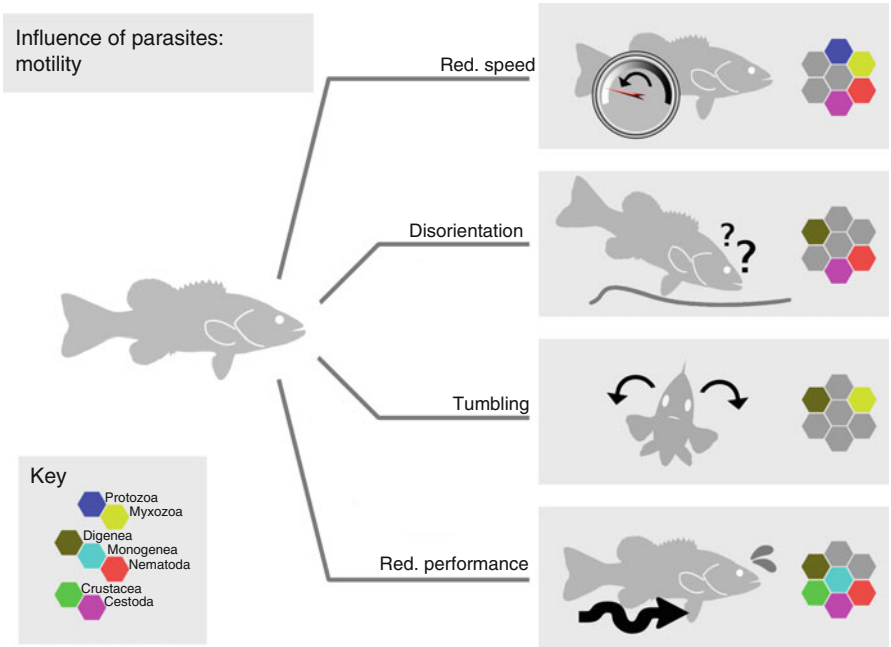

Fig. 9.2 Influence of parasites on motility of fish host

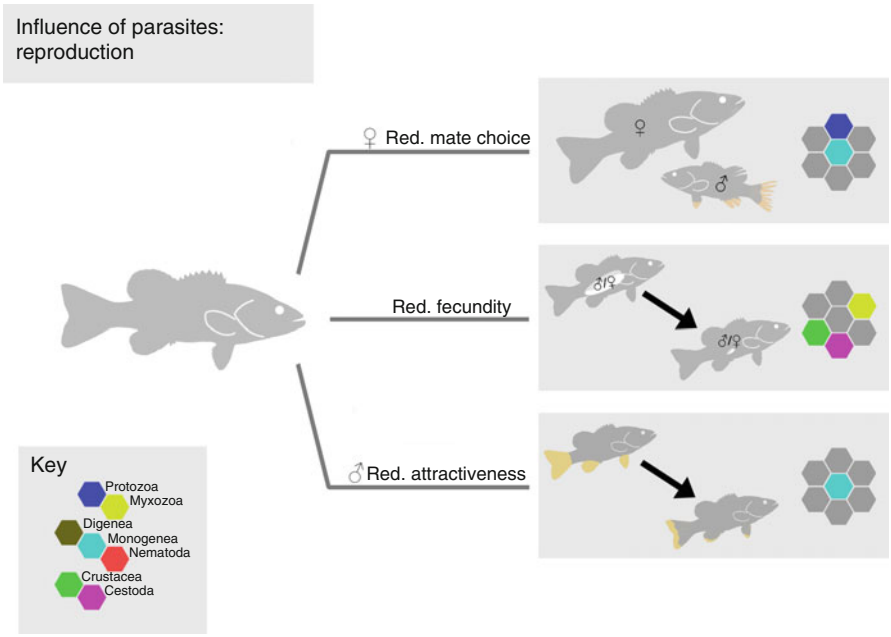

Fig. 9.3 Influence of parasites on reproduction of fish host

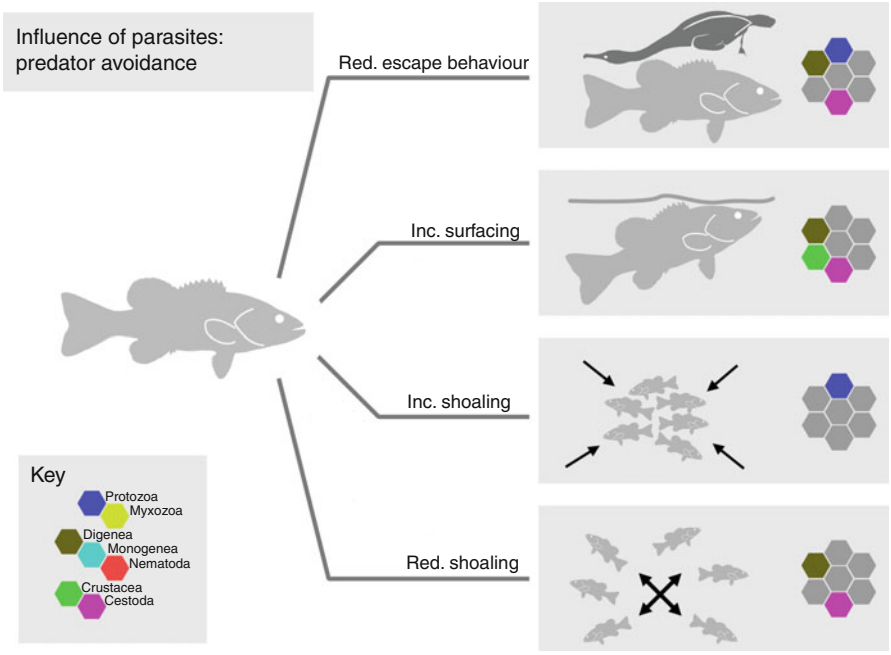

Fig. 9.4 Influence of parasites on predator avoidance of fish host

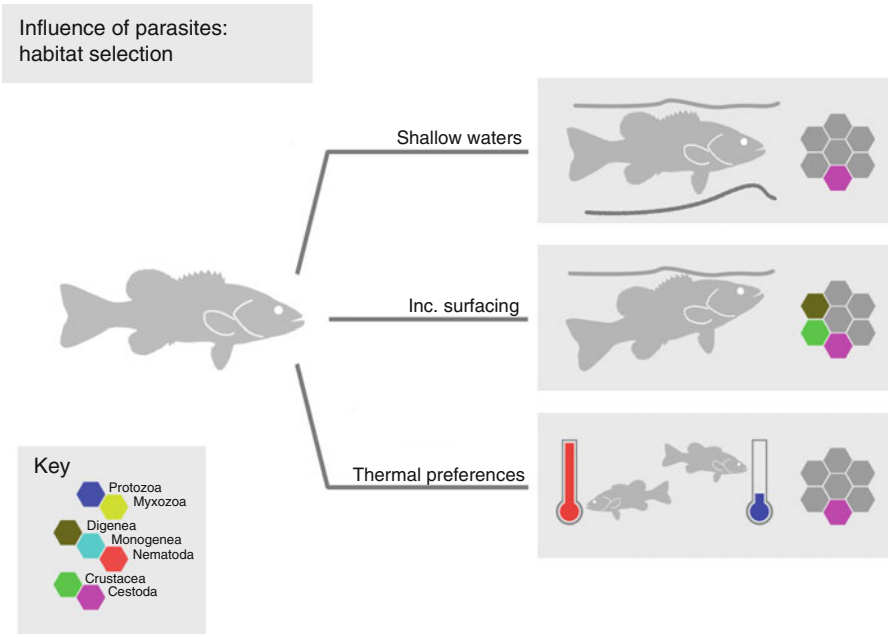

Fig. 9.5 Influence of parasites on habitat selection of fish host

foraging, which is a typical behaviour of hosts infected by large parasite species (Barber and Wright 2005; Östlund-Nilsson et al. 2005). Conversely, decreased foraging is observed in hosts infected with highly pathogenic parasites and might be caused by decreased appetite, which may be an adaptive strategy by the host to deprive energy for the parasite and consequently lower the growth rate of parasites (Bernier 2006, 2010; Chin et al. 2004).

9.2.2 Implications on Motility (Fig. 9.2)

Motility is a key element of organisms and a prerequisite for flight and foraging behaviour. Changes in motility can be found in a wide variety of fish genera. Here, parasite infections mostly result in reduced, but versatile, swimming behaviour, e.g. due to muscle atrophy, a damaged nervous system or impairment of blood circulation (Barber 2007; Coleman 1993; Shirakashi and Goater 2005; Sweeting 1977). Frequent infection sites are organs necessary for orientation such as eyes, inner ear, nostrils and linea lateralis (Barber 2007). Fish motility might also be affected by infestations of the cardio-visceral system or infections with blood sucking ectoparasites compromising the endurance and swimming performance (Barber 2007; Coleman 1993). Whether ectoparasites increase the host's energetic costs of

swimming, e.g. by changing hydrodynamics, is controversially discussed (Binning et al. 2014; Östlund-Nilsson et al. 2005).

9.2.3 *Reproduction (Fig. 9.3)*

How parasites alter the reproductive behaviour of their hosts includes a broad research spectrum. Here, only gonad development, mate choice, courtship, and parental care will be addressed briefly. A widely distributed strategy of parasites is the interference with host reproductive effort (Barber et al. 2000). Fecundity reduction can be caused by parasites through simple nutrient theft ('consumers') or manipulation of energy allocation away from reproduction to growth ('castrators') (Baudoin 1975; Hall et al. 2007; Heins et al. 2010). Most likely as a response to the reduced fecundity, two phenomena, known as 'gigantism' and 'early infection fecundity compensation', are known from infected hosts (see Hall et al. 2007). Host castration occurs widely among taxa, but most often occurs in invertebrates such as crustaceans, echinoderms, and molluscs. This can be explained by a higher investment in reproductive tissues relative to the body mass in smaller species (Lafferty and Kuris 2009). However, a variety of fish are also affected (in Fogelman et al. 2009).

Alternatively to direct physical implications, parasites can also alter mating behaviour. Sexual selection is the preference of certain mating partners over others in order to increase fitness. Traits that are selected include benefits such as parental care, attractiveness of offspring, and resistance against pathogens and parasites (Andersson 1994). The Hamilton-Zuk (H-Z) hypothesis (1982) states that females choose their mating partners based on the evolved secondary sexual characters, which should reflect the heritable resistance to parasites. More specifically, it is hypothesized that female sticklebacks prefer brighter males because (1) colouration reflects the healthiness of the mating partner, i.e. males would be pale if they were infected with white-spot disease (2) after spawning males do parental care and healthier males should be more able to defend the eggs (Milinski and Bakker 1990), and (3) the offspring are more resistant to parasites which is especially beneficial in habitats with high parasite abundance (Barber et al. 2000). On the latter point, a study has been conducted that supported the sexual ornamentation theory (H-Z hypothesis) and showed a trade-off between growth and parasite resistance, which may reflect the maintenance of heritable variation in infection resistance and male colouration (Barber et al. 2000). In order to further study the heritability of resistance to pathogens and parasites, a variety of studies has focused on the diversity of major histocompatibility complex (MHC) alleles which is important in controlling the vertebrate immune system and plays a considerable role in mate choice (Consuegra and Garcia de Leaniz 2008; Eizaguirre et al. 2012; Reusch et al. 2001).

9.2.4 *Predator Avoidance and Microhabitat Selection (Figs. 9.4 and 9.5)*

Trophically transmitted parasites may facilitate their transmission by manipulating their hosts for higher vulnerability to predation (Parasite transmission hypothesis, Kuris 1997; Moore 2002). As predation has a serious fitness consequence for both hosts and parasites there should be strong selection on avoidance traits (Barber et al. 2000). Parasite-induced host vulnerability to predators should occur in a way that targets an increase in predation by a definitive host, as otherwise a non-host predation would lead to the end of the parasite life-cycle (Mouritsen and Poulin 2003). Predators themselves should avoid infected fish if parasites pose a high impact on their constitution (Barber et al. 2000). There are several ways of parasite-induced changes on predator avoidance which facilitate a transmission of parasites from intermediate to final hosts.

Protective colouring is a host adaptation to decrease the risk of being detected by a predator and can be lost by parasite-induced morphological changes such as white- and black-spot disease making parasites more visible on the host (Bakker et al. 1997; Krause and Godin 1996; Milinski 1985). Another example is the orange-yellow acanthocephalan parasite *Pomphorhynchus laevis*. As it is visible through the transparent cuticle of crustacean *Gammerus pulex* the crustacean becomes more prone to fish predators (Bakker et al. 1997).

In order to not encounter their predators, fish avoid being present at the same time and place as their predators (Barber et al. 2000). Hosts that have been parasitized, however, need to increase foraging activity and thus, seem to return to feeding more quickly after a frightening event compared to uninfected individuals (Giles 1983; Godin and Sproul 1988). A form of predator avoidance is shoaling. Fish form preferentially large shoals, especially after a predator attack, due to the effects of predator confusion, risk dilution and early predator detection (see Krause and Godin 1994a). A social adaptation of fish against parasites may be to form larger shoals in their presence in order to reduce the individual risk to acquire a parasite (Poulin and FitzGerald 1989). Conversely, parasitized fish have been shown to spend less time in shoals and occur more frequently in the more risky peripheral shoal positions (Krause and Godin 1994b).

Parasite-induced alterations in predator avoidance often overlap with habitat choice. Habitat choice is associated with predator avoidance, mating, and foraging behaviour (Barber et al. 2000). Parasites may alter aggression levels and territorial behaviour which affect vulnerability to predators due to reduced avoidance (Mikheev et al. 2010). Alterations in habitat choice can also be related to physiological restrictions. Parasites might pose high metabolic demands, e.g. ectoparasites on the gills reduce the oxygen level for host respiration or impair gas exchange efficiency (Barber and Wright 2005; Smith 1972). As a consequence fish need to compensate the respiratory deficiency through location of habitats with higher oxygen levels. Such habitats are usually near the water surface where fish are more visible to avian predators (Barber and Wright 2005; Lester 1971). Physiological restrictions such as

cataracts caused by eye-infecting parasites lead to surface-swimming behaviour and consequently increase the risk of being detected (Crowden and Broom 1980). Impairments in the visual performance forces fish to sojourn at habitats with better light conditions, and reduce the ability to recognize predators (Seppälä et al. 2004).

9.3 Examples of Phenotypic Changes in Fish

Based mainly on the reviews by Moore (2002) and Barber et al. (2000), 57 studies were chosen to represent common parasite-fish behavioural interactions and covering as many different parasite species and hosts as possible. Behavioural changes were found among seven different parasite groups: Protozoa (Microsporidia, Sporozoa), Myxozoa, Digenea, Monogenea, Cestoda, Nematoda, Crustacea. Changes were categorized into five major categories (Table 9.1 and Fig. 9.6) based on former classifications used by Barber et al. (2000): foraging, habitat selection, motility, predator avoidance and reproduction. A behaviour that could not be unequivocally assigned was noted as indetermined, e.g. aggressiveness.

The most common behavioural change was involving motility with 34 cases, followed by predator avoidance (10), reproduction (8), foraging (5), and habitat selection (3). Most species involved in behavioural changes were found among the group of Digenea, with 13 different parasite species, followed by Cestoda with 6 different species. All other groups were more or less equally represented by 3 or 4 different parasite species. Within the Digenea *Diplostomum spathaceum* seems to infest different host species causing a different behavioural change in each. In contrast to this, *Myxobolus cerebralis*, a species belonging to the Myxozoa, occurs in many different fish species but evokes only changes in motility, known as whirling disease. In the group of Cestoda, *Ligula intestinalis* seems to infect at least three different fish species of which all show a different behavioural change, either in reproduction, habitat choice or foraging (Table 9.1).

Glugea anomala, a protozoan species, uses *Gasterosteus aculeatus* as its host and three different types of behavioural alterations have been observed, i.e. foraging, motility and predator avoidance. However, this last example, which is based on two studies (Milinski 1985; Ward et al. 2005), clearly suggests that parasite infections might not only lead to changes in one type of host behaviour (always characterized and interpreted from a human perspective) but might rather be an amalgamation of different behavioural changes possibly associated with other phenotypic changes in the host (e.g. in morphology, physiology). Altogether, these changes might enhance successful trophic transmissions of the parasite.

In the following section some examples of parasite-host interactions depicted in Table 9.1 will be presented in more detail for each parasite group.

Table 9.1 Reported forms of fish host manipulation, including parasite and host species, its phenotypic changes and the respective references

Parasite species	Host species	Form of manipulation	Phenotypic change	References
Protozoa				
Cryptobia salmositica	*Oncorhynchus mykiss*	Foraging	Anorexia	Woo (2011)
Glugea anomala	*Gasterosteus aculeatus*	Foraging	Increased food intake	Milinski (1985), Ward et al. (2005)
G. anomala	*G. aculeatus*	Motility	Reduced swimming speed	Milinski (1985), Ward et al. (2005)
G. anomala	*G. aculeatus*	Predator avoidance	Dorsal spine not raised in presence of predator	Milinski (1985)
G. anomala	*G. aculeatus*	Predator avoidance	Increased shoaling behaviour	Ward et al. (2005)
Ichthyophthirius multifiliis	*G. aculeatus*	Reproduction	Mate choice influenced	Milinski and Bakker (1990)
Pleistophora ladogensis	*Osmerus eperlanus*	Motility	Reduced swimming speed	Sprengel and Lüchtenberg (1991)
Myxozoa				
Kudoa ovivora	Labridae	Reproduction	Reduced fecundity	Swearer and Robertson (1999)
Myxobolus arcticus	*Oncorhynchus nerka*	Motility	Reduced swimming speed	Moles and Heifetz (1998)
M. cerebralis	*Hucho hucho*	Motility	Tumbling movement (whirling disease)	Steinbach Elweell et al. (2009)
M. cerebralis	*Oncorhynchus aguabonita*	Motility	Tumbling movement (whirling disease)	Gilbert and Granath (2003)
M. cerebralis	*O. clarkii*	Motility	Tumbling movement (whirling disease)	Gilbert and Granath (2003), Steinbach Elweell et al. (2009)
M. cerebralis	*O. mykiss*	Motility	Tumbling movement (whirling disease)	El-Matbouli et al. (1999), Gilbert and Granath (2003)
M. cerebralis	*O. nerka*	Motility	Tumbling movement (whirling disease)	Gilbert and Granath (2003)

Table 9.1 (continued)

Parasite species	Host species	Form of manipulation	Phenotypic change	References
M. cerebralis	*O. tshawytscha*	Motility	Tumbling movement (whirling disease)	Gilbert and Granath (2003)
M. cerebralis	*Salvelinus confluentus*	Motility	Tumbling movement (whirling disease)	Gilbert and Granath (2003)
M. cerebralis	*S. fontinalis*	Motility	Tumbling movement (whirling disease)	Gilbert and Granath (2003)
Digenea				
Acanthocollaritrema umbilicatum	*Poecilia vivipara*	Motility	Changes in locomotion	Santos et al. (2011)
Ascocotyle pachycystis	*Cyprinodon variegatus*	Motility	Reduced swimming performance	Coleman (1993)
A. pindoramensis	*Poecilia vivipara*	Motility	Changes in locomotion	Santos and Santos Portes (2013)
Austrodiplostomum mordax	*Basilichthys* sp.	Motility	Tumbling movement, surfacing behaviour	Szidat (1969)
Crassiphiala bulboglossa	*Fundulus diaphanus*	Predator avoidance	Shoaling not increased after predator attack	Krause and Godin (1994a, b)
Diplostomum phoxini	*Cyprinodon variegatus*	Motility	Altered swimming behaviour in heavily infected fish	Rees (1957)
D. spathaceum	*Leuciscus leuciscus*	Foraging	Frequently near surface, reduced feeding efficiency	Crowden and Broom (1980)
D. spathaceum	*Oncorhynchus mykiss*	Indet.	Increased aggressiveness towards conspecifics	Mikheev et al. (2010)
D. spathaceum	*O. mykiss*	Predator avoidance	Reduced escape behaviour in presence of predator	Seppälä et al. (2004)

(continued)

Table 9.1 (continued)

Parasite species	Host species	Form of manipulation	Phenotypic change	References
D. spathaceum	*O. mykiss*	Predator avoidance	Reduced shoaling behaviour in presence of predator	Seppälä et al. (2008)
D. spathaceum	*Poecilia reticulata*	Motility	Sluggish movements	Brassard et al. (1982)
Euhaplorchis californiensis	*Fundulus parvipinnis*	Motility	Erratic motion, surfacing	Lafferty (1997), Lafferty and Morris (1996)
Nanophyetus salmincola	*Oncorhynchus kisutch*	Motility	Reduced swimming performance	Butler and Milleman (1971)
N.salmincola	*O. mykiss*	Motility	Reduced swimming performance	Butler and Milleman (1971)
N. salmincola	Salmonidae	Motility	Reduced swimming performance	Butler and Milleman (1971)
Ornithodiplostomum ptychocheilus	*Pimephales promelas*	Motility	Reduced schooling, reduced optomotor performance	Radabaugh (1980a, b), Shirakashi and Goater (2002)
Psilostomum ondatrae	*Perca flavescens*	Motility	Disorientation	Beaver (1939)
Psilotrema spiculigerum	*P. flavescens*	Motility	Disorientation	Beaver (1939)
Telogaster opisthorchis	*Galaxias vulgaris*	Predator avoidance	Decreased antipredator response	Poulin (1993)
T. opisthorchis	*Gobiomorphus breviceps*	Predator avoidance	Decreased antipredator response	Poulin (1993)
Monogenea				
Gyrodactylus bullatarudis	*Poecilia reticulata*	Motility	Abnormal swimming behaviour	Scott (1985)
Gyrodactylus sp.	*Micropterus salmoides*	Motility	Sluggish movements	Herting and Witt (1967)
G. turnbulli	*Poecilia reticulata*	Reproduction	Females less selective in mate choice	López (1999)
G. turnbulli	*P. reticulata*	Reproduction	Males less showy, reduced colour intensity	Houde and Torio (1992)

Table 9.1 (continued)

Parasite species	Host species	Form of manipulation	Phenotypic change	References
Cestoda				
Diphyllobothrium dendriticum	*Oncorhynchus nerka*	Motility	Disorientation	Garnick and Margolis (1990)
Eubothrium salvelini	*O. nerka*	Motility	Reduced swimming speed, increased fatigue, disoriented migration	Boyce (1979)
Ligula intestinalis	Cyprinidae	Reproduction	Gonadal retardation	Arme and Owen (1968)
L. intestinalis	*Luxilus cornutus*	Habitat selection	Occurrence in shallow water	Dence (1958)
L. intestinalis	*L. cornutus*	Indet.	Indet. (easy to catch)	Dence (1958)
L. intestinalis	*Rutilus rutilus*	Indet.	Indet. (increased predation risk)	Sweeting (1976)
L. intestinalis	*R. rutilus*	Reproduction	Gonadal retardation	Trubiroha et al. (2010)
L. intestinalis	*Scardinius erythropthalmus*	Foraging	Reduced shoaling behaviour	Orr (1966)
Proteocephalus sp.	*Oncorhynchus nerka*	Motility	Disorientation	Garnick and Margolis (1990)
Schistocephalus solidus	*Gasterosteus aculeatus*	Foraging	Reduced feeding efficiency, reduced predator avoidance	Arme and Owen (1967), Barber and Huntingford (1995), Giles (1983), Godin and Sproul (1988), Lester (1971), LoBue and Bell (1993), Milinski (1985), Ness and Foster (1999), Tierney et al. (1993)
S. solidus	*G. aculeatus*	Habitat selection	Altered thermal preferences	MacNab and Barber (2012)
S. solidus	*G. aculeatus*	Reproduction	Reduced fecundity	Heins et al. (2010)
S. solidus	*Pungitius pungitius*	Habitat selection	Occurrence in surface waters	Smith and Kramer (1987)

(continued)

Table 9.1 (continued)

Parasite species	Host species	Form of manipulation	Phenotypic change	References
Schistocephlaus sp.	*P. pungitius*	Predator avoidance	Less time away from surface in presence of predator	Smith and Kramer (1987)
Nematoda				
Anguillicoloides (*Anguillicola*) *crassus*	*Anguilla anguilla*	Motility	Reduced swimming speed, increased O2 consumption	Palstra et al. (2007), Sprengel and Lüchtenberg (1991)
Philonema oncorhynchi	*Oncorhynchus nerka*	Motility	Disorientation	Garnick and Margolis (1990)
Pseudoterranova decipiens	*Osmerus eperlanus*	Motility	Reduced swimming speed	Sprengel and Lüchtenberg (1991)
Crustacea				
Anilocra apogonae	*Cheilodipterus quinquelineatus*	Motility	Reduced swimming performance	Östlund-Nilsson et al. (2005)
A. apogonae	*C. quinquelineatus*	Reproduction	Castration	Fogelman et al. (2009)
Argulus canadensis	*Gasterosteus* spp.	Predator avoidance	Seek surface to avoid parasites	Poulin and Fitzgerald (1989)
Lernaeocera branchialis	*Gadus morhua*	Predator avoidance	Occurrence near surface, reduced fecundity	Khan (1988)
Olencira praegustator	*Brevoortia* sp.	Indet.	Indet. (easy to catch)	Guthrie and Kroger (1974)

9.3.1 Protozoa (Microsporidia, Sporozoa)

Protozoa have developed a great diversity in terrestrial as well as aquatic habitats, with over 100.000 species in more than 40 phyla, and many of them have a parasitic life strategy (O'Donoghue 2005). Some of the parasitic protozoa are suspected to cause changes in host behaviour. These include species, belonging to Mastigophora (e.g. *Cryptobia salmositica*) and Microsporidia (e.g. *Pleistophora ladogensis*, *Glugea anomala*). In the division of Microsporidia more than 1300 species in 150 genera are known, most of them parasitizing invertebrates, but approx. 100 species have been found in fish already. One shared characteristic is their reproduction being linked to host cells (Moodie 2005). The Microsporidia *Glugea anomala* uses three-spined sticklebacks, *Gasterosteus aculeatus* as a common host. Teleost hosts

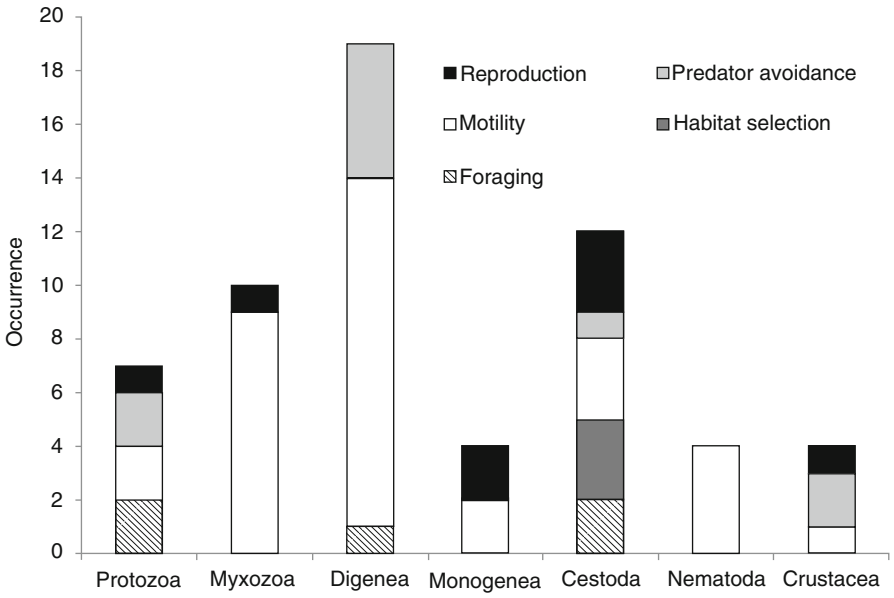

Fig. 9.6 Occurrences of different types of host manipulation found for each parasite group

of *G. anomala* become infected by ingesting spores directly from the water column or by preying on infected invertebrates. In the host tissue *G. anomala* forms xenoma by hypertrophic grows of the host cells accumulating millions of spores within them (Weissenberg 1968). Xenoma usually form in the head region of the fish as visible small white cysts, which burst open and release the containing spores (Ward et al. 2005). Moodie (2005) speculated that migratory movements are effected by cysts in muscle tissue. Ward et al. (2005) observed weight loss of naturally infected *G. aculeatus*, compared to none infected. Therefore, *Glugea anomala* seems to influence the fish host energetic costs. It also seems to have an impact on predator avoidance and shoaling behaviour: Under experimental conditions infected specimens showed increased tendency to form shoals, presumably as a predator avoidance mechanism and to take leading positions, within it, which is probably a concession to the higher food supply as it increases their chance to prey more, compared to other positions in the shoal (Krause 1994; Milinski 1985; Ward et al. 2005).

An example for decreased foraging behaviour is *Cryptobia salmositica* and its host, the rainbow trout (*Oncorhynchus mykiss*). *Cryptobia salmositica* is a parasitic flagellate (class Kinetoplastea) that has been categorized as haemotozoic (Woo 2011). Rainbow trout get infected either when *C. salmositica* multiplies in the crop of infected blood-sucking leech (*Pisciola salmositica*) that transmit the kinetoplast with the following blood meals (Woo 1994), or from fish to fish (Woo 2011). Clinical signs of infections are high amounts of mucus on the body surface, lethargy, and less movement of the fish. During the acute phase of the infection, the host has obvious lesions in haemopoietic tissues, and up to five weeks after the infection

the fish shows anorexia causing an energetic drain (Woo 2011). On the one hand, this can lead to immune-depression, which often facilitates secondary diseases (Jones et al. 1986; Thomas and Woo 1992). On the other hand, anorexia has been shown to be beneficial because it lowers the plasma protein level and consequently reduces the severity of the infection (Li and Woo 1991). Anorexia and anaemia are most consistent clinical signs of the parasite infection (Woo 2011).

9.3.2 Myxozoa

Myxozoa are economically important spore-forming metazoan endoparasites, occurring predominantly in fish (MacKenzie and Kalavati 2014; Yokoyama et al. 2012). Hitherto more than 1350 species, belonging to 52 different genera are described, occurring in freshwater and marine habitats. For a long time it was controversially discussed whether they belong to the proto- or metazoan just as long they were assumed to perform a monoxenous life cycle, until 1986 the alternation of *Myxobolus cerebralis* between *Oncorhynchus mykiss* and *Tubifex tubifex* was proven (Smothers et al. 1994; Wolf et al. 1986). Today, the heteroxenous life cycle, including invertebrates and vertebrates, is common knowledge (Hedrick et al. 1998; Kent et al. 2001). The life cycle of Myxosporea alternates mostly between annelids and teleost. The life cycle includes an actinosporea-spore as infectious stadium in the invertebrate and a myxosporea-spore in the vertebrate host. Previously these spores had been classified as different species. While oligochaetes serve mostly as invertebrate hosts in freshwater waters, in marine waters only polychaetes are known (see review MacKenzie and Kalavati 2014). The vertebrate host gets infected by consuming myxosporea-spores, which anchor themselves in the host gut epithelium using polar filaments and inject an infectious sporoplasm (El-Matbouli and Hoffmann 1998). The sporoplasm then develops into a species-specific actinosporea-spore (e.g. tricatinomyxon (*Myxobolus cerebralis*), hexactinomyxon (*Myxobolus pavlovskii*), or aurantiactinomyxon (*Hofferellus carassii*) (El-Matbouli and Hoffmann 1998; Kent et al. 2001). These spores are released with the faeces into the water column, where they attach themselves to the teleost host skin and release again a sporoplasm into mucous cells which develop into myxosporea-spores. Later again, these are, depending on the species, released with the faeces into the water column or are otherwise set free after death of the teleost host (Kent et al. 2001). Spores, e.g. of *Myxobolus cerebralis*, can be set free, after digestion of predatory fish or birds with their faeces (Gilbert and Granath 2001; Hedrick et al. 1998). *Myxobolus cerebralis* is the known agent of the whirling disease and is mainly infecting different economically important salmonids in freshwater (Hedrick et al. 1998). Particularly young fish seem to be very susceptible to the effects of the disease and heavy infections often result in their death (Gilbert and Granath 2001). Beside morphological changes such as a black-ended tail and deformations, *Myxobolus cerebralis* causes specific behavioural changes in its teleost host (Gilbert and Granath 2001; Hedrick et al. 1998). Rose et al. (2000) observed three specific

behaviours associated with whirling disease in *Oncorhynchus mykiss*, (a) a repeated rapid circular swimming, a kind of startle response, (b) lack of corrective movement while in a static position in the water, resulting in a tail-up head-down posture, (c) discontinued swimming movement and sinking to the bottom. The whirling movement is probably caused by a constriction of the spinal cord, repeatedly triggering impulses for tight turns until the signals are interrupted by competing sensory stimuli (Rose et al. 2000). It can be assumed that those changes, caused by *M. cerebralis*, increase the risk of predation, hence accelerating the release of the myxosporea-spores back into the water column.

9.3.3 Digenea

Digenean trematodes are endoparasites with complex life cycles that vary considerably between the taxa. These parasites commonly occur in the alimentary tract of their definitive host, which is, in most cases, a vertebrate (Cribb 2005). A typical life cycle includes the motile miracidium stage that hatches from an egg dispersed within the host's faeces. Molluscs are the first obligate intermediate hosts in which the miracidium develops into an asexually reproducing sporocyst that may either produce further generations of sporocysts or alternatively one or more generations of rediae which themselves release infectious stages known as cercariae. Cercariae leave the mollusc and will be either encysted (metacercariae) in or on a second intermediate host (e.g. crustaceans, plants) or directly infect the final host and grow into the adult stage (Cribb 2005; Möller and Anders 1986). Additional intermediate hosts may be incorporated before infecting the definitive host. Digenea typical for fish are represented by the families Derogenidae, Hemiuridae, Lecithasteridae and Lepocreadiidae (Klimpel et al. 2009).

Most behavioural changes in marine and freshwater fish can be attributed to parasites belonging to the group of Digenea, with 13 species in at least 13 different host species. Whether these numbers are the result of a high sampling effort due to their enormous medical relevance or are simply reflecting their complex life and thus the various possibilities for host alterations to occur, is not clear. Whilst changes in foraging behaviour of infected fish hosts (*Leuciscus leuciscus*) as well as avoidance of predators (e.g. *Galaxias vulgaris*, *Oncorhynchus mykiss*) have been documented six times, alterations in locomotion and/or motility of fish are by far the most documented changes associated with Digenean infections (Table 9.1).

A popular and very well documented example of motility implications caused by the presence of digenean trematodes in fish is *Euhaplorchis californiensis* infecting killifish, *Fundulus parvipinnis* (Lafferty and Morris 1996). The authors provided probably the best example for a case of increased predation on infected intermediate hosts by definitive hosts. *Euhaplorchis californiensis* is a common trematode in salt marshes of southern California. It has a three-host life cycle, which includes a number of birds as definitive and horn snails *Cerithidea californica* as first intermediate hosts (Lafferty and Morris 1996). When killifish *F. parvipinnis*, the second

intermediate host, becomes infected with cercariae, they show "conspicuous behaviour", i.e., abrupt dashes up to the surface (surfacing), turning laterally so that one side of the body is faced up (flashing), dorsal-ventral bending (contorting) and vibrating for a few seconds (Lafferty and Morris 1996). These behavioural changes have been associated with the parasites encysting the brain case. In experiments, the authors demonstrated that infected specimens had a 10-fold increase susceptibility to be eaten by the definitive hosts than their non-infected conspecifics.

An increased likelihood of detection and attack by predators of hosts has also been associated with infections of *Diplostomum spathaceum* (Fig. 9.7a). After their development in lymnaeid snails (e.g. *Lymnea* sp., *Radix* sp.), the free-swimming cercariae of *D. spathaceum* penetrate the fish skin and migrate into the crystalline lense of the fish (Lyholt and Buchmann 1996). Adult parasites live in the intestines of piscivorously feeding birds (mainly from the family Laridae). The presence of large numbers of parasites in the eye of their host can cause the lense to become opaque which results in a complete lack of responsiveness to visual stimuli as shown for heavily infected trout (Crowden and Broom 1980; Ferguson and Hayford 1941). Generally, reduced visual acuity seems to diminish the host's ability to locate and capture food with the consequence that the feeding efficiency is significantly reduced. Infected fish, e.g. *Leuciscus leuciscus*, compensate this by increasing the net amount of time devoted to feeding and also by foraging in better-illuminated surface waters where they are more prone to predation (Crowden and Broom 1980; Dobson 1988).

In a recent experimental study, rainbow trout (*Onchorhynchus mykiss*) infected with *D. spathaceum* showed increased aggressiveness and altered territorial behaviour (Mikheev et al. 2010). After an initial decrease, the aggression rates of infected *O. mykiss* exceeded that of uninfected control fish, yet, quite surprisingly, they seemed to face reduced "contest ability" in territorial fights. Similarly, Seppälä et al. (2004, 2008) reported reduced escape behaviour as well as shoaling of experimentally infected, juvenile *O. mykiss* in the presence of artificial aerial predators. The authors argued that the reduction in vision is the definitive mechanism that causes the altered fish behaviour and increased susceptibility to predators.

Motility is another trait that can be affected by parasites infesting the cardiovisceral system and therefore compromising the endurance and swimming performance of the fish host (Barber 2007; Coleman 1993). One parasite inducing those changes is *Ascocotyle pachycystis*, usually parasitizing in the bulbus of the sheepshead minnow *Cyprinodon variegatus*. Especially during cold conditions, the negative effect of decreased oxygen transport, caused by increased blood flow resistance by the cysts of *A. pachycystis*, leads to faster exhaustion of parasitized specimens compared to unparasitized specimens (Coleman 1993).

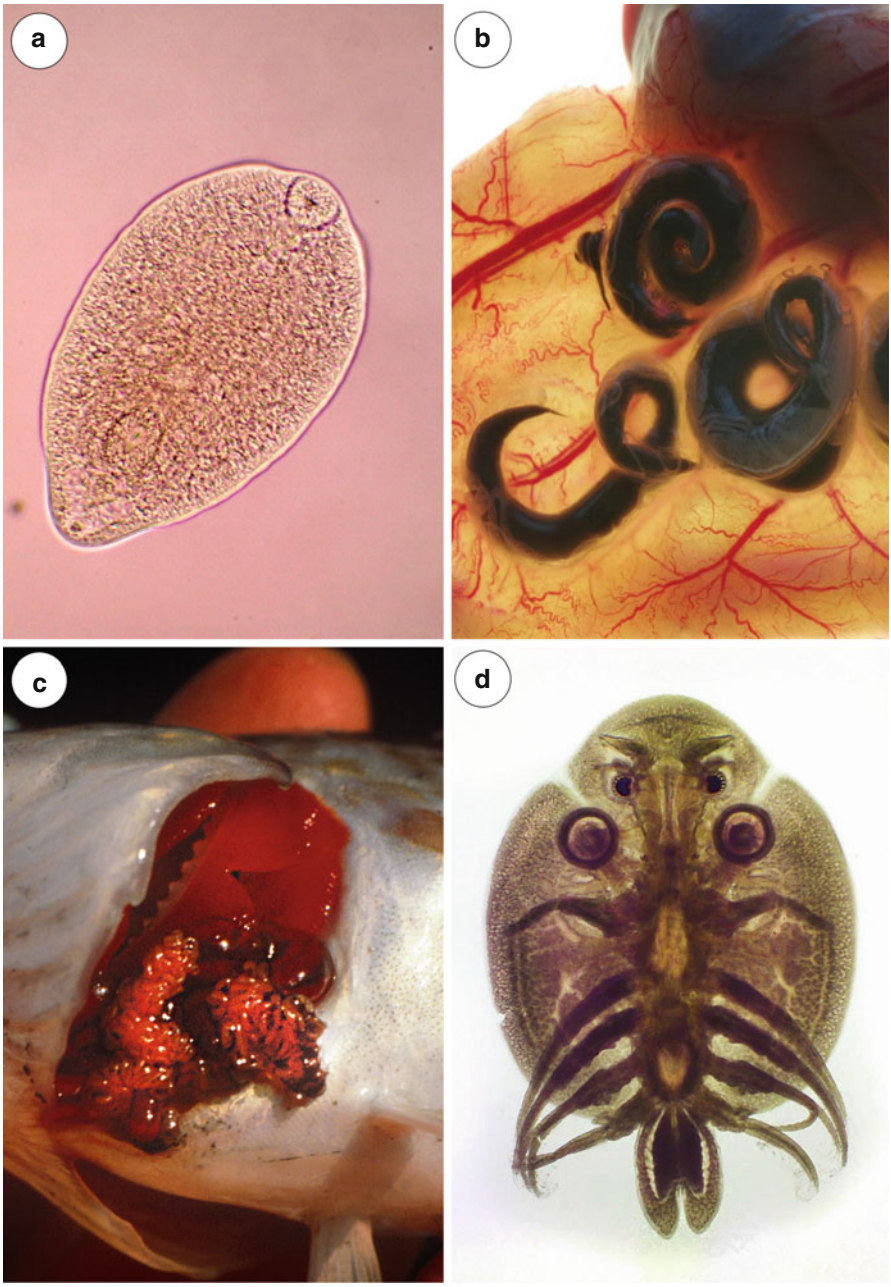

Fig. 9.7 Examples of host manipulating parasites. (**a**) *Diplostomum spathaceum* (Digenea). (**b**) *Anguillicoloides crassus* (Nematoda) in eel swim bladder. (**c**) *Lernaeocera branchiails* (Crustacea) in cod gills. (**d**) *Argulus* sp. (Crustacea) (Photo (a): Emde)

9.3.4 Monogenea

The taxon Monogenea is one of the largest groups of parasitic flatworms. A vast majority is ectoparasitic on the external surfaces (fins, gills, skin) of marine and freshwater fish while some are secondarily endoparasitic in body orifices (e.g. mouth cavity, urinary bladder) (Hayward 2005). A few additional species live on aquatic invertebrates and higher vertebrates such as cephalopods, turtles and amphibians (Möller and Anders 1986). The taxon consists of two sister groups (Monoopisthocotylea, Polyopisthocotylea) that can easily be distinguished by the morphology of their posterior attachment organ (opisthaptor) (Whittington 2005). The development of the monogenean species is direct (i.e. they infect only a single host) and they usually show high degrees of host specificity. The eggs of most species have long appendages used for attachment to the gill filaments of their hosts or to bottom substrates. They can also be found on artificial substrates like e.g. the net caging of aquaculture facilities where mass infections can cause enormous ecological losses (e.g. mass mortality of aquaculture specimens) due to the serious pathological effects on their attachment sites (e.g. skin) caused by their opisthaptor (Hayward 2005). Ciliated larvae (=Oncomiracidium) hatch from eggs, infect the vertebrate host and develop into a single adult parasite.

The role of Monogenea as inducer of phenotypic changes of fish can be considered rather insignificant. Among all the literature, only four descriptions of species were found which all belong to the same genus, *Gyrodactylus* (Table 9.1).

Infections with viviparous *Gyrodactylus bullatarudis* have been associated with the occurrence of an abnormal swimming behaviour of guppys *Poecilia reticulata* (Scott 1985). Heavily infected guppies became lethargic and their fins often sticked together. It is suggested that the abnormal swimming behaviour attracts the attention of conspecifics which, in turn, increases the number of contacts between infected and uninfected hosts (Dobson 1988; Scott 1985).

López (1999) examined the effects on mate choice behaviour of female *P. reticulata* experimentally infected with *Gyrodactylus turnbulli*. The author observed that infected females were significantly less discriminatory than healthy ones when they were exposed to attractive (showy: higher "individual display rate", higher "orange brightness") and unattractive (less showy: lower "individual display rate", lower "orange brightness") males in a simultaneous choice test. López (1999) pointed out that although the results point towards an indirect effect of parasitic infections, where females are probably weakened by infection and, as a result, energetically constrained in their mate choice behaviour (i.e. costs for actively resisting sneaky, less attractive males or cooperation in copulation), a direct manipulation by the parasite, thus a selective advantage, could also be the case. Regardless whether a direct or indirect effect of the infection, parasite transmission and reproduction should be enhanced as infected females come into contact with male conspecifics more often than uninfected ones. In an earlier study, Houde and Torio (1992) reported that male guppies infected with *G. turnbulli* appear to reduce the degree of expression of carotenoid colours (cf. showiness) and that female guppies may be

able to avoid becoming infected themselves by discriminating against these infected males. However, avoidance behaviour of females against infected males would result in a decreased transmission probability and thus putting selective pressure on the parasites.

9.3.5 Cestoda

Cestodes (subclass Eucestoda, true tapeworms) are exclusively endoparasitic with more than 5000 known species (Caira and Reyda 2005). Marine cestodes encompass the four orders Diphyllobothriidea, Bothriocephalidea (the latter formerly known as Pseudophyllidea), Trypanorhyncha and Tetraphyllidea (Caira and Reyda 2005; Kuchta et al. 2008), which are characterized by the morphology of the scolex (Möller and Anders 1983). The life cycles of marine cestodes are complex and require three hosts for completion. In the following section, *Schistocephalus solidus* will be presented as an example for an indirect life cycle. Eggs of *S. solidus* enter the aquatic system with the faeces of infected birds and hatch and develop to a coracidium, i.e. a motile embryo. After ingestion by cycloid copepods they develop into procercoids, which are then eaten by three-spined sticklebacks. In the fish they develop into plerocercoids. The parasite larvae penetrate through the gut wall and grow in the peritoneal cavity until they reach infectivity at a weight of 50 mg (Tierney et al. 1993). Piscivorous birds feeding on infected sticklebacks serve as final hosts (LoBue and Bell 1993).

A well-studied example for host behavioural changes is the host-parasite interaction between the pseudophyllidean cestode *Schistocephalus solidus* and his intermediate host, the three-spined stickleback *Gasterosteus aculeatus*. The rapidly growing parasite induces swelling of the abdomen (Arme and Owen 1967) and places high energy demands on the fish host during the time of parasite growth (Barber and Huntingford 1995). Similar to the effect of a gastric banding the large cestode constricts the stomach and inhibits greater distension (Wright et al. 2006). As a consequence, infected fish prefer smaller, less profitable prey species (Milinski 1984). Furthermore, it has been suggested that the competitive ability might be decreased due to the reduced streamlined shape and smaller energy reserves (Lester 1971; Milinski 1984). In an experiment, Arnott et al. (2000) showed that although energetic demands increased, infected sticklebacks grew faster and had the same or better body condition when being exposed to abundant food resources. Another alteration of behaviour is the willingness to take higher risk under threat of predation (Giles 1983; Godin and Sproul 1988; Milinski 1985). Such ‘boldness’ could be experimentally shown in parasitized *G. aculeatus* that returned more quickly to feeding behaviour after a stimulated predator attack (Giles 1983; Godin and Sproul 1988).

Another result from energy theft caused by *S. solidus* is an alteration of fecundity in three-spined sticklebacks revealed by a reduction in clutch size, egg mass, and clutch mass (Heins et al. 2010). As shown by Heins et al. (2010) infected and

uninfected female sticklebacks produced egg clutches at the same body size and age, however, their egg masses and egg numbers differed.

Reduced fecundity was also found in cyprinids infected with plerocercoids of *Ligula intestinalis* (Arme and Owen 1968; Trubiroha et al. 2010). Although both *S. solidus* and *Ligula intestinalis* are considered to be castrators with similar life cycles, they differ in the way of altering the host reproduction. In roach (*Rutilus rutilus*) gonad development can be retarded in males and females at an early stage of gametogenesis, which may constitute an inhibition of host reproduction through endocrine disruption (Trubiroha et al. 2010). This seems to be a parasite strategy which allocates the host's energy from reproduction to parasitic growth without decreasing host viability (Hurd 2001; Lafferty and Kuris 2009).

9.3.6 Nematoda

The phylum Nematoda represents one of the most species diverse phyla within the Metazoa (Anderson 2000; McClelland 2005). The general nematode life cycle includes four moults and four larval stages. Heteroxeny and paratenesis are common phenomena in the transmission pathways of parasitic species and include intermediate and definitive hosts in nearly every trophic level (McClelland 2005). Because of the dilute nature of aquatic habitats, parasitic nematodes have evolved numerous elaborate means of maintaining themselves in an environment where contact between successive hosts within a life cycle may be periodic or even rare. The use of paratenic hosts, a low host specificity, free living stages that actively search for susceptible hosts as well as the infection of short-lived organisms (e.g. small invertebrates) that occur in vast numbers are only a few examples how nematodes support their temporal and spatial dispersal and increase the likelihood to encounter a successive host (Marcogliese 2005; McClelland 2005). Despite these elaborate means, documentation on parasite induced phenotypic changes of hosts caused by nematode species in aquatic habitats is fairly scarce (Table 9.1). The physical presence of the nematode, e.g. in the musculature of the fish, often results in an impairment of the musculoskeletal system.

The occurrence of certain nematodes (e.g. Anisakidae: *Pseudoterranova*, *Anisakis*) in the musculature or internal organs of their (paratenic) intermediate hosts is well documented and has been extensively investigated on a variety of fish, especially those with high commercial value (for recent studies see e.g. Karl et al. 2011: *Anisakis*; Klapper et al. 2015: *Anisakis*, *Hysterothylacium*; Kuhn et al. 2013: *Pseudoterranova*). Anisakid nematodes have a heteroxenous, aquatic life cycle with vertebrate hosts (pinnipeds, cetaceans, piscivorous birds) as definitive hosts. A broad spectrum of micro- and macroinvertebrates as well as teleost fish serve as intermediate/transport hosts (Mattiucci and Nascetti 2008). Möller and Klatt (1990) found that an infection of smelt *Osmerus eperlanus* with larvae of the sealworm *Pseudoterranova decipiens* reduces overall condition of the host and proposed an increasing susceptibility to predation by their definitive hosts, pinnipeds of the

families Otariidae and Phocidae. Sprengel and Lüchtenberg (1991) demonstrated that a single sealworm in the musculature of a smelt reduced the swimming speed in a circular experimental chamber by 14.7 % compared to uninfected individuals. Infections with more than three nematodes reduced the average speed by up to 32.2 % and co-infections with the microsporidian *Pleistophora ladogensis* led to a decrease of 29.9 %, a higher reduction than that in smelt infected by two nematodes or by microsporidians only (Sprengel and Lüchtenberg 1991). The same test was performed for the swim bladder nematode *Anguillicoides* (*Anguillicola*) *crassus* (Fig. 9.7b) which revealed a reduction of swimming speed by 2.9 % (single nematode) to 18.6 % (more than ten nematodes). In this context, Boon et al. (1990) reported decreased quantities of plasma proteins and a lower haematocrit value in experimentally, heavily infected *A. anguilla*. Sanguivorous activities of the L4 and pre-adult stages decrease the number of circulating erythrocytes and therefore the O_2 carrying capacities. The resulting decreased aerobic performance (energy drain) as well as the mechanical damage of the swim bladder caused by the direct invasion of the pre-adult stages impair the swimming performance of the host and increase overall energy consumption (Palstra et al. 2007).

Parasites can also influence migratory behaviour of their hosts as shown by Garnick and Margolis (1990). The authors measured the interference of three cestodes (*Eubothrium salvelini*, *Diphyllobothrium dendriticum*, *Proteocephalus* sp.) and the nematode *Philonema oncorhynchi* with the orientation of seaward migrating sockeye salmon (*Onchorynchus nerka*) smolts and suggested that parasite infections may account, at least to some extent, for the variability observed in migratory behaviour of smolts (Garnick and Margolis 1990).

Whilst a reduced swimming speed of the intermediate host is advantageous for the transmission of *P. decipiens* into the next host, there seems to be no such benefit for *A. crassus* and *P. onchorhynchi* as both are infecting their final hosts.

9.3.7 Crustacea

Crustaceans comprise a species-rich taxon of metazoan parasites that parasitize a wide range of fishes and invertebrate hosts (Fig. 9.7c, d) (Busch et al. 2012). There are seven groups of crustaceans in which parasitic forms occur: Copepoda (infecting sponges, cnidarians, echinoderms, fishes and mammals), Isopoda (mostly ectoparasitic on crustaceans and fish), Branchiura (only fish lice of the genus *Argulus* in the marine environment), Tantulocarida (ectoparasites of other crustaceans), Cirripedia including Thoracica (parasitic on dogfish and polychaetes) and Rhizocephala (infecting other crustaceans, mainly Decapoda), Ascothoracida (parasitizing echinoderms and cnidarians), and Amphipoda (suborder Hyperiidea on gelatinous zooplankton and Caprellidea on whales). The different groups are described in detail in Rohde (2005) and only life cycles of the main fish parasite groups, namely copepods, isopods, and branchiurans are summarized in the following section.

The life cycle of copepods, a species-rich group of metazoan ectoparasites, is mostly direct and comprises two phases, a naupliar stage with a maximum of six stages and the copepodid stage with a maximum of five stages (Boxshall 2005a). Most parasitic copepods extrude their eggs into paired egg sacs or uniseriate egg strings. Sexual dimorphism is common with females typically larger and more transformed bodies compared to dwarf males (e.g. Chondracanthidae, Lernaeopodidae) (Boxshall 2005a). Eggs of Isopoda hatch in a brood pouch called 'marsipium' where they moult to the 'manca' or 'pullus II' stage (Lester 2005). Mancae larvae are then released to find an intermediate fish host to take their first meal. In the isopod genus *Anilocra* the mancae leave the optional intermediate host, has to find a new fish host, moults, and this is repeated until they settle on the final (fish) host, while the mancae of other species e.g. gill-inhabiting forms or tongbiters and tissue dwellers attach only to one final host (Fogelman and Grutter 2008; Lester 2005). Cymothoids are protandrous hermaphrodites, i.e. the first male that infects a host changes its sex into female, whereas all following males remain males (Lester 2005). In the life-cycle of the branchiuran *Argulus* (Fig. 9.7d), a mature female leaves its host after taking a meal, lays eggs on any hard submerged surface, these eggs hatch, and the free-swimming larvae moult into the second stage which is parasitic as all other subsequent stages (Boxshall 2005b). They change their host at intervals throughout the development until they reach maturation at the fifth larval stage (Boxshall 2005b).

Lernaeocera branchialis (Fig. 9.7c) is a parasitic copepod that infects the gills or mantle cavity of various gadoid species in its adult phase (Kabata 1970). The two-host life cycle involves two nauplius stages, after them copepod larvae parasitize an intermediate fish host on which they mature and mate. The mated adult female leaves the host and has to find a second fish or sometimes a marine mammal as definitive host (Boxshall 2005a). Parasitisation of cod *Gadus morhua* with *L. branchialis* impacts on growth and mortality (Khan 1988). In an experiment young fish infected with *L. branchialis* fed less, were smaller, had a lower weight, and showed reduced fecundity. Additionally, they frequently swam close to the surface probably due to an excess of air in the swim bladder and displayed hyperactivity (Khan 1988).

Parasite-induced alterations in swimming behaviour were detected in brook trout fry *Salvelinus fonatlis* infected with the copepod *Salmincola edwardsii* (Poulin et al. 1991). In an experiment brook trout stayed more time motionless when exposed to *Salmincola edwardsii*, and this decreases the chance to be attacked by the parasite because the parasites reacts to stimuli such as passing shadows. After an initial parasite infection, the time spent motionless in the water is diminished and the fish increases the risk of acquiring further parasite infections.

Sticklebacks (*Gasterosteus* spp.) are parasitized by the branchiuran ectoparasite *Argulus canadensis*, which is a free-living, blood-sucking parasite (Poulin and FitzGerald 1989). Three-spined and black-spotted sticklebacks form larger shoals when the parasite is present in the water and this behaviour was attributed to be selective by lowering the risk for an individual fish to become a target of the branchiuran parasite waiting for suitable hosts to pass (Poulin and FitzGerald 1989).

Cymothoid isopods are usually ectoparasites attached to the skin, gills, or oral cavity (Bunkley-Williams and Williams 1998). Cymothoids have been found to reduce growth, motility, and reproduction (Adlard and Lester 1995; Fogelman et al. 2009; Östlund-Nilsson et al. 2005). In the Great Barrier Reef, cardinal fish *Cheilodipterus quinquelineatus* is regularly parasitized with *Anilocra apogonae*, a large, asymmetrically cymothoid isopod attached on the skin of its host. Besides the need to increase food intake, a decreased swimming speed and endurance of the fish host was noted which might be have been a consequence of the relative increase in size and asymmetric attachment of the parasite negatively impacting the host's hydrodynamics (Östlund-Nilsson et al. 2005). The authors concluded that the energetic stress must be compensated for by increasing foraging, which may at the same time lead to decreased predator avoidance behaviour. Additionally, *A. apogonae* may act as a parasitic castrator parasitized fish were observed to have smaller gonads, fail to mouth-brood (males), or have fewer and smaller ova (female) (Fogelman et al. 2009).

A further example of a cymothoid isopod as parasitic castrator is *Riggia paranensis*. After burrowing into the flesh of freshwater fish *Cyphocharax gilbert*, infections lead to increased growth, but inhibition of the gonadal development through affection of the endocrine system (Azevedo et al. 2006; Lima et al. 2007).

9.4 Concluding Remarks

Regardless of whether caused directly or indirectly, and whether adaptive or a by-product, parasites have a great capability of manipulating host behaviour. Considering only fish as hosts, most examples of parasites altering fish host behaviour are known from the group Digenea and the most common manipulation involves host motility. However, a differentiation of manipulative behavioural changes (direct and indirect) as well as the isolation of specific mechanisms has proven to be difficult. Another problem is that lab studies with freshwater specimens are largely overrepresented reflecting the difficulty of undertaking research in this subject with marine and field studies clearly being much less feasible. Similarly, results might only be valid under controlled conditions and their relevance in the field needs to be considered carefully.

References

Adlard R, Lester R (1995) The life-cycle and biology of *Anilocra pomacentri* (Isopoda, Cymothoidae), an ectoparasitic isopod of the coral-reef fish, *Chromis nitida* (Perciformes, Pomacentridae). Aust J Zool 43:271–281

Anderson RC (2000) Nematode parasites of vertebrates: their development and transmission. CABI Publishing, Wallingford, 676 pp

Andersson M (1994) Sexual selection. Princeton University Press, Princeton, 624 pp

Arme C, Owen RW (1967) Infections of the three-spined stickleback, *Gasterosteus aculeatus* L., with the plerocercoid larvae of *Schistocephalus solidus* (Muller, 1776), special reference to pathological effects. Parasitology 57:301–314

Arme C, Owen RW (1968) Occurrence and pathology of *Ligula intestinalis* infections in British fishes. J Parasitol 54:272–280

Arnott SA, Barber I, Huntingford FA (2000) Parasite–associated growth enhancement in a fish–cestode system. Proc R Soc Lond B Biol Sci 267:657–663

Bakker TCM, Mazzi D, Zala S (1997) Parasite-induced changes in behavior and color make *Gammarus pulex* more prone to fish predation. Ecology 78:1098

Barber I (2007) Parasites, behaviour and welfare in fish. Appl Anim Behav Sci 104:251–264

Barber I, Huntingford FA (1995) The effect of *Schistocephalus solidus* (Cestoda: Pseudophyllidea) on the foraging and shoaling behaviour of three-spined sticklebacks, *Gasterosteus aculeatus*. Behaviour 132:1223–1240

Barber I, Wright HA (2005) Effects of parasites on fish behaviour: interactions with host physiology. In: Wilson RW, Balshine S, Sloman KA (eds) Fish physiology: behaviour and physiology of fish. Elsevier Academic Press, Amsterdam/London, pp 109–149

Barber I, Hoare D, Krause J (2000) Effects of parasites on fish behaviour: a review and evolutionary perspective. Rev Fish Biol Fish 10:131–165

Baudoin M (1975) Host castration as a parasitic strategy. Evolution 29:335–352

Beaver PC (1939) The morphology and life history of *Psilostomum ondatrae* Price, 1931 (Trematoda: Psilostomidae). J Parasitol 25:383–393

Bernier NJ (2006) The corticotropin-releasing factor system as a mediator of the appetite-suppressing effects of stress in fish. Gen Comp Endocrinol 146:45–55

Bernier NJ (2010) Food intake regulation and disorders. In: Leatherland JF, Woo PTK (eds) Fish diseases and disorders, vol 2, Non-infectious disorders. CAB International, Wallingford/Cambridge, pp 238–266

Binning SA, Barnes JI, Davies JN, Backwell PRY, Keogh JS, Roche DG (2014) Ectoparasites modify escape behaviour, but not performance, in a coral reef fish. Anim Behav 93:1–7

Boon JH, Cannaerts VMH, Augustijn H, Machiels MAM, De Charleroy D, Ollevier F (1990) The effect of different infection levels with infective larvae of *Anguillicola crassus* on haematological parameters of European eel (*Anguilla anguilla*). Aquaculture 87:243–253

Boxshall GA (2005a) Copepoda (copepods). In: Rohde K (ed) Marine parasitology. CABI Publishing, Wallingford, pp 123–138

Boxshall GA (2005b) Branchiura (branchurians). In: Rohde K (ed) Marine parasitology. CABI Publishing, Wallingford, pp 145–147

Boyce NP (1979) Effects of *Eubothrium salvelini* (Cestoda: Pseudophyllidea) on the growth and vitality of sockeye salmon, *Oncorhynchus nerka*. Can J Zool 57:597–602

Brassard P, Curtis MA, Rau ME (1982) Seasonality of *Diplostomum spathaceum* (Trematoda: Strigeidae) transmission to brook trout (*Salvelinus fontinalis*) in northern Quebec, Canada. Can J Zool 60:2258–2263

Bunkley-Williams L, Williams JEH (1998) Isopoda associated with fishes: a synopsis and corrections. J Parasitol 84:893–896

Busch MW, Kuhn T, Münster J, Klimpel S (2012) Marine crustaceans as potential hosts and vectors for metazoan parasites. In: Mehlhorn H (ed) Arthropods as vectors of emerging diseases. Springer, Berlin Heidelberg, pp 329–360

Butler JA, Millemann RE (1971) Effect of the "salmon poisoning" trematode, *Nanophyetus salmincola*, on the swimming ability of juvenile salmonid fishes. J Parasitol 57:860–865

Caira JN, Reyda FB (2005) Eucestoda (true tapeworms). In: Rohde K (ed) Marine parasitology. CABI Publishing, Wallingford, pp 92–104

Cézilly F, Thomas F, Médoc V, Perrot-Minnot M-J (2010) Host-manipulation by parasites with complex life cycles: adaptive or not? Trends Parasitol 26:311–317

Chin A, Guo FC, Bernier NJ, Woo PT (2004) Effect of *Cryptobia salmositica*-induced anorexia on feeding behavior and immune response in juvenile rainbow trout *Oncorhynchus mykiss*. Dis Aquat Organ 58:17–26

Coleman FC (1993) Morphological and physiological consequences of parasites encysted in the bulbus arteriosus of an estuarine fish, the sheepshead minnow, *Cyprinodon variegatus*. J Parasitol 79:247

Combes C (1991) Ethological aspects of parasite transmission. Am Nat 138:866–880

Consuegra S, Garcia de Leaniz C (2008) MHC-mediated mate choice increases parasite resistance in salmon. Proc R Soc B Biol Sci 275:1397–1403

Cribb TH (2005) Digenea (endoparasitic flukes). In: Rohde K (ed) Marine parasitology. CABI Publishing, Wallingford, pp 76–87

Crowden AE, Broom DM (1980) Effects of the eyefluke, *Diplostomum spathaceum*, on the behaviour of dace (*Leuciscus leuciscus*). Anim Behav 28:287–294

Dence WA (1958) Studies on Ligula-infected common shiners (*Notropis cornutus frontalis* Agassiz) in the Adirondacks. J Parasitol 44:334–338

de Souza Azevedo J, da Silva LG, Bizerri CRSF, Dansa-Petretski MA, Lima NRW (2006) Infestation pattern and parasitic castration of the crustacean *Riggia paranensis* (Crustacea: Cymothoidea) on the fresh water fish *Cyphocharax gilbert* (Teleostei: Curimatidae). Neotropical Ichthyol 4:363–369

Dobson AP (1988) The population biology of parasite-induced changes in host behavior. Q Rev Biol 63:139–165

Eizaguirre C, Lenz TL, Kalbe M, Milinski M (2012) Rapid and adaptive evolution of MHC genes under parasite selection in experimental vertebrate populations. Nat Commun 3:621

El-Matbouli M, Hoffmann RW (1998) Light and electron microscopic studies on the chronological development of *Myxobolus cerebralis* to the actinosporean stage in *Tubifex tubifex*. Int J Parasitol 28:195–217

El-Matbouli M, Hoffmann RW, Schoel H et al (1999) Whirling disease: host specificity and interaction between the actinosporean stage of *Myxobolus cerebralis* and rainbow trout *Oncorhynchus mykiss*. Dis Aquat Org 35:1–12

Ferguson MS, Hayford RA (1941) The life history and control of an eye fluke: an account of a serious hatchery disease caused by a parasitic worm. Progress Fish-Cult 8:1–13

Fogelman RM, Grutter AS (2008) Mancae of the parasitic cymothoid isopod, *Anilocra apogonae*: early life history, host-specificity, and effect on growth and survival of preferred young cardinal fishes. Coral Reefs 27:685–693

Fogelman RM, Kuris AM, Grutter AS (2009) Parasitic castration of a vertebrate: effect of the cymothoid isopod, *Anilocra apogonae*, on the five-lined cardinalfish, *Cheilodipterus quinquelineatus*. Int J Parasitol 39:577–583

Garnick E, Margolis L (1990) Influence of four species of helminth parasites on orientation of seaward migrating sockeye salmon (*Oncorhynchus nerka*) smolts. Can J Fish Aquat Sci 47:2380–2389

Gilbert MA, Granath WO (2001) Persistent infection of *Myxobolus cerebralis*, the causative agent of salmonid whirling disease, in *Tubifex tubifex*. J Parasitol 87:101–107

Gilbert MA, Granath WO (2003) Whirling disease of salmonid fish: life cycle, biology, and disease. J Parasitol 89:658–667

Giles N (1983) Behavioural effects of the parasite *Schistocephalus solidus* (Cestoda) on an intermediate host, the three-spined stickleback, *Gasterosteus aculeatus* L. Anim Behav 31:1192–1194

Godin J-GJ, Sproul CD (1988) Risk taking in parasitized sticklebacks under threat of predation: effects of energetic need and food availability. Can J Zool 66:2360–2367

Guthrie JF, Kroger RL (1974) Schooling habits of injured and parasitized menhaden. Ecology 55:208–210

Hall SR, Becker C, Caceres CE (2007) Parasitic castration: a perspective from a model of dynamic energy budgets. Integr Comp Biol 47:295–309

Hamilton WD, Zuk M (1982) Heritable true fitness and bright birds: a role for parasites? Science 218:384–387

Hayward C (2005) Monogenea Polyopisthocotylea (ectoparasitic flukes). In: Rohde K (ed) Marine parasitology. CABI Publishing, Wallingford, pp 55–63

Hedrick RP, Adkison MA, El-Matbouli M, MacConnell E (1998) Whirling disease: re-emergence among wild trout. Immunol Rev 166:365–376

Heins DC, Baker JA, Toups MA, Birden EL (2010) Evolutionary significance of fecundity reduction in threespine stickleback infected by the diphyllobothriidean cestode *Schistocephalus solidus*. Biol J Linn Soc 100:835–846

Herting GE, Witt A (1967) The role of physical fitness of forage fishes in relation to their vulnerability to predation by Bowfin (*Amia calva*). T Am Fish Soc 96:427–430

Houde AE, Torio AJ (1992) Effect of parasitic infection on male color pattern and female choice in guppies. Behav Ecol 3:346–351

Hurd H (1990) Physiological and behavioural interactions between parasites and invertebrate hosts. Adv Parasitol 29:271–318

Hurd H (2001) Host fecundity reduction: a strategy for damage limitation? Trends Parasitol 17:363–368

Jones SRM, Woo PTK, Stevenson RMW (1986) Immunosuppression in rainbow trout, *Salmo gairdneri* Richardson, caused by the haemoflagellate *Cryptobia salmositica* Katz, 1951. J Fish Dis 9:431–438

Kabata Z (1970) Diseases of fishes: Crustacea as enemies of fishes. T.F.H. Publishers, Jersey City, 171 pp

Karl H, Baumann F, Ostermeyer U, Kuhn T, Klimpel S (2011) *Anisakis simplex* (ss) larvae in wild Alaska salmon: no indication of post-mortem migration from viscera into flesh. Dis Aquat Org 94:201

Kent ML, Andree KB, Bartholomew JL, El-Matbouli M, Desser SS, Devlin RH, Feist SW, Hedrick RP, Hoffmann RW, Khattra J, Hallett SL, Lester RJG, Longshaw M, Palenzeula O, Siddall ME, Xiao C (2001) Recent advances in our knowledge of the Myxozoa. J Eukaryot Microbiol 48:395–413

Khan RA (1988) Experimental transmission, development, and effects of a parasitic copepod, *Lernaeocera branchialis*, on Atlantic cod, *Gadus morhua*. J Parasitol 74:586

Klapper R, Kuhn T, Münster J, Levsen A, Karl H, Klimpel S (2015) Anisakid nematodes in beaked redfish (*Sebastes mentella*) from three fishing grounds in the North Atlantic, with special notes on distribution in the fish musculature. Vet Parasitol 207:72–80

Klimpel S, Busch MW, Kellermanns E, Kleinertz S, Palm HW (2009) Metazoan deep-sea fish parasites. Natur u Wissenschaft, Solingen, 384 pp

Krause J (1994) The influence of food competition and predation risk on size-assortative shoaling in juvenile chub (*Leuciscus cephalus*). Ethology 96:105–116

Krause J, Godin J-GJ (1994a) Shoal choice in the banded killifish (*Fundulus diaphanus*, Teleostei, Cyprinodontidae): effects of predation risk, fish size, species composition and size of shoals. Ethology 98:128–136

Krause J, Godin J-GJ (1994b) Influence of parasitism on the shoaling behaviour of banded killifish, *Fundulus diaphanus*. Can J Zool 72:1775–1779

Krause J, Godin J-GJ (1996) Influence of parasitism on shoal choice in the banded killifish (*Fundulus diaphanus*, Teleostei, Cyprinodontidae). Ethology 102:40–49

Kuchta R, Scholz T, Brabec J, Bray RA (2008) Suppression of the tapeworm order Pseudophyllidea (Platyhelminthes: Eucestoda) and the proposal of two new orders, Bothriocephalidea and Diphyllobothriidea. Int J Parasitol 38:49–55

Kuhn T, Benninghoff T, Karl H, Landry T, Klimpel S (2013) Sealworm *Pseudoterranova decipiens* ss infection of European smelt *Osmerus eperlanus* in German coastal waters: ecological implications. Dis Aquat Organ 102:217–224

Kuris AM (1997) Host behavior modification: an evolutionary perspective. In: Beckage NE (ed) Parasites and pathogens. Chapman & Hall, New York, pp 293–315
Lafferty KD (1997) The ecology of parasites in a salt marsh ecosystem. In: Beckage NE (ed) Parasites and Pathogens. Springer, US, pp 316–332
Lafferty KD (1999) The evolution of trophic transmission. Parasitol Today 15:111–115
Lafferty KD, Kuris AM (2009) Parasitic castration: the evolution and ecology of body snatchers. Trends Parasitol 25:564–572
Lafferty KD, Morris AK (1996) Altered behavior of parasitized killifish increases susceptibility to predation by bird final hosts. Ecology 77:1390–1397
Lafferty KD, Shaw JC (2013) Comparing mechanisms of host manipulation across host and parasite taxa. J Exp Biol 216:56–66
Lester RJG (1971) The influence of *Schistocephalus plerocercoids* on the respiration of *Gasterosteus* and a possible resulting effect on the behavior of the fish. Can J Zool 49:361–366
Lester RJG (2005) Isopoda (isopods). In: Rohde K (ed) Marine parasitology. CABI Publishing, Wallingford, pp 138–144
Li S, Woo PT (1991) Anorexia reduces the severity of cryptobiosis in *Oncorhynchus mykiss*. J Parasitol 77:467–471
Lima NR, de Souza Azevedo J, da Silva LG, Dansa-Petretski M (2007) Parasitic castration, growth, and sex steroids in the freshwater bonefish *Cyphocharax gilbert* (Curimatidae) infested by *Riggia paranensis* (Cymothoidea). Neotropical Ichthyol 5:471–478
LoBue CP, Bell MA (1993) Phenotypic manipulation by the cestode *parasite Schistocephalus solidus* of its intermediate host, *Gasterosteus aculeatus*, the threespine stickleback. Am Nat 142:725–735
López S (1999) Parasitized female guppies do not prefer showy males. Anim Behav 57:1129–1134
Lyholt HCK, Buchmann K (1996) *Diplostomum spathaceum*: effects of temperature and light on cercarial shedding and infection of rainbow trout. Dis Aquat Organ 25:169–173
MacKenzie K (1999) Parasites as pollution indicators in marine ecosystems: a proposed early warning system. Mar Pollut Bull 38:955–959
Macnab V, Barber I (2012) Some (worms) like it hot: fish parasites grow faster in warmer water, and alter host thermal preferences. Glob Change Biol 18:1540–1548
MacKenzie K, Kalavati C (2014) Myxosporean parasites of marine fishes: their distribution in the world's oceans. Parasitology 141:1709–1717
Marcogliese DJ (2005) Transmission of marine parasites. In: Rohde K (ed) Marine parasitology. CABI Publishing, Wallingford, pp 280–286
Mattiucci S, Nascetti G (2008) Advances and trends in the molecular systematics of anisakid nematodes, with implications for their evolutionary ecology and host—parasite co-evolutionary processes. Adv Parasitol 66:47–148
McClelland G (2005) Nematoda (roundworms). In: Rohde K (ed) Marine parasitology. CABI Publishing, Wallingford, pp 104–115
Mikheev VN, Pasternak AF, Taskinen J, Valtonen ET (2010) Parasite-induced aggression and impaired contest ability in a fish host. Parasit Vectors 3:17
Milinski M (1984) Parasites determine a predator's optimal feeding strategy. Behav Ecol Sociobiol 15:35–37
Milinski M (1985) Risk of predation of parasitized sticklebacks (*Gasterosteus aculeatus* L.) under competition for food. Behaviour 93:203–216
Milinski M, Bakker TCM (1990) Female sticklebacks use male coloration in mate choice and hence avoid parasitized males. Nature 344:330–333
Moles A, Heifetz J (1998) Effects of the brain parasite *Myxobolus arcticus* on sockeye salmon. J Fish Biol 52:146–151
Möller H, Anders K (1983) Krankheiten und Parasiten der Meeresfische. Verlag Heino Möller, Kiel, 258 pp
Möller H, Anders K (1986) Diseases and parasites of marine fishes. Verlag Heino Möller, Kiel, 365 pp

Möller H, Klatt S (1990) Smelt as host of the sealworm (*Pseudoterranova decipiens*) in the Elbe estuary. Can Bull Fish Aquat Sci 222:129–138
Moodie E (2005) Microsporidia (microsporans). In: Rohde K (ed) Marine parasitology. CABI Publishing, Wallingford, pp 30–34
Moore J (1984) Altered behavioral responses in intermediate hosts - an Acanthoceptalan parasite strategy. Am Nat 123:572–577
Moore J (2002) Parasites and the behavior of animals. Oxford University Press, New York, 338 pp
Moore J (2013) An overview of parasite-induced behavioral alterations - and some lessons from bats. J Exp Biol 216:11–17
Moore J, Gotelli NJ (1990) A phylogenetic perspective on the evolution of altered host behaviours: A critical look at the manipulation hypothesis. In: Barnard CJ, Behnke JM (eds) Parasitism and host behaviour. Taylor & Francis, London, pp 193–233
Mouritsen KN, Poulin R (2003) Parasite-induced trophic facilitation exploited by a non-host predator: a manipulator's nightmare. Int J Parasitol 33:1043–1050
Ness JH, Foster SA (1999) Parasite-associated phenotype modifications in threespine stickleback. Oikos 85:127
O'Donoghue P (2005) Protistan biodiversity. In: Rohde K (ed) Marine parasitology. CABI Publishing, Wallingford, pp 11–17
Orr TSC (1966) Spawning behaviour of rudd, *Scardinius erythrophthalmus* infested with plerocercoids of *Ligula intestinalis*. Nature 212:736–736. 11
Östlund-Nilsson S, Curtis L, Nilsson G, Grutter A (2005) Parasitic isopod *Anilocra apogonae*, a drag for the cardinal fish *Cheilodipterus quinquelineatus*. Mar Ecol Prog Ser 287:209–216
Palstra AP, Heppener DFM, Van Ginneken VJT, Székely C, Van den Thillart G (2007) Swimming performance of silver eels is severely impaired by the swim-bladder parasite *Anguillicola crassus*. J Exp Mar Biol Ecol 352:244–256
Poulin R (1993) Age-dependent effects of parasites on anti-predator responses in two New Zealand freshwater fish. Oecologia 96:431–438
Poulin R (1994) Meta-analysis of parasite-induced behavioural changes. Anim Behav 48:137–146
Poulin R (1995) "Adaptive" changes in the behaviour of parasitized animals: a critical review. Int J Parasitol 25:1371–1383
Poulin R (2010) Parasite manipulation of host behavior: an update and frequently asked questions. In: Brockmann HJ (ed) Advances in the study of behavior. Elsevier, Amsterdam, pp 151–186
Poulin R, FitzGerald GJ (1989) Shoaling as an anti-ectoparasite mechanism in juvenile sticklebacks (*Gasterosteus* spp.). Behav Ecol Sociobiol 24:251–255
Poulin R, Morand S (2004) Parasite biodiversity. Smithsonian Institution Scholarly Press, Washington, DC, 216 pp
Poulin R, Thomas F (1999) Phenotypic variability induced by parasites: extent and evolutionary implications. Parasitol Today 15:28–32
Poulin R, Curtis MA, Rau ME (1991) Size, behaviour, and acquisition of ectoparasitic copepods by brook trout, *Salvelinus fontinalis*. Oikos 61:169
Radabaugh DC (1980a) Changes in minnow, *Pimephales promelas* Rafinesque, schooling behaviour associated with infections of brainencysted larvae of the fluke, *Ornithodiplostomum ptychocheilus*. J Fish Biol 16:621–628
Radabaugh DC (1980b) Encystment site selection in the brain-inhabiting metacercariae of *Ornithodiplostomum ptychocheilus* (Trematoda: Strigeoidea). J Parasitol 66:183–184
Rees G (1957) Cercaria *diplostomi phoxini* (Faust), a furcocercaria which develops into *Diplostomulum phoxini* in the brain of the minnow. Parasitology 47:126–137
Reusch TB, Häberli MA, Aeschlimann PB, Milinski M (2001) Female sticklebacks count alleles in a strategy of sexual selection explaining MHC polymorphism. Nature 414:300–302
Rohde K (2005) Marine parasitology. CABI Publishing, Wallingford, p 565
Rose JD, Marrs GS, Lewis C, Schisler G (2000) Whirling disease behavior and its relation to pathology of brain stem and spinal cord in rainbow trout. J Aquat Anim Health 12:107–118

Rossiter W (2013) Current opinions: zeros in host–parasite food webs: are they real? Int J Parasitol Parasites Wildl 2:228–234

Santos EGN, Cunha RA, Santos Portes C (2011) Behavioral responses of *Poecilia vivipara* (Osteichthyies: Cyprinodontiformes) to experimental infections of *Acanthocollaritrema umbilicatum* (Digenea: Cryptogonimidae). Exp Parasitol 127:522–526

Santos EGN, Santos Portes C (2013) Parasite-induced and parasite development-dependent alteration of the swimming behavior of fish hosts. Acta Tropica 127:56–62

Sasal P, Thomas F (2005) Parasite induced changes in host behaviour and morphology. In: Rohde K (ed) Marine parasitology. CABI Publishing, Wallingford, pp 259–263

Scott M (1985) Experimental epidemiology of *Gyrodactylus bullatarudis* (Monogenea) on guppies (*Poecilia reticulata*): short- and long-term studies. In: Rollinson E, Anderson RM (eds) Ecology and genetics of host-parasite interactions. Academic, London, pp 21–38

Seppälä O, Karvonen A, Tellervo Valtonen E (2004) Parasite-induced change in host behaviour and susceptibility to predation in an eye fluke–fish interaction. Anim Behav 68:257–263

Seppälä O, Valtonen ET, Benesh DP (2008) Host manipulation by parasites in the world of dead-end predators: adaptation to enhance transmission? Proc R Soc B Biol Sci 275:1611–1615

Shirakashi S, Goater CP (2002) Intensity-dependent alteration of minnow (*Pimephales promelas*) behavior by a brain- encysting trematode. J Parasitol 88:1071–1074

Shirakashi S, Goater CP (2005) Chronology of parasite-induced alteration of fish behaviour: effects of parasite maturation and host experience. Parasitology 130:177–183

Smith JW (1972) The blood flukes (Digenea: Sanguinicolidae and Spirorchidae) of cold-blooded vertebrates and some comparison with the schistosomes. Helminthol Abstr 41:161–204

Smith RS, Kramer DL (1987) Effects of a cestode (*Schistocephalus* sp.) on the response of ninespine sticklebacks (*Pungitius pungitius*) to aquatic hypoxia. Can J Zool 65:1862–1865

Smothers JF, von Dohlen C, Smith LH, Spall RD (1994) Molecular evidence that the myxozoan protists are metazoans. Science 265:1719–1721

Sprengel G, Lüchtenberg H (1991) Infection by endoparasites reduces maximum swimming speed of European smelt *Osmerus eperlanus* and European eel *Anguilla anguilla*. Dis Aquat Organ 11:31–35

Steinbach Elweell LC, Eagle Stromberg K, Ryce EKN, Bartholomew JL (2009) Whirling disease in the United States. A summary of progress in research and management. Montana Water Center. Bozeman

Swearer SE, Robertson DR (1999) Life history, pathology, and description of *Kudoa ovivora* n. sp. (Myxozoa, Myxosporea): an ovarian parasite of Caribbean labroid fishes. J Parasitol 85:337–353

Sweeting RA (1976) Studies on *Ligula intestinalis* (L.) effects on a roach population in a gravel pit. J Fish Biol 9:515–522

Sweeting RA (1977) Studies on *Ligula intestinalis* Some aspects of the pathology in the second intermediate host. J Fish Biol 10:43–50

Szidat L (1969) Structure, development, and behaviour of new *Strigeatoid metacercariae* from subtropical fishes of South America. J Fish Res Bd Can 26:753–786

Thomas PT, Woo PTK (1992) Anorexia in rainbow trout, *Oncorhynchus mykiss* (Walbaum), infected with *Cryptobia salmositica* (Sarcomastigophora: Kinetoplastida): its onset and contribution to the immunodepression. J Fish Dis 15:443–447

Thomas F, Adamo S, Moore J (2005) Parasitic manipulation: where are we and where should we go? Behav Processes 68:185–199

Thomas F, Rigaud T, Brodeur J (2012) Evolutionary routes leading to host manipulation by parasites. In: Hughes DP, Brodeur J, Thomas F (eds) Host manipulation by parasites. Oxford University Press, Oxford, pp 16–33

Tierney JF, Huntingford FA, Crompton DWT (1993) The relationship between infectivity of *Schistocephalus solidus* (Cestoda) and anti-predator behaviour of its intermediate host, the three-spined stickleback, *Gasterosteus aculeatus*. Anim Behav 46:603–605

Trubiroha A, Kroupova H, Wuertz S, Frank SN, Sures B, Kloas W (2010) Naturally-induced endocrine disruption by the parasite *Ligula intestinalis* (Cestoda) in roach (*Rutilus rutilus*). Gen Comp Endocrinol 166:234–240

Ward AJ, Duff AJ, Krause J, Barber I (2005) Shoaling behaviour of sticklebacks infected with the microsporidian parasite, *Glugea anomala*. Environ Biol Fishes 72:155–160

Weissenberg R (1968) Intracellular development of the microsporidan *Glugea anomala* Moniez in hypertrophying migratory cells of the fish *Gasterosteus aculeatus* L., an example of the formation of "xenoma" tumors. J Protozool 15:44–57

Whittington I (2005) Monogenea Monopisthocotylea (ectoparasitic flukes). In: Rohde K (ed) Marine parasitology. CABI Publishing, Wallingford, pp 63–72

Windsor DA (1998) Most of the species on Earth are parasites. Int J Parasitol 28:1939–1941

Wolf K, Markiw ME, Hiltunen JK (1986) Salmonid whirling disease: *Tubifex tubifex* (Müller) identified as the essential oligochaete in the protozoan life cycle. J Fish Dis 9:83–85

Woo PTK (1994) Flagellate parasites of fish. In: Kreier JP (ed) Parasitic protozoa, vol 8, 2nd edn. Academic, London, pp 1–80

Woo PTK (2011) Cryptobia (Trypanoplasma) salmositica. In: Woo PTK, Buchmann K (eds) Fish parasites: pathobiology and protection. CABI Publishing, Wallingford, pp 30–54

Wright HA, Wootton RJ, Barber I (2006) The effect of *Schistocephalus solidus* infection on meal size of three-spined stickleback. J Fish Biol 68:801–809

Yokoyama H, Grabner D, Shirakashi S (2012) Transmission biology of the Myxozoa. In: Carvalho E (ed) Health and environment in aquaculture. INTECH Open Access Publisher, Rijeka, Croatia

Chapter 10
Virus-Induced Behavioural Changes in Insects

Yue Han, Monique M. van Oers, Stineke van Houte, and Vera I.D. Ros

10.1 Introduction

Insects are thought to be the most successful class among all known living organisms due to their high diversity and wide distribution: more than a million insect species have been described, which represent more than half of all known animal species, and insects can be found in almost all environments (Chapman 2006; Cranston 2010). Throughout their life cycle, insects encounter a variety of parasites, ranging from the smallest and simplest viruses to larger and more complex organisms like nematodes and parasitoids (van Houte et al. 2013; Cézilly et al. 2010). Insects are affected in many different ways upon infestation by parasites and this includes changes in development, metabolism, morphology, physiology and, most intriguingly, behaviour. The most well-known examples of host behavioural changes include the suicidal water-seeking behaviour of the cricket *Nemobius sylvestris* infested with the hairworm *Paragordius tricuspidatus* (Thomas et al. 2002) and the climbing behaviour of the carpenter ant *Camponotus leonardi* infected with the fungus *Ophiocordyceps unilateralis* (Hughes et al. 2011). Though many parasites have been reported to induce behavioural changes in insect hosts (Lefèvre et al. 2009; van Houte et al. 2013), the documentation on virus-induced changes in insect behaviour is scarce. Given the high prevalence of viruses among insects, either in a pathogenic interaction or in a virus-vector relationship (Miller and Ball 1998),

Y. Han • M.M. van Oers (✉) • V.I.D. Ros
Laboratory of Virology, Wageningen University,
Droevendaalsesteeg 1, 6708 PB Wageningen, The Netherlands
e-mail: monique.vanoers@wur.nl

S. van Houte
Laboratory of Virology, Wageningen University,
Droevendaalsesteeg 1, 6708 PB Wageningen, The Netherlands

Department of Biosciences, Centre for Ecology and Conservation, University of Exeter,
Penryn, Cornwall, UK

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viruses might have a huge impact on insect behaviour. In this review, we give an overview of the documented changes of insect behaviour upon infection by viruses and reveal what is known about the underlying molecular mechanisms.

Host behavioural changes upon infection by a parasite can be adaptive to the parasite or to the host. Many cases that clearly show enhancement of parasite transmission have been treated as compelling examples of the concept of the "extended phenotype" (Thomas et al. 2005; van Houte et al. 2013). The concept was proposed by Dawkins in 1982, and is defined as "genes from one organism (the parasite) having phenotypic effects on another organism (the host)" (Dawkins 1982). However, the behavioural changes are not always advantageous for the parasites, but can also be adaptive to the host to reduce the pathogenic effects of the infection to the individual or the population, or just be pathological side effects (Thomas et al. 2005; van Houte et al. 2013).

The first part of this review deals with the known examples of insect behavioural changes following infection by viruses that use insects as hosts or vectors, and, if known, the underlying mechanisms of such behavioural changes are explained. An overview of these virus-induced behavioural changes is given in Table 10.1. Special attention is given to baculovirus-induced behavioural changes in caterpillars. Because extensive information is available on baculovirus genomics and virus mutants can be easily made, several viral genes behind baculovirus-induced behavioural changes have successfully been identified. In the second part of this review we discuss the ecological and evolutionary consequences of virus-induced insect behavioural changes.

10.2 *Leptopilina boulardi* Filamentous Virus (LbFV) Induces Superparasitism in the Parasitoid Wasp *L. boulardi*

Leptopilina boulardi is a solitary parasitoid (order Hymenoptera) that usually lays a single egg per *Drosophila* host larva (order Diptera) and rejects already parasitized larvae, since only one wasp larva can successfully develop within the body of a *Drosophila* larva. Upon superparasitism (when a wasp parasitizes a *Drosophila* larva that has already been parasitized by another wasp), within-host larval competition occurs and only one of the wasp larvae survives. Usually, egg-laying wasp females avoid superparasitism, although it might occur under specific circumstances when fly hosts are rare (van Alphen and Visser 1990). *L. boulardi* filamentous virus (LbFV, an unclassified double-stranded (ds) DNA virus) infects *L. boulardi* wasps and increases the tendency of *L. boulardi* females to accept already parasitized fly hosts, which allows horizontal transmission of the virus from infected to uninfected *L. boulardi* larvae within the superparasitized *Drosophila* host (Patot et al. 2009; Varaldi et al. 2003, 2009). Theoretical models predict that such superparasitism behaviour is beneficial to the virus (Gandon et al. 2006), since the virus can invade new wasp lineages. It is hypothesized that the virus is injected together with the

Table 10.1 Overview of viruses and the described changes in insect host or vector behaviour

	Host/vector insect order	Insect species[a]	Virus name	Abbreviated virus name	Virus family	Virus genome	Virus morphology	Insect behavioural change	References
Insect as host (insect viruses)	Lepidoptera	*Bombyx mori*	*Bombyx mori* NPV[b]	BmNPV	*Baculoviridae*	Circular dsDNA[d]	Rod-shaped, enveloped	Hyperactivity	Kamita et al. (2005); Katsuma et al. (2012)
		Lymantria dispar	*Lymantria dispar* MNPV[c]	LdMNPV	*Baculoviridae*	Circular dsDNA	Rod-shaped, enveloped	Pre-death climbing	Hoover et al. (2011)
		Lymantria monacha	*Unidentified baculovirus*	n.a.	*Baculoviridae*	Circular dsDNA	Rod-shaped, enveloped	Pre-death climbing	Hofmann (1891)
		Mamestra brassicae	*Mamestra brassicae* MNPV	MbMNPV	*Baculoviridae*	Circular dsDNA	Rod-shaped, enveloped	Hyperactivity, pre-death climbing	Goulson (1997); Vasconcelos et al. (1996)
		Operophtera brumata	*Operopthera brumata NPV*	OpbuNPV	*Baculoviridae*	Circular dsDNA	Rod-shaped, enveloped	Pre-death downward movement	Raymond et al. (2005)
		Spodoptera exigua	*Spodoptera exigua* MNPV	SeMNPV	*Baculoviridae*	Circular dsDNA	Rod-shaped, enveloped	Pre-death climbing, positive phototaxis	Van Houte et al. (2014b)
		Spodoptera exigua Trichoplusia ni	*Autographa californica* MNPV	AcMNPV	*Baculoviridae*	Circular dsDNA	Rod-shaped, enveloped	Pre-death climbing, hyperactivity	Van Houte et al. (2012, 2014a); Ros et al. (2015)
		Helicoverpa zea	*Helicoverpa zea* nudivirus 2	HzNV-2	*Nudiviridae*	Circular dsDNA	Rod-shaped, enveloped	Altered mating behaviour (prolonged calling behaviour)	Burand et al. (2005); Burand and Tan (2006)

(continued)

Table 10.1 (continued)

	Host/vector insect order	Insect species[a]	Virus name	Abbreviated virus name	Virus family	Virus genome	Virus morphology	Insect behavioural change	References
	Hymenoptera	*Leptopilina boulardi*	*Leptopilina boulardi* filamentous virus	LbFV	unassigned	dsDNA[e]	Filamentous, enveloped	Superparasitism, reduced locomotor activity in females	Varaldi et al. (2005, 2009); Patot et al. (2009)
		Apis mellifera	Deformed wing virus	DWV	*Iflaviridae*	(+) ssRNA[f]	Icosahedral, non-enveloped	Learning disabilities, altered hygienic behaviour	Iqbal and Mueller (2007)
		Apis mellifera	Kakugo virus	KV	*Iflaviridae*	(+) ssRNA	Icosahedral, non-enveloped	Aggressive behaviour	Fujiyuki et al. (2004, 2005)
		Apis mellifera	Israeli acute paralysis virus	IAPV	*Dicistroviridae*	(+) ssRNA	Icosahedral, non-enveloped	Learning disabilities, navigation problems	Li et al. (2013)
	Orthoptera	*Gryllus texensis*	Cricket strain of invertebrate iridescent virus 6	IIV-6/CrIV	*Iridoviridae*	Linear dsDNA	Icosahedral, ± enveloped	Suppression of sickness behaviour	Adamo et al. (2014)
	Coleoptera	*Coleomegilla maculata*	*Dinocampus coccinellae* paralysis virus	DcPV	*Iflaviridae*	(+) ssRNA	Icosahedral, non-enveloped	Paralysis and tremors[j]	Dheilly et al. (2015)
		Phyllophaga vandinei	*Chilo* iridescent virus strain of IIV-6	IIV-6/CIV	*Iridoviridae*	Linear dsDNA	Icosahedral, ± envelope	Reduced mating behaviour	Jenkins et al. (2011)

	Hemiptera	*Rhopalosiphum padi*	Aphid lethal paralysis virus	ALPV	*Dicistroviridae*	(+) ssRNA	Icosahedral, non-enveloped	Orientation	Williamson et al. (1988)
		Rhopalosiphum padi	*Rhopalosiphum padi* virus	RhPV	*Dicistroviridae*	(+) ssRNA	Icosahedral, non-enveloped	Changes in aggregation behaviour	Ban et al. (2008)
Insect as vector (plant viruses)		*Rhopalosiphum padi*	Barley yellow dwarf virus	BYDV	*Luteoviridae*	(+) ssRNA	Icosahedral, non-enveloped	Changes in plant preference	Ingwell et al. (2012)
		Myzus persicae	Potato leaf roll virus	PLRV	*Luteoviridae*	(+) ssRNA	Icosahedral, non-enveloped	Changes in plant preference	Rajabaskar et al. (2014)
		Bemisia tabaci	Tomato yellow leaf curl virus	TYLCV	*Geminiviridae*	circular ssDNA[g]	Icosahedral, non-enveloped	Change host feeding behaviour	Moreno-Delafuente et al. (2013)
	Thysanoptera	*Franklinella occidentalis*	Tomato spotted wilt virus	TSWV	*Bunyaviridae*	(±) ssRNA[h]	Spherical, enveloped	Increased feeding rate	Stafford et al. (2011)
Insect as vector (vertebrate viruses)	Diptera	*Aedes aegypti*	Dengue virus	DENV	*Flaviviridae*	(+) ssRNA	Spherical, enveloped	Prolonged feeding times, increased locomotor activity	Platt et al. (1997); Lima-Camara et al. (2011)
		Aedes triseriatus	La Crosse virus	LACV	*Bunyaviridae*	(±) ssRNA	Spherical, enveloped	Increased re-feeding rate, mating at earlier age	Grimstad et al. (1980); Jackson et al. (2012); Reese et al. (2009)

(continued)

Table 10.1 (continued)

	Host/vector insect order	Insect species[a]	Virus name	Abbreviated virus name	Virus family	Virus genome	Virus morphology	Insect behavioural change	References
		Culex pipiens	Rift Valley fever virus	RVFV	*Bunyaviridae*	(±) ssRNA	Spherical, enveloped	Decreased feeding success	Turell et al. (1985)
		Culicoides sonorensis	Vesicular stomatitis virus	VSV	*Rhabdoviridae*	(−) ssRNA[i]	Bullet-shaped, enveloped	Reduced feeding rates	Bennett et al. (2008)
		Culex tarsalis	Western equine encephalomyelitis virus	WEEV	*Togaviridae*	(+) ssRNA	Spherical, enveloped	Decreased flight activity	Lee et al. (2000)

[a]Host/vector insect species for which behavioural changes have been described
[b]Nucleopolyhedrovirus (NPV)
[c]Multiple (M) NPV
[d]Double-stranded DNA (ds DNA)
[e]Positive single-stranded RNA: (+) ssRNA
[f]Virus unassigned to family, but data indicate dsDNA virus (Patot et al. 2009)
[g]Single-stranded DNA: ssDNA
[h]Ambisense single-stranded RNA: (±) ssRNA
[i]Negative single-stranded RNA: (−) ssRNA
[j]DcPV is a virus of the parasitoid *D. coccinellae*, that uses DcPV as a 'biological weapon' to manipulate the behaviour of the ladybeetle *C. maculate* (see text)

wasp egg into the *Drosophila* host during oviposition and that it infects the emerging parasitoid during its larval development (during which the parasitoid consumes the virus-infected *Drosophila* hemocoel). If a single parasitoid egg is present, vertical transmission occurs, because the parasitoid larva picks up the virus that was injected by its mother into the hemocoel of the *Drosophila* host. If two or more wasp eggs are present in one *Drosophila* larva, horizontal transmission may occur (when the progeny from an uninfected wasp present in the *Drosophila* larva picks up the virus delivered during subsequent superparasitsm by a virus-infected wasp female). The efficiency of horizontal transfer depends on the time between successive ovipositions (Varaldi et al. 2009), which determines the difference in age and hence competition ability of the already present and incoming larvae. *L. boulardi* females pierce host larvae with their ovipositor to detect chemical cues associated with previous infestations. Although the exact mechanism behind the LbFV-induced superparasitism is unknown, it is hypothesized that LbFV affects chemoreceptor neurons in the ovipositors used to detect chemical cues associated with previous infestations, either through cell lysis or modulation of gene expression (Varaldi et al. 2009).

The influence of LbFV on other behavioural traits of the parasitoid wasps has also been investigated (Varaldi et al. 2006, 2009). The virus did not affect the circadian rhythms of the wasps, nor the ability of infected males to locate females through detection of sex pheromones, the ability of females to locate odours of fly larvae, the search patterns of foraging females, or the ability of females to discriminate between good and poor quality fly larvae. On the other hand, viral infection lead to a strong reduction (45 %) of locomotor activity of infected wasp females (while no effect was detected in males), possibly because of resource-allocation to wasp traits that benefit virus transmission, like egg-load, which was increased by 11 % for infected females (Varaldi et al. 2005). This increase in egg-load might compensate for the higher risk of an infected female being egg-limited (due to superparasitism; single wasp females have been found to lay more than 9 eggs in a single *Drosophila* host). The increase in egg-load might be an adaptive response of the parasitoid to the presence of the virus, or a component of the virus-induced manipulation (Gandon et al. 2006). LbFV also affects the immune response of the *Drosophila* larvae against the parasitoids (Martinez et al. 2012). Virus-infected parasitoids are less frequently encapsulated (the main defense mechanism against parasitoids) than uninfected ones. This is not just a consequence of increased rates of superparasitism, but is also found in monoparasitized larvae.

10.3 Iridovirus Infection Changes Sexual Behaviour in Crickets and Beetles

Activation of the immune system has been shown to reduce sexual activity in a variety of animals, including invertebrates (Adamo 2008; Lawniczak et al. 2007). In general, induction of immune responses in the field cricket *Gryllus campestris*, the ground cricket *Allonemobius socius* and the sagebrush cricket *Cyphoderris*

strepitans (order Orthoptera) reduces the calling frequency of males, thereby limiting their chances to mate with females (Fedorka and Mousseau 2007; Jacot et al. 2004; Leman et al. 2009). Reduced mating rates and other sickness behaviour that signal danger to healthy individuals are beneficial for the host population in which a sick animal lives, but would negatively affect sexually transmitted parasites that rely on mating for their dispersal (Adamo 2014). It is therefore evident that sexually transmitted viruses should have developed strategies to counteract host immune responses that lead to reduced sexual activity in order to safeguard their transmission.

An example is seen in an iridovirus isolated from crickets (CrIV, a strain of invertebrate iridescent virus 6 (IIV-6), family *Iridoviridae,* genus *Iridovirus*) (Kleespies et al. 1999; Jakob et al. 2002), which is sexually transmitted between *Gryllus texensis* crickets. Induction of immune responses normally leads to sickness behaviour, including a reduction in male calling rates, but this was not the case upon IIV-6/CrIV infection (Adamo et al. 2014). CrIV infection did not induce other sickness behaviours either, such as illness-related anorexia (Adamo et al. 2010). When CrIV-infected crickets were immune-challenged with heat-inactivated bacteria, they took longer to start courtship singing, in contrast to uninfected crickets that showed a shorter latency to court upon immune-challenge. A likely explanation for these observations is that CrIV infects the major components of the insect's immune system. The virus infects hemocytes and massive virus replication in the fat body has been reported (Kleespies et al. 1999). As a consequence of fat body infection, the level of immune-related host proteins strongly declined (Adamo 2014; Adamo et al. 2014). The hypothesis is that due to the reduced level of circulating immunomodulators the communication between the immune system and nervous system is hampered, preventing the induction of sickness behaviour. Since the immune system itself is attacked by CrIV, the crickets can no longer respond to bacterial stimuli either.

In contrast, *Phyllophaga vandinei* beetles (order Coleoptera) infected with the IIV-6 strain *Chilo* iridescent virus (IIV-6/CIV) showed strongly reduced mating behaviour (Jenkins et al. 2011). Pathologically not much is known of this virus/host combination, but it may be that infection is not efficient enough to completely overtake the fat body in this putatively non-natural virus/host combination. On the other hand the CIV strain is known to be transmitted efficiently via contaminated food (Nalçacıoğlu et al. 2009) and, therefore, it may not be advantageous for virus transmission to keep host mating levels high.

10.4 *Helicoverpa zea* Nudivirus 2 Alters the Mating Behaviour of the Corn Earworm Moth *H. zea*

Helicoverpa zea nudivirus 2 [HzNV-2, formerly known as Hz-2 V and as gonad-specific virus (GSV); family *Nudiviridae*] manipulates the physiology and behaviour of its host, the corn earworm moth *H. zea* (order Lepidoptera), in such a way that viral transmission is enhanced (Burand 2009; Burand et al. 2005). HzNV-2

replicates exclusively in the reproductive tissues of both male and female moths and this leads to malformation of these tissues and sterility of the moths (Raina and Adams 1995; Burand et al. 2005). In addition, female moths can be fertile, asymptomatic carriers that can transmit the virus vertically to their offspring (Hamm et al. 1996).

H. zea females may mate several times, but generally mate once during a given night (Burand 2009; Raina et al. 1994). This mating pattern is regulated by the sex pheromone level of the adult female. Pheromone production peaks during the second and third night after adult emergence and triggers female mating and calling behaviour, which attracts males. After mating, pheromone levels decline, and transfer of male-derived anti-calling factors that are part of the seminal fluid result in the loss of female sexual receptivity (Burand et al. 2005). Virus-infected females, however, continue calling after contact with males. This is a consequence of the presence of a 'virus plug' covering the reproductive opening of the female moths, preventing the transfer of anti-calling factors. Moreover, it was shown that infected females attracted twice as many males as uninfected females, which was a result of increased pheromone levels. However, males could not effectively mate with infected females due to presence of the virus plug. Nevertheless, during the short contacts (mating attempts) males could be contaminated with the virus, which they could transfer to other (uninfected) females during subsequent matings (Burand et al. 2004).

While uninfected males were more attracted to infected females than to uninfected females, HzNV-2 infected males had no preference for infected over uninfected females, and in fact responded less quickly to female calls. Most mating attempts of infected males were unsuccessful, although sexual contacts did occur, long enough for the virus to be transmitted. Infected males lacked accessory glands and most likely do not produce anti-calling factors. Therefore, females continued calling after mating attempts with infected males. Subsequent mating of these females with healthy males resulted in infected offspring (either asymptomatic or sterile progeny) being produced (Burand and Tan 2006).

10.5 Hygienic Measures of Honeybees Against Virus Infections

Kulinčević and co-authors reported in 1969 that honeybees (order Hymenoptera) that were infected with an as yet unidentified virus, causing the bees to become black and hairless, were attacked by conspecifics and were occasionally stung to death (Kulinčević et al. 1969). It is not exactly clear which virus is responsible, but this phenomenon reflects the ability of social insects to recognise infected nest mates. Social insects, such as honeybees (*Apis mellifera)* live together in dense populations with a high frequency of physical contact and a high degree of genetic homogeny. To limit the risks of disease transmission, social insects display various forms of antiseptic behaviour, reviewed by Wilson-Rich et al. (2009). Worker bees

may limit damage by early removal of diseased brood from the colony, a phenomenon described as hygienic behaviour. Hygienic behaviour may occur in addition to undertaking (the removal of dead adults from the hive) and grooming (Wilson-Rich et al. 2009).

Bee virus infections often occur together with brood parasitism by *Varroa destructor* mites (Ball 1989). These mites parasitize bee nymphs, increase virus susceptibility of bees (Yang and Cox-Foster 2005) and serve as vectors for virus transmission, e.g. Gisder et al. (2009). The combination of *Varroa* mites and bee viruses poses a severe threat to bee colonies. A theoretical study showed that beehives that can reduce *Varroa* infestation by grooming and hygienic behaviour could in theory limit virus prevalence (Sumpter and Martin 2004). In practice, worker bees are able to recognise *Varroa* mite infestation and remove infested brood. Brood infested by mites with high virus titres were more efficiently removed, as was shown for deformed wing virus (DWV, family *Iflaviridae*, genus *Iflavirus*) (Schöning et al. 2012).

Bee colonies seem to vary considerably in the ability to recognise *Varroa* infested brood (Harris 2007). Changes in cuticular hydrocarbon profiles in bee pupae and emerging bee adults may be responsible for the recognition of *Varroa*-infested brood and parasitized emerging adults (Salvy et al. 2001). Changes in hydrocarbon composition were also reported for DWV-infected adult bees and these bees had a much higher chance of being bitten and removed from the hive than non-infected nest mates (Baracchi et al. 2012). Cuticular hydrocarbon profile changes were also found after immune stimulation with bacteria (Richard et al. 2008, 2012). The altered hydrocarbon composition seems to be a general immune response that may signal healthy workers to avoid or actively remove infected nest mates, allowing counter action against disease at a population level.

10.6 Bee Viruses and Changes in Honeybee Neuronal Physiology

Viruses that infect honeybees may affect sensory perception and learning ability. Infection with DWV alters the responsiveness to sensory information, leading to proboscis extension at lower sucrose concentrations than seen for non-infected bees (Iqbal and Mueller 2007). In addition, associative learning and memory formation were disturbed in DWV-infected bees. When an olfactory signal was given before a rewarding sucrose stimulus, infected animals did not learn to respond to the olfactory signal (Iqbal and Mueller 2007). This could be caused by replication of DWV in the brains, especially in regions associated with vision and olfaction (Shah et al. 2009). Brain infection may also have led to the aggressive bees observed in Japan that were infected with a genetic variant of DWV, Kakugo virus (Fujiyuki et al. 2004, 2005), but DWV itself has not been associated with aggressiveness (Rortais et al. 2006). Honeybees infected with Israeli acute paralysis virus (IAPV, family *Dicistroviridae)*, also showed a lower sucrose threshold (Li et al. 2013). IAPV

significantly reduced the ability of pollen foragers to return to the hive, in line with the fact that IAPV diseased bees are often found outside the hives. These changes in behaviour were accompanied by high IAPV titers in the heads, leading to the hypothesis that IAPV infection interfered with brain functions responsible for learning and navigation (Li et al. 2013). A possible advantage for the bee population is that this virus-induced mal-orientation may protect against further virus-spread within the hive.

10.7 The Parasitoid *Dinocampus coccinellae* Uses an Iflavirus to Change the Behaviour of the Ladybeetle *Coleomegilla macaluta*

A unique example of parasitic manipulation is seen for *Dinocampus coccinellae* (order Hymenoptera), a parasitic wasp that lays its eggs in the ladybeetle *Coleomegilla maculate* (order Coleoptera) and uses a virus as a 'biological weapon' to manipulate the behaviour of the ladybeetle (Dheilly et al. 2015). The wasp larvae develop within the body of the ladybeetle and after circa 20 days a single prepupa egresses and spins a cocoon between the ladybeetle's legs. The ladybeetle serves as a bodyguard to protect the parasitoid cocoon from predation by covering the cocoon with its body (Dheilly et al. 2015; Maure et al. 2013). The behaviour of the ladybeetle is altered during this process; it is partially paralysed and displays tremors, suggesting a neurological disorder. A new virus was discovered, *D. coccinellae* paralysis virus (DcPV) (family *Iflaviridae*), which replicates mainly in *D. coccinellae* larvae, and is highly abundant in the oviduct cells of adult wasps. Before egression, the parasitoid larva transmits DcPV to the ladybeetle. The virus then replicates in the cerebral ganglia of the ladybeetles and induces a severe neuropathy, resulting in paralysis and tremors. Even so, an antiviral immune response is induced in the ladybeetle, which eventually leads to elimination of the virus, and recovery of normal behaviour. A range of parasitoids induce bodyguarding behaviour in their insect hosts (Maure et al. 2013; van Houte et al. 2013), and while the mechanisms have rarely been explored, other parasitoids may use viruses to induce bodyguarding behaviour.

10.8 Baculovirus-Induced Behavioural Changes in Caterpillars

The earliest known description of behavioural alterations in diseased insects dates from 1891, likely representing the oldest written account of behavioural manipulation by parasites in history. In this work Hofmann illustrates how larvae of the nun moth *Lymantria monacha* (order Lepidoptera) climb up and die in tree canopies. These larvae succumbed to an unknown agent, which made them crawl out of their

common diurnal hiding place to die on exposed parts of the trees. This phenomenon was named Wipfelkrankheit, more commonly known as tree-top disease (Hofmann 1891). It was discovered several decades later that these larvae had died due to an infection with a baculovirus, causing behavioural alterations in the infected caterpillars and liquefying them to efficiently spread progeny viruses into the environment. Subsequent studies reported higher dispersal rates and aberrant climbing behaviour of infected caterpillars compared with healthy ones, leading to death at elevated positions (Smirnoff 1965; Evans and Allaway 1983). The first quantitative studies on baculovirus-induced changes of host behaviour were performed using *Mamestra brassicae* larvae infected with the baculovirus *M. brassicae* multiple nucleopolyhedrovirus (MbMNPV) (Vasconcelos et al. 1996; Goulson 1997). Infected larvae were found to move 3–5 times further within a given time than uninfected ones, and the majority of larvae died on the apical, more exposed part of plant leaves.

The behavioural repertoire induced by baculoviruses (family *Baculoviridae*) in their caterpillar hosts (order Lepidoptera) includes both tree-top disease (pre-death climbing behaviour) and hyperactivity (wandering over larger areas). For a long time, nothing was known about the proximate mechanisms that might govern these behavioural changes. In 2005, Kamita and co-authors identified the first 'behavioural' gene in a baculovirus by demonstrating the involvement of the protein tyrosine phosphatase (*ptp*) gene from *Bombyx mori* (Bm) NPV in hyperactive behaviour in larvae of the silkworm *B. mori*. Similarly, van Houte et al. (2012) showed that the *ptp* gene of *Autographa californica* (Ac) MNPV induced hyperactive behaviour in its host *Spodoptera exigua*. It was hypothesized that the viral *ptp* gene plays a conserved role in the induction of hyperactivity in a subset of baculoviruses (a monophyletic clade in the genus *Alphabaculovirus*, named group I) (van Houte et al. 2012).

A study on *Lymantria dispar* (Ld) MNPV showed that the viral ecdysteroid-UDP-glucosyl transferase (*egt*) gene is required for death at elevated positions (tree-top disease) of gypsy moth (*L. dispar)* larvae (Hoover et al. 2011). However, the role of *egt* as a 'gene for an extended phenotype' (Hoover et al. 2011) seems not generally applicable: in tree-top disease induced by the baculovirus AcMNPV in both *S. exigua* and *Trichoplusia ni* caterpillars the viral *egt* gene does not play a role (Ros et al. 2015). When the *egt* gene was deleted from the viral genome, infected larvae died at the same height as wild type-infected larvae. Earlier studies on *egt* had shown that the encoded enzyme suppresses larval moulting, leading to an extended time to death. In certain caterpillar species, moulting is preceded by up- or downward movement of larvae; therefore, in some virus-host combinations, *egt* might have an effect on tree-top disease through an effect on larval moulting (Ros et al. 2015). In AcMNPV-infected *S. exigua* and *T. ni* the *egt* gene did affect moulting-related climbing behaviour. It did however not affect tree-top disease, which, in these virus-host combinations, occurred at a later stage of the infection than the moulting-related climbing. The apparent effect of *egt* on tree-top disease is dependent on the specific virus-host interaction and likely is influenced by factors such as the viral dose, time of infection (e.g. compared to the time of moulting), time of death and the intrinsic behaviour of the host. Since the role of *egt* in tree-top disease is not universal (Ros et al. 2015), other viral genes are likely to be involved.

While AcMNPV infection induces tree-top disease in the two lepidopteran hosts *T. ni* and *S. exigua*, the phenotype appears to be host-dependent (Ros et al. 2015). In *T. ni* infected as 3rd instars, virus infection always caused the larvae to climb up and die at elevated positions, regardless of the larval stage at death. For *S. exigua* however, only larvae that had moulted during the infection (from 3rd to 4th instar) climbed up and died at elevated positions. Those that did not undergo moulting moved downwards and died at low positions. Additional experiments showed that this moulting-dependent climbing behaviour was also seen for 2nd instar larvae, and hence may be independent of the stage of the larvae at infection. When 2nd instar larvae were infected, only larvae that moulted during the infection (from 2nd to 3rd instar) died at elevated positions (80.0 mm ± 9.5), while those that did not moult (died as 2nd instar) moved downwards and died at low positions (0.0 mm ± 0.0) (Fig. 10.1). These moulting-dependent differences in pre-death climbing behaviour might be related to the normal (moulting-related) climbing behaviour that these two species display in the absence of virus infection. Downward movement was also observed for larvae of the winter moth *Operopthera brumata* infected with *O. brumata* NPV (OpbuNPV) (Raymond et al. 2005). Infected larvae descended from the foliage to the lower tree stems to die there, which might contribute to virus persistence and transmission. OpbuNPV occlusion bodies persist better on stems than on foliage and virus transmission differs in this system, since *O. brumata* is a forest dwelling species.

Another important factor involved in the induction of tree-top disease is light (van Houte et al. 2014b). The specialist baculovirus *S. exigua* (Se) MNPV induced tree-top disease in *S. exigua* larvae, and prior to death, larvae were strongly attracted to light.

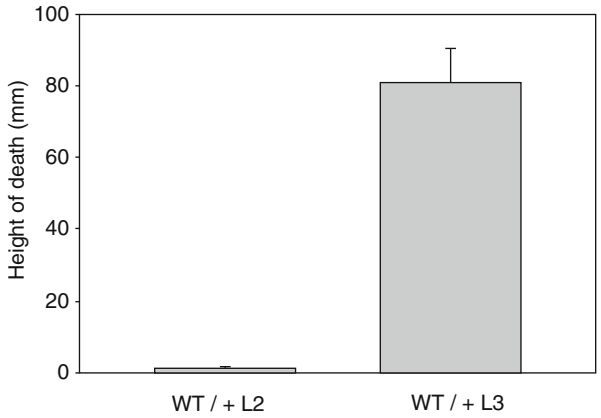

Fig. 10.1 Average height at death (mm) of wild type (WT) AcMNPV-infected larvae (infected as second instars) that died as either second († L2; n = 6) or third († L3; n = 10) instars. Error bars indicate standard error of the mean. [Methods: *S. exigua* late 1st instar larvae were starved overnight. The next morning, newly moulted 2nd instar larvae were infected by droplet feeding using a viral dose of 10^7 OBs/ml of WT AcMNPV as described previously (van Houte et al. 2012). Larvae were placed individually in glass jars (van Houte et al. 2014a) to allow climbing and their final position of death was monitored when all larvae were dead (see Fig. 10.2b for experimental set-up]

When light was presented from above, infected larvae died at elevated positions, however, when light was presented from below, or no light was present at all, larvae died at low positions. Since climbing of uninfected larvae was light-independent (pre-moult climbing behaviour occurred also under completely dark conditions), the light-dependent climbing seen in tree-top disease was specifically evoked by virus infection (van Houte et al. 2014b). Possibly, baculoviruses hijack existing host pathways, that are for instance required for moulting-related climbing behaviour (through *egt*), or pathways related to light perception or phototaxis. However, baculoviruses do not use light as a uniform mechanism to trigger tree-top disease in caterpillars. Tree-top disease induced by LdMNPV in *L. dispar* larvae (K. Hoover, personal communication) or by AcMNPV in *T. ni* larvae (V.I.D. Ros, unpublished data) was light-independent, since it was also observed in dark conditions. This indicates that baculoviruses may use different mechanisms to trigger tree-top disease.

While hyperactivity and tree-top disease are both induced by baculoviruses in caterpillar hosts, and can both be induced in a single infection, they seem to be caused by two independent manipulative mechanisms (van Houte et al. 2014a). The AcMNPV *ptp* gene was shown to induce hyperactivity, but not tree-top disease in its *S. exigua* host (van Houte et al. 2014a). Another indication that tree-top disease and hyperactivity are governed by different mechanisms is that these two phenotypes are triggered at different time points: hyperactivity is induced at 3 days post infection (around 70 h post infection) (van Houte et al. 2012), and the climbing behaviour leading to tree-top disease starts from 75 hpi onwards (Ros et al. 2015).

In conclusion, baculovirus-induced manipulation of caterpillar behaviour seems the result of a complex interplay between virus and host. Different behavioural displays are induced (hyperactivity and tree-top disease), by different causative mechanisms (see above). The expression of the different phenotypes is dependent on the virus-host system studied. Although the role of the viral *ptp* in hyperactivity seems to be conserved within group I NPVs, this gene is absent in group II NPVs and in granuloviruses (genus *Betabaculovirus*). Viruses in these latter two groups have also been shown to induce hyperactive behaviour in lepidopteran hosts [e.g. MbMNPV in *M. brassicae* larvae, (Goulson 1997)], which implies that different viral genes might be involved in inducing hyperactivity. Which virus and/or host genes, proteins or pathways act downstream of the viral *ptp* and *egt* gene need to be determined. A genome-wide approach (transcriptomics/proteomics) can aid in selecting candidate genes or proteins involved in behavioural manipulation (van Houte et al. 2013).

10.9 Dicistroviruses Affect Aphid Behaviour

Aphids are hosts to a wide variety of microorganisms, including viruses, bacteria and fungi. All these microorganisms potentially have a major impact on aphid ecology (Ban et al. 2008). Two viruses have been reported to change the behaviour of aphids. Aphid lethal paralysis virus (ALPV, family *Dicistroviridae*) induced an unusual movement syndrome in its aphid host *Rhopalosiphum padi* (order

Hemiptera): infected aphids moved away from their food source and became uncoordinated (Williamson et al. 1988). Whether this behavioural change is beneficial to the virus or to the host is not known. *Rhopalosiphum padi* virus (RhPV, family *Dicistroviridae*) is closely related to ALPV and was found to change the aggregation behaviour of aphids. Normally, *R. padi* aphids aggregate and are attracted to the odour of conspecific aphids. However, when *R. padi* aphids were infected with RhPV, they were not attracted to the odour of uninfected aphids any longer. Moreover, both infected and uninfected aphids were not attracted to infected aphids (Ban et al. 2008). The perception of repellent chemicals also changed after virus infection: infected aphids did not respond to methyl salicylate, an indicator of host suitability, and became more sensitive to the aphid alarm pheromone (Ban et al. 2008). It might be that these behavioural changes are beneficial to the host population, aimed at reducing the risk of infection for other aphids (usually of the same clone) sharing the host plant, and/or are beneficial to the virus since the virus is spread over a larger area, where aphids of other clones are more likely to be encountered.

10.10 Plant Viruses Change the Behaviour of Aphid, Thrips and Whitefly Vectors

Insects may function as vectors for plant viruses. Since the hosts for plant viruses are sessile, the potential for behavioural manipulation is restricted to the vectors, although viruses may affect the volatile profiles secreted by plants (Medina-Ortega et al. 2009). Several plant viruses have been shown to increase their transmission by affecting the feeding behaviour of the insect vector, changing food choices and altering the probing period and frequency (Ingwell et al. 2012; Fereres et al. 1990; Hu et al. 2013). The type of transmission (persistent versus non-persistent) appears to have a direct correlation with the feeding behaviour observed for plant virus vectors (see review by Mauck et al. 2012). Non-viruliferous vectors show a strong attraction to infected plants, both for plants infected with persistently and non-persistently transmitted viruses. Persistently transmitted plant viruses such as potato leaf roll virus (PLRV, *Luteoviridae*) induce longer feeding times in aphid vectors needed to guarantee sufficient uptake of the virus from the phloem. For non-persistently transmitted viruses such as Potato virus Y (PVY, *Potyviridae*) aphids generally leave more quickly from infected plants than from healthy plants and the aphids can immediately transmit the virus after probing (Mauck et al. 2012). Ingwell et al. (2012) showed that *R. padi* aphids carrying barley yellow dwarf virus (BYDV, family *Luteoviridae*) preferred uninfected wheat plants, which promoted viral transmission. On the other hand, aphids that did not carry BYDV preferred BYDV-infected wheat plants, which promoted the acquisition of this virus. The switch of the aphids' preference from infected plants to uninfected plants after acquiring BYDV maximized the pathogen transmission potential (Ingwell et al. 2012). A similar observation was made for potato leaf roll virus (PLRV, family *Luteoviridae*) and its aphid vector *Myzus persicae* (Rajabaskar et al. 2014).

M. persicae aphids that did not carry PLRV preferred infected potato plants, while *M. persicae* carrying the virus preferred healthy plants. This switch in host plant preference seems to enhance virus acquisition and transmission. Both the BYDV- and PLRV-induced changes in feeding preference can be a direct result of virus-vector interactions, but may also be affected by the exposure of the vector to infected plants (Rajabaskar et al. 2014).

Tomato spotted wilt virus (TSWV), a member of the only plant-infecting genus (*Tospovirus*) in the family *Bunyaviridae*, alters the feeding behaviour of its thrips vector *Frankliniella occidentalis* (order Thysanoptera) (Stafford et al. 2011). Male thrips infected with TSWV showed an up to threefold increase in feeding frequency compared with uninfected thrips. Infected male thrips made more non-ingestion probes (probes in which they salivate, but leave cells largely intact), which cause less damage to the plant cells. Functional plant leaf cells are very important for successful TSWV infection, and due to this altered feeding behaviour, infected males transmit TSWV in a more efficient manner than females (van de Wetering et al. 1998; Stafford et al. 2011).

Tomato yellow leaf curl virus (TYLCV, family *Geminiviridae*) was found to change the feeding behaviour of its whitefly vector *Bemisia tabaci* (order Hemiptera). Female whiteflies carrying TYLCV remained motionless for a longer time and moved slower after their first contact with the host plant (Moreno-Delafuente et al. 2013). In addition, probing and feeding behaviour changed. Plants are inoculated with virus during salivation in phloem sieve elements and this happens before phloem sap ingestion. *B. tabaci* carrying TYLCV fed more from phloem sieve elements and made more frequent phloem contacts. The duration of the salivation phase in the phloem sieve elements was also longer. All these behavioural changes are thought to enhance virus transmission.

10.11 Arboviruses Change Mosquito and Midge Behaviour

Many human and veterinary viruses use arthropods, such as mosquitoes, midges (both Diptera) or ticks (class Arachnida) as vectors. Arthropod-borne viruses (arboviruses) belong to various virus families and several have been found to change vector behaviour to increase virus transmission rates (van Houte et al. 2013; Lefèvre and Thomas 2008). These changes include alterations in feeding behaviour (probing time and/or frequency), locomotion and flight activity, and in mating behaviour.

Arboviruses classified in the family *Bunyaviridae* cause disease in their vertebrate host, but can also replicate in their insect vector. Many viruses from this family have been reported to change their vector's behaviour. Grimstad et al. (1980) first reported that the mosquito *Aedes triseriatus,* when infected orally with La Crosse virus (LACV), probed more on mice, with reduced rates of blood engorgement; a similar behavioural change was found by Jackson et al. (2012). LACV-infected *Ae. triseriatus* mosquitoes took a significantly smaller blood meal than uninfected

mosquitoes, and the refeeding rate of LACV-infected *Ae. triseriatus* mosquitoes was twice as high as that of uninfected mosquitoes. The decreased blood meal size combined with increased refeeding potentially intensifies the number of contacts between virus-carrying insects and vulnerable animal hosts, thus enhancing horizontal transmission of LACV. The changes in blood feeding behaviour were accompanied by altered serotonin levels in the mosquito brain (Jackson et al. 2012). LACV is not the only animal-infecting virus from the family *Bunyaviridae* that can change vector feeding behaviour. Rift Valley fever virus-infected *Culex pipiens* mosquitoes also showed decreased feeding (Turell et al. 1985).

Many other arboviruses have been reported to alter vector feeding behaviour. Vesicular stomatitis virus (VSV, family *Rhabdoviridae*) infection significantly reduced the number of female *Culicoides sonorensis* midges that took a blood meal at 2 days post infection (d.p.i.), when the virus titer was at its highest (Bennett et al. 2008). Whether this behavioural change is beneficial for virus transmission has yet to be determined. *Aedes aegypti* mosquitoes infected with Dengue 3 virus (family *Flaviviridae*) required a significantly longer time to feed on a host to complete the blood meal than uninfected mosquitoes, mainly due to extended periods of probing, which is expected to enhance dengue virus transmission (Platt et al. 1997). In contrast, Putnam and Scott (1995) reported that Dengue 2 virus infection did not impair the feeding efficiency of *Ae. aegypti*, although the absence of an effect might be due to the infection method used (intrathoracic inoculation), the time of measurement, or the mosquito and virus strains used (maintained in the laboratory for a long time). Sindbis virus (SINV, family *Togaviridae*) infected *Ae. aegypti* females required more time for blood engorgement than uninfected ones. Meanwhile, infected mosquitoes also spent more time on blood meal localization (Qualls et al. 2012). A longer feeding period per meal potentially increases the virus transmission rate, but it could also impose a greater risk of death of the vector if detected by the blood donor, which may finally reduce virus transmission efficiency.

Besides feeding behaviour, arboviruses manipulate other behavioural traits of their hosts, such as mating behaviour or locomotion/flight behaviour. Gabitzsch et al. (2006) described that the percentage of females inseminated by males was substantially higher for *Ae. triseriatus* females orally infected with LACV than for uninfected females. Similar results were found for *Ae. triseriatus* females that had been infected with LACV by transovarial (vertical) transmission (Reese et al. 2009). Additionally, it was found that LACV-infected mosquitoes mated earlier in their life than uninfected ones. More interestingly, the virus titer was not correlated with increased insemination, but an earlier insemination of LACV-infected female mosquitoes might increase the number and percentage of virus progeny in the next mosquito generation, thus leading to enhanced virus transmission (Reese et al. 2009). The higher mating efficiencies might be achieved via an effect of LACV on sex pheromone expression in *Ae. triseriatus* (Reese et al. 2009).

Ae. aegypti mosquitoes infected with Dengue 2 virus showed up to a 50 % increase in their locomotor activity compared with uninfected females (Lima-Camara et al. 2011). Whether this increase in locomotor activity leads to higher virus transmission needs further investigation. The authors speculate that modulation of the

circadian clock is involved in inducing this alteration (Lima-Camara et al. 2011). In other cases a reduction in flight activity was seen, which might be a pathological consequence of the infection and is in fact less favourable for virus transmission. Female *Culex tarsalis* mosquitoes, for instance, showed a reduced flight activity when infected with Western equine encephalomyelitis virus (family *Togaviridae*) and fewer spontaneous flights were recorded (Lee et al. 2000). The idea that this virus has pathological consequences for the mosquito is reflected by a reduction in longevity, which was shown to be dependent on the viral load.

10.12 Ecological and Evolutionary Aspects of Behavioural Manipulation

How behavioural manipulation by viruses occurs and evolves is a central question, not only for virologists, but also for evolutionary biologists. Many evolutionary scenarios have been proposed that might underlie behavioural manipulation by parasites, including manipulation *sensu stricto* (selection of parasite genes that directly affect host behaviour), exploitation of host compensatory responses (selection of parasite genes on their pathological effects), mafia-like manipulation (selection of parasite genes on host collaborative behaviour) and manipulation by parasites with complex life cycles (selection of other parasite traits) (Lefèvre et al. 2009; Cézilly et al. 2010). However, experimental data supporting these theories are lacking and hard to obtain.

Viruses within the same family can target and modify the same host behavioural trait, e.g. locomotion or feeding behaviour, indicating that the ability to manipulate that trait might be conserved among this viral family or part thereof. For example, LACV, RVF and TSWV all belong to the family *Bunyaviridae* and all three can alter the feeding behaviour of their vector, suggesting that altered vector feeding behaviour might be a conserved trait among bunyaviruses (Jackson et al. 2012; Turell et al. 1985; Stafford et al. 2011). The baculoviruses BmNPV and AcMNPV both induce hyperactivity (Kamita et al. 2005; van Houte et al. 2012) and several baculoviruses including LdMNPV, AcMNPV, SeMNPV, MbNPV have been reported to induce tree-top disease in their lepidopteran hosts (Hoover et al. 2011; Ros et al. 2015; van Houte et al. 2014b; Goulson 1997). These data demonstrate that the ability of inducing hyperactivity and tree-top disease in lepidopteran hosts is, at least to some degree, conserved among baculoviruses.

Though the ability to modify the same behavioural trait might be conserved, different viruses may use different mechanisms to achieve this. For example, although both BmNPV and AcMNPV can induce hyperactivity in their hosts, the exact role of the encoded PTP protein might be different depending on the virus-host interaction. In BmNPV-infected *B. mori* larvae, the phosphatase activity of the PTP protein is not needed for the induction of hyperactivity (Katsuma et al. 2012). As deletion of the BmNPV *ptp* gene was shown to affect budded virus (BV) production in many different tissues including the larval brain, it was hypothesized that BmNPV PTP

may exert its behavioural function as a structural component of the virus particles rather than as an enzyme. In contrast, in AcMNPV-infected *S. exigua* larvae the PTP phosphatase activity is required for induction of hyperactivity, since mutating the catalytic site of the encoded protein blocked induction of hyperactivity in *S. exigua* larvae, providing strong evidence that a host or viral protein is targeted by the enzymatic activity of the viral PTP to cause this behavioural change (van Houte et al. 2012). Another example of varying mechanisms can be seen in baculovirus-induced tree-top disease: both LdMNPV and AcMNPV can induce tree-top disease in their host; the *egt* gene from LdMNPV is involved in this behavioural change, while the *egt* gene from AcMNPV is not (Hoover et al. 2011; Ros et al. 2015).

Alternatively, unrelated viruses might use the same proximate mechanism to induce a similar host behavioural change, representing a case of convergent evolution (Ponton et al. 2006; van Houte et al. 2013). For example, both LbFV and HzNV-2 are present in the female host reproduction tract (of wasps and moths, respectively) and enhanced their transmission via affecting the reproduction behaviour of their host (Burand 2009; Varaldi et al. 2012).

Behavioural changes following infection by viruses can be adaptive to the host or to the parasite, or simply be pathological side effects of the infection (Thomas et al. 2005; van Houte et al. 2013). However, in many examples it is hard to exactly identify costs and benefits for both the parasite and the host. For the behavioural changes to be adaptive to the parasites, two features are critical: strong manipulation of the host and high prevalence within the host population (Lafferty and Kruis 2012). Some baculoviruses have a high prevalence within their host and a strong ability to induce behaviour changes (tree-top disease and hyperactivity), at least in laboratory settings. However, whether manipulation leads to enhanced viral transmission in the field needs further support from experimental field data. Greater dispersal of infected larvae can be interpreted as spreading virus over larger areas, thus increasing viral transmission, but can also be interpreted as removing infected individuals from uninfected conspecifics, which would be adaptive to the host. Death at elevated positions combined with liquefaction of host cadavers may spread the virus over larger areas and on lower foliage. However, liquefaction at elevated positions can also decrease virus transmission, because baculoviruses will be inactivated more quickly by increased exposure to UV light. Therefore, death at lower positions might lead to a higher infection rate in the next generation (viral progeny are better protected from UV light at lower positions), though the within-generation transmission might be reduced (due to limited spread of the virus) (Hamblin and Tanaka 2013). Downward movement was seen for OpbuNPV-infected *O. brumata* (Raymond et al. 2005; see above), where occlusion bodies were better protected from light on stems than on foliage.

An interesting question is to what extent laboratory studies can be used to study ecological scenarios. Behaviour is a complex phenotype, which not only relies on parameters of host and virus (such as genetic properties, physiological condition, virus dose and virulence), but may also depend on many environmental factors such as light, temperature, quality and availability of resources, and the presence of other parasites (de Bekker et al. 2014). Therefore, the environmental context should be

taken into account when studying behavioural manipulation. Taking the baculovirus-induced behavioural changes as an example, it is known that behavioural changes like hyperactivity and tree-top disease are observed in nature (Goulson 1997; Hofmann 1891), but little is known to what extent environmental factors play a role in determining these phenotypes. However, it is known that the host plant species can affect insect susceptibility to baculoviruses and therefore, indirectly can affect insect host behaviour (Cory and Hoover 2006). To be able to study the genetic basis of baculovirus-induced behavioural changes in the laboratory, many environmental factors are usually standardized (see Fig. 10.2 for a schematic view of a laboratory set-up used to measure hyperactivity and tree-top disease in lepidopteran larvae infected with baculoviruses).

However, in nature, environmental conditions are constantly changing. An example is seen for LbFV infecting *L. boulardi* wasps. The distribution of LbFV, able to induce superparasitism in *L. boulardi* wasps is dependent on geographical location. The virus is highly prevalent in central populations of the *L. boulardi* distribution range, intermediately prevalent in marginal populations, and almost absent in newly established populations of *L. boulardi* (Patot et al. 2010). Though LbFV has a strong ability to induce superparasitism, few cases of superparasitism have been reported in newly established populations. However, in the central *L. boulardi* populations, superparasitism occurs more frequently, which might lead to high prevalence of the virus. It is predicted that superparasitism can complement imperfect vertical transmission of the virus (when the transmission rate is low) to maintain the virus at high frequencies (Gandon et al. 2006). Varaldi et al. (2012) even hypothesized that the superparasitism manipulation seen in the LbFV/*L. boulardi* system might be a common strategy among all parasitoid-associated viruses that infect the genital tract to maintain the virus in the host population. Without a certain level of horizontal transmission it is likely that the virus will die out eventually (assuming that vertical transmission never reaches 100 %).

Host manipulation by parasites can affect the ecological characteristics of host species by changing host population size, host mating system, the ecological community structures or food web structures. These effects can be substantial when the infected host displays a completely new behaviour or occupies a new niche. For example, the hairworm *Gordionus chinensis* induces water seeking behaviour in crickets (*Tachycines* spp.). Since this manipulation can be highly prevalent, the cricket cadavers can provide up to 60 % of the energetic needs for the Kirikuchi charr (*Salvelinus leucomaenis japonicas*), a trout living in a local river in Japan (Sato et al. 2011). Even so, lepidopteran larvae infected with a baculovirus climb to the top parts of the canopy, which makes them visible for birds and other predators. This potentially will spread the virus over long distances. Dispersal of viral occlusion bodies by birds has been shown for *Panolis flammea* (Pf) MNPV-infected larvae of the pine beauty moth (Entwistle et al. 1993). If increased visibility to predators is a common phenomenon among baculovirus-infected caterpillar hosts, the behavioural change of "tree-top disease" may lead to changes in the food web structure.

Many insect hosts and vectors are of great medical, agricultural and environmental importance. Though the study of virus-induced behavioural manipulation is still

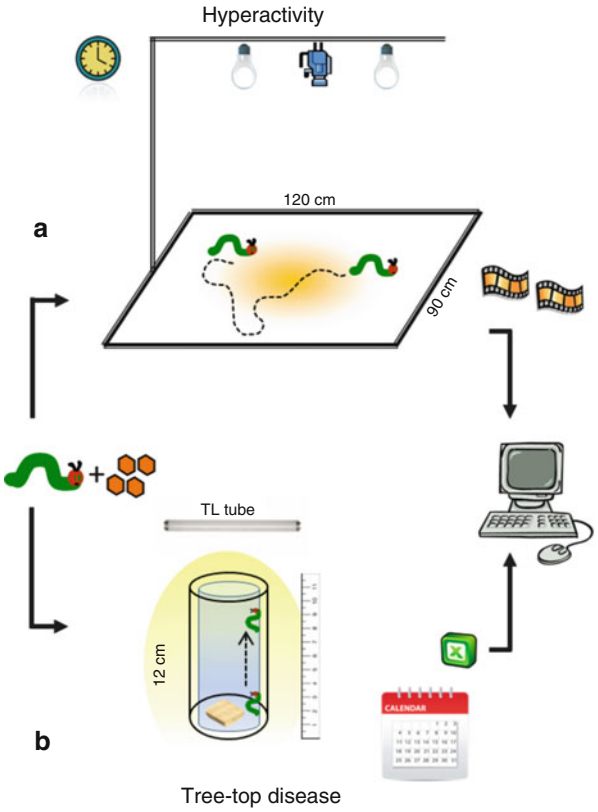

Fig. 10.2 Laboratory settings used to study the genetic basis of baculovirus-induced behavioural changes in moth larvae (van Houte et al. 2014b; Ros et al. 2015; van Houte et al. 2012, 2014a). Larvae that were either mock infected or infected with wild type or mutant baculoviruses were used to study hyperactivity (**a**) or tree-top disease (**b**). (**a**) The system used for studying hyperactivity, consisting of a horizontal surface (arena) of 120×90 cm equipped with a digital video camera positioned at 200 cm above the surface. The camera is flanked by two photography studio lights of 40 W each. The temperature in the arena was 24.5 °C±0.7. To measure larval activity, individual larvae were placed in the arena and video-tracked for 10 min. The total distance moved within this timeframe was calculated using EthoVision tracking software (Noldus Information Technology, The Netherlands). (**b**) The system used for studying tree-top disease consisting of sterile glass jars (120 mm tall×71 mm wide) lined with mesh wire to facilitate climbing. A block of artificial diet (approximately 3.5 cm^3) was placed on the bottom of each jar, and jars were closed with a metal lid containing small holes to allow ventilation. When light was applied only from above, jar walls were protected from light using aluminium foil and jars were covered with a piece of transparent plastic wrap containing three holes for ventilation. Jars were incubated at 27 °C with 50 % relative humidity, and a 14 L: 10 D photoperiod. Vertical position of the larvae was monitored twice per day, starting from 1 day post-infection until all larvae were dead or had pupated

in its infancy, this phenomenon has great potential in applied science, especially in the areas of pest management and vector control. As described above, altered behavioural traits, which can vary from slightly modified existing behavioural traits to

completely new developed traits (van Houte et al. 2013), may have considerable impact on the insect population and on ecosystem dynamics. Understanding how viruses change insect behaviour may lead to broadly applicable strategies to modulate insect behaviour, facilitating regulation of insect population sizes and limiting virus transmission by vectors. This may be beneficial for agriculture, as well as human and veterinary health.

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References

Adamo SA (2008) Bidirectional connections between the immune system and the nervous system in insects. In: Beckage NE (ed) Insect immunology. Academic, San Diego, pp 129–149

Adamo SA (2014) Parasitic aphrodisiacs: manipulation of the hosts' behavioral defenses by sexually transmitted parasites. Integr Comp Biol 54:159–165

Adamo SA, Bartlett A, Le J, Spencer N, Sullivan K (2010) Illness-induced anorexia may reduce trade-offs between digestion and immune function. Anim Behav 79:3–10

Adamo SA, Kovalko I, Easy RH, Stoltz D (2014) A viral aphrodisiac in the cricket *Gryllus texensis*. J Exp Biol 217:1970–1976

Ball BV (1989) *Varroa jacobsoni* as a virus vector. In: Cavalloro R (ed) Present status of varroatosis in Europe and progress in the *Varroa* mite control. Office Official Publications EC, Luxembourg, pp 241–244

Ban L, Ahmed E, Ninkovic V, Delp G, Glinwood R (2008) Infection with an insect virus affects olfactory behaviour and interactions with host plant and natural enemies in an aphid. Entomol Exp Appl 127:108–117

Baracchi D, Fadda A, Turillazzi S (2012) Evidence for antiseptic behaviour towards sick adult bees in honey bee colonies. J Insect Physiol 58:1589–1596

Bennett KE, Hopper JE, Stuart MA, West M, Drolet BS (2008) Blood-feeding behavior of vesicular stomatitis virus infected *Culicoides sonorensis* (Diptera: Ceratopogonidae). J Med Entomol 45:921–926

Burand JP (2009) The sexually transmitted insect virus, Hz-2 V. Virol Sin 24:428–435

Burand JP, Tan W (2006) Mate preference and mating behavior of male *Helicoverpa zea* (Lepidoptera: Noctuidae) infected with the sexually transmitted insect virus Hz-2 V. Ann Entomol Soc Am 99:969–973

Burand JP, Rallis CP, Tan W (2004) Horizontal transmission of Hz-2 V by virus infected *Helicoverpa zea* moths. J Invertebr Pathol 85:128–131

Burand JP, Tan W, Kim W, Nojima S, Roelofs W (2005) Infection with the insect virus Hz-2v alters mating behavior and pheromone production in female *Helicoverpa zea* moths. J Insect Sci 5:1–6

Cézilly F, Thomas F, Médoc V, Perrot-Minnot M-J (2010) Host-manipulation by parasites with complex life cycles: adaptive or not? Trends Parasitol 26:311–317

Chapman AD (2006) Numbers of living species in Australia and the World. Australian Biological Resources Study, Canberra

Cory JS, Hoover K (2006) Plant-mediated effects in insect-pathogen interactions. Trends Ecol Evol 21:278–286

Cranston PS (2010) Insect biodiversity and conservation in Australasia. Annu Rev Entomol 55:55–75

Dawkins RL (1982) The extended phenotype. Oxford University Press, Oxford
de Bekker C, Merrow M, Hughes DP (2014) From behavior to mechanisms: an integrative approach to the manipulation by a parasitic fungus (*Ophiocordyceps unilateralis* s.l.) of its host ants (*Camponotus* spp.). Integr Comp Biol 54:166–176
Dheilly NM, Maure F, Ravallec M, Galinier R, Doyon J, Duval D, Leger L, Volkoff AN, Misse D, Nidelet S, Demolombe V, Brodeur J, Gourbal B, Thomas F, Mitta G (2015) Who is the puppet master? Replication of a parasitic wasp-associated virus correlates with host behaviour manipulation. Proc R Soc B 282:20142773
Entwistle PF, Forkner AC, Green BM, Cory JS (1993) Avian dispersal of nuclear polyhedrosis viruses after induced epizootics in the pine beauty moth, *Panolis flammea* (Lepidoptera: Noctuidae). Bio Control 3:61–69
Evans HF, Allaway GP (1983) Dynamics of baculovirus growth and dispersal in *Mamestra brassicae* L. (Lepidoptera: Noctuidae) larval populations introduced into small cabbage plots. Appl Environ Microbiol 45:493–501
Fedorka KM, Mousseau TA (2007) Immune system activation affects male sexual signal and reproductive potential in crickets. Behav Ecol 18:231–235
Fereres A, Shukle RH, Araya JE, Foster JE (1990) Probing and feeding behavior of *Sitobion avenae* (F.) (Horn., Aphididae) on three wheat cultivars infected with barley yellow dwarf virus. J Appl Entomol 109:29–36
Fujiyuki T, Takeuchi H, Ono M, Ohka S, Sasaki T, Nomoto A, Kubo T (2004) Novel insect Picorna-like virus identified in the brains of aggressive worker honeybees. J Virol 78:1093–1100
Fujiyuki T, Takeuchi H, Ono M, Ohka S, Sasaki T, Nomoto A, Kubo T (2005) Kakugo virus from brains of aggressive worker honeybees. Adv Virus Res 65:1–27
Gabitzsch ES, Blair CD, Beaty BJ (2006) Effect of La Crosse Virus infection on insemination rates in female *Aedes triseriatus* (Diptera: Culicidae). J Med Entomol 43:850–852
Gandon S, Rivero A, Varaldi J (2006) Superparasitism evolution: adaptation or manipulation? Am Nat 167:1–22
Gisder S, Aumeier P, Genersch E (2009) Deformed wing virus: replication and viral load in mites (*Varroa destructor*). J Gen Virol 90:463–467
Goulson D (1997) Wipfelkrankheit: modification of host behaviour during baculoviral infection. Oecologia 109:219–228
Grimstad PR, Ross QE, Craig GB Jr (1980) *Aedes triseriatus* (Diptera: Culicidae) and La Crosse virus. II. Modification of mosquito feeding behavior by virus infection. J Med Entomol 17:1–7
Hamblin S, Tanaka M (2013) Behavioural manipulation of insect hosts by *Baculoviridae* as a process of niche construction. BMC Evol Biol 13:170
Hamm JJ, Carpenter JE, Styer EL (1996) Oviposition day effect on incidence of agonadal progeny of *Helicoverpa zea* (Lepidoptera: Noctuidae) infected with a virus. Ann Entomol Soc Am 89:266–275
Harris JW (2007) Bees with *Varroa* Sensitive Hygiene preferentially remove mite infested pupae aged ≤ five days post capping. J Apicult Res 46:134–139
Hofmann O (1891) Insektentötende Pilze mit bosenderer Berücksichtigung der Nonne. P. Weber, Frankfurt
Hoover K, Grove M, Gardner M, Hughes DP, McNeil J, Slavicek J (2011) A gene for an extended phenotype. Science 333:1401
Hu Z, Zhao H, Thieme T (2013) Modification of non-vector aphid feeding behavior on virus-infected host plant. J Insect Sci 13:1–11
Hughes DP, Andersen SB, Hywel-Jones NL, Himaman W, Billen J, Boomsma JJ (2011) Behavioral mechanisms and morphological symptoms of zombie ants dying from fungal infection. BMC Ecol 11:173
Ingwell LL, Eigenbrode SD, Bosque-Perez NA (2012) Plant viruses alter insect behavior to enhance their spread. Sci Rep 2:578
Iqbal J, Mueller U (2007) Virus infection causes specific learning deficits in honeybee foragers. Proc R Soc B 274:1517–1521

Jackson BT, Brewster CC, Paulson SL (2012) La Crosse virus infection alters blood feeding behavior in *Aedes triseriatus* and *Aedes albopictus* (Diptera: Culicidae). J Med Entomol 49:1424–1429

Jacot A, Scheuber H, Brinkhof MW (2004) Costs of an induced immune response on sexual display and longevity in field crickets. Evolution 58:2280–2286

Jakob NJ, Kleespies RG, Tidona CA, Müller K, Gelderblom HR, Darai G (2002) Comparative analysis of the genome and host range characteristics of two insect iridoviruses: Chilo iridescent virus and a cricket iridovirus isolate. J Gen Virol 83:463–470

Jenkins DA, Hunter WB, Goenaga R (2011) Effects of invertebrate iridescent virus 6 in *Phyllophaga vandinei* and its potential as a biocontrol delivery system. J Insect Sci 11:44

Kamita SG, Nagasaka K, Chua JW, Shimada T, Mita K, Kobayashi M, Maeda S, Hammock BD (2005) A baculovirus-encoded protein tyrosine phosphatase gene induces enhanced locomotory activity in a lepidopteran host. Proc Natl Acad Sci U S A 102:2584–2589

Katsuma S, Koyano Y, Kang W, Kokusho R, Kamita S, Shimada T (2012) The baculovirus uses a captured host phosphatase to induce enhanced locomotory activity in host caterpillars. PLoS Pathog 8:e1002644

Kleespies RG, Tidona CA, Darai G (1999) Characterization of a new iridovirus isolated from crickets and investigations on the host range. J Invertebr Pathol 73:84–90

Kulinčević JM, Stairs GR, Rothenbuhler WC (1969) A disease of the honey bee causing behavioral changes and mortality. J Invertebr Pathol 14:13–17

Lafferty KD, Kruis AM (2012) Ecological consequences of manipulative parasites. In: Hughes DP, Brodeur J, Thomas F (eds) Host manipulation by parasites. Oxford University Press, Oxford, pp 158–171

Lawniczak MKN, Barnes AI, Linklater JR, Boone JM, Wigby S, Chapman T (2007) Mating and immunity in invertebrates. Trends Ecol Evol 22:48–55

Lee JH, Rowley WA, Platt KB (2000) Longevity and spontaneous flight activity of *Culex tarsalis* (Diptera: Culicidae) infected with western equine encephalomyelitis virus. J Med Entomol 37:187–193

Lefèvre T, Thomas F (2008) Behind the scene, something else is pulling the strings: emphasizing parasitic manipulation in vector-borne diseases. Infect Genet Evol 8:504–519

Lefèvre T, Adamo S, Biron D, Misse D, Hughes D, Thomas F (2009) Invasion of the body snatchers: the diversity and evolution of manipulation strategies in host-parasite interactions. Adv Parasitol 68:45–83

Leman JC, Weddle CB, Gershman SN, Kerr AM, Ower GD, St John JM, Vogel LA, Sakaluk SK (2009) Lovesick: immunological costs of mating to male sagebrush crickets. J Evol Biol 22:163–171

Li Z, Chen Y, Zhang S, Chen S, Li W, Yan L, Shi L, Wu L, Sohr A, Su S (2013) Viral infection affects sucrose responsiveness and moming ability of forager honey bees, *Apis mellifera* L. PLoS One 8:e77354

Lima-Camara TN, Bruno RV, Luz PM, Castro MG, Lourenco-de-Oliveira R, Sorgine MH, Peixoto AA (2011) Dengue infection increases the locomotor activity of *Aedes aegypti* females. PLoS One 6:0017690

Martinez J, Duplouy A, Woolfit M, Vavre F, O'Neill SL, Varaldi J (2012) Influence of the virus LbFV and of *Wolbachia* in a host-parasitoid interaction. PLoS One 7:e35081

Mauck K, Bosque-Pérez NA, Eigenbrode SD, de Moraes CM, Mescher MC (2012) Transmission mechanisms shape pathogen effects on host–vector interactions: evidence from plant viruses. Funct Ecol 26:1162–1175

Maure F, Daoust SP, Brodeur J, Mitta G, Thomas F (2013) Diversity and evolution of bodyguard manipulation. J Exp Biol 216(1):36–42

Medina-Ortega KJ, Bosque-Perez NA, Ngumbi E, Jimenez-Martinez ES, Eigenbrode SD (2009) *Rhopalosiphum padi* (Hemiptera: Aphididae) responses to volatile cues from Barley yellow dwarf virus-infected wheat. Environ Entomol 38:836–845

Miller LK, Ball LA (1998) The insect viruses. Plenum Press, New York

Moreno-Delafuente A, Garzo E, Moreno A, Fereres A (2013) A plant virus manipulates the behavior of its whitefly vector to enhance its transmission efficiency and spread. PLoS One 8:e61543

Nalçacıoğlu R, Ince I, Demirbağ Z (2009) The biology of Chilo iridescent virus. Virol Sin 24:285–294

Patot S, Lepetit D, Charif D, Varaldi J, Fleury F (2009) Molecular detection, penetrance, and transmission of an inherited virus responsible for behavioral manipulation of an insect parasitoid. Appl Environ Microbiol 75:703–710

Patot S, Martinez J, Allemand R, Gandon S, Varaldi J, Fleury F (2010) Prevalence of a virus inducing behavioural manipulation near species range border. Mol Ecol 19:2995–3007

Platt K, Linthicum K, Myint K, Innis B, Lerdthusnee K, Vaughn D (1997) Impact of dengue virus infection on feeding behavior of *Aedes aegypti*. Am J Trop Med Hygiene 57:119–125

Ponton F, Lefèvre T, Lebarbenchon C, Thomas F, Loxdale HD, Marché L, Renault L, Perrot-Minnot MJ, Biron DG (2006) Do distantly related parasites rely on the same proximate factors to alter the behaviour of their hosts? Proc R Soc B 273:2869–2877

Putnam JL, Scott TW (1995) Blood-feeding behavior of dengue-2 virus-infected *Aedes aegypti*. Am J Trop Med Hyg 52:225–227

Qualls WA, Day JF, Xue RD, Bowers DF (2012) Sindbis virus infection alters blood feeding responses and DEET repellency in *Aedes aegypti* (Diptera: Culicidae). J Med Entomol 49:418–423

Raina AK, Adams JR (1995) Gonad-specific virus of corn earworm. Nature 374:770

Raina AK, Kingan TG, Giebltowicz JM (1994) Mating-induced loss of sex pheromone and sexual receptivity in insects with emphasis on *Helicoverpa zea* and *Lymantria dispar*. Arch Insect Biochem Physiol 25:317–327

Rajabaskar D, Bosque-Pérez NA, Eigenbrode SD (2014) Preference by a virus vector for infected plants is reversed after virus acquisition. Virus Res 186:32–37

Raymond B, Hartley SE, Cory JS, Hails RS (2005) The role of food plant and pathogen-induced behaviour in the persistence of a nucleopolyhedrovirus. J Invertebr Pathol 88:49–57

Reese SM, Beaty MK, Gabitzsch ES, Blair CD, Beaty BJ (2009) *Aedes triseriatus* females transovarially infected with La Crosse virus mate more efficiently than uninfected mosquitoes. J Med Entomol 46:1152–1158

Richard FJ, Aubert A, Grozinger CM (2008) Modulation of social interactions by immune stimulation in honey bee, *Apis mellifera*, workers. BMC Biol 6:50

Richard FJ, Holt HL, Grozinger CM (2012) Effects of immunostimulation on social behaviour, chemical communication and genome-wide gene expression in honey bee workers (*Apis mellifera*). BMC Genomics 13:558

Rortais A, Tentcheva D, Papachristoforou A, Gauthier L, Arnold G, Colin ME, Bergoin M (2006) Deformed wing virus is not related to honey bees' aggressiveness. Virol J 3:61

Ros VID, van Houte S, Hemerik L, van Oers MM (2015) Baculovirus-induced tree-top disease: how extended is the role of *egt* as a gene for the extended phenotype? Mol Ecol 24:249–258

Salvy M, Martin C, Bagnères AG, Provost É, Roux M, Le Conte Y, Clément JL (2001) Modifications of the cuticular hydrocarbon profile of *Apis mellifera* worker bees in the presence of the ectoparasitic mite *Varroa jacobsoni* in brood cells. Parasitology 122:145–159

Sato T, Watanabe K, Kanaiwa M, Niizuma Y, Harada Y, Lafferty KD (2011) Nematomorph parasites drive energy flow through a riparian ecosystem. Ecology 92:201–207

Schöning C, Gisder S, Geiselhardt S, Kretschmann I, Bienefeld K, Hilker M, Genersch E (2012) Evidence for damage-dependent hygienic behaviour towards *Varroa destructor*-parasitised brood in the western honey bee, *Apis mellifera*. J Exp Biol 215:264–271

Shah KS, Evans EC, Pizzorno MC (2009) Localization of deformed wing virus (DWV) in the brains of the honeybee, *Apis mellifera* Linnaeus. Virol J 6:182

Smirnoff WA (1965) Observations on the effect of virus infection on insect behavior. J Invertebr Pathol 7:387–388

Stafford CA, Walker GP, Ullman DE (2011) Infection with a plant virus modifies vector feeding behavior. Proc Natl Acad Sci U S A 108:9350–9355

Sumpter DJT, Martin SJ (2004) The dynamics of virus epidemics in *Varroa*-infested honey bee colonies. J Anim Ecol 73:51–63

Thomas F, Schmidt-Rhaesa A, Martin G, Manu C, Durand P, Renaud F (2002) Do hairworms (Nematomorpha) manipulate the water seeking behaviour of their terrestrial hosts? J Evol Biol 15:356–361

Thomas F, Adamo S, Moore J (2005) Parasitic manipulation: where are we and where should we go? Behav Processes 68:185–199

Turell MJ, Gargan TP, Bailey CL (1985) *Culex pipiens* (Diptera: Culicidae) morbidity and mortality associated with Rift Valley fever virus infection. J Med Entomol 22:332–337

van Alphen JJ, Visser ME (1990) Superparasitism as an adaptive strategy for insect parasitoids. Annu Rev Entomol 351:59–79

van de Wetering F, Hulshof J, Posthuma K, Harrewijn P, Goldbach R, Peters D (1998) Distinct feeding behavior between sexes of *Frankliniella occidentalis* results in higher scar production and lower tospovirus transmission by females. Entomol Exp Appl 88:9–15

van Houte S, Ros VID, Mastenbroek TG, Vendrig NJ, Hoover K, Spitzen J, van Oers MM (2012) Protein tyrosine phosphatase-induced hyperactivity is a conserved strategy of a subset of baculoviruses to manipulate lepidopteran host behavior. PLoS One 7:e46933

van Houte S, Ros VID, van Oers MM (2013) Walking with insects: molecular mechanisms behind parasitic manipulation of host behaviour. Mol Ecol 22:3458–3475

van Houte S, Ros VID, van Oers MM (2014a) Hyperactivity and tree-top disease induced by the baculovirus AcMNPV in *Spodoptera exigua* larvae are governed by independent mechanisms. Naturwissenschaften 101:347–350

van Houte S, van Oers MM, Han Y, Vlak JM, Ros VID (2014b) Baculovirus infection triggers a positive phototactic response in caterpillars to induce 'tree-top' disease. Biol Lett 10:20140680

Varaldi J, Fouillet P, Ravallec M, Lopez-Ferber M, Bouletreau M, Fleury F (2003) Infectious behaviour in a parasitoid. Science 302:1930

Varaldi J, Bouletreau M, Fleury F (2005) Cost induced by viral particles manipulating superparasitism behaviour in the parasitoid *Leptopilina boulardi*. Parasitology 131:161–168

Varaldi J, Petit S, Bouletreau M, Fleury F (2006) The virus infecting the parasitoid *Leptopilina boulardi* exerts a specific action on superparasitism behaviour. Parasitology 132:747–756

Varaldi J, Patot S, Nardin M, Gandon S (2009) A virus-shaping reproductive strategy in a *Drosophila* parasitoid. Adv Parasitol 70:333–363

Varaldi J, Martinez J, Patot S, Lepetit D, Fleury F, Gandon S, Drezen JM, Beckage NE (2012) An inherited virus manipulating the behaviour of its parasitoid host: epidemiology and evolutionary consequences. In: Beckage NE, Drezen JM (eds) Parasitoid viruses: symbionts and pathogens. Academic, San Diego, pp 203–214

Vasconcelos SD, Cory JS, Wilson KR, Sait SM, Hails RS (1996) Modified behaviour in baculovirus-infected lepidopteran larvae and its impact on the spatial distribution of inoculum. Bio Contr 7:299–306

Williamson C, Rybicki EP, Kasdorf GGF, Von Wechmar MB (1988) Characterization of a new picorna-like virus isolated from aphids. J Gen Virol 69:787–795

Wilson-Rich N, Spivak M, Fefferman NH, Starks PT (2009) Genetic, individual, and group facilitation of disease resistance in insect societies. Annu Rev Entomol 54:405–423

Yang X, Cox-Foster DL (2005) Impact of an ectoparasite on the immunity and pathology of an invertebrate: evidence for host immunosuppression and viral amplification. Proc Natl Acad Sci U S A 102:7470–7475

Further Reading

This chapter contains a selection of papers which are not or not intensely considered in the preceeding chapters. However, they may be helpful to get quick access to additional information, since all those papers cite additional literature, which makes it easier to get a better survey in a given field of interest.

Selection of papers, which contribute to the contents of the chapters of this booklet

Adamec R (2001) Does long term potentiation in periacqueductal gray (PAG) mediate lasting changes in rodent anxiety-like behavior (ALB) produced by predator stress?—effects of low frequency stimulation (LFS) of PAG on place preference and changes in ALB produced by predator stress. Behav Brain Res 120:111–135

Adamo SA (1998) Feeding suppression in the tobacco hornworm, *Manduca sexta*: costs and benefits to the parasitic wasp *Cotesia congregata*. Can J Zool 76:1634–1640

Adamo SA (2002) Modulating the modulators: parasites, neuromodulators and host behavioral change. Brain Behav Evol 60:370–377

Adamo SA (2013) Parasites: evolution's neurobiologists. J Exp Biol 216:3–10

Adamo SA, Shoemaker KL (2000) Effects of parasitism on the octopamine content of the central nervous system of *Manduca sexta*: a possible mechanism underlying host behavioural change. Can J Zool 78:1580–1587

Anderson RA, Koella JC, Hurd H (1999) The effect of *Plasmodium yoelii nigeriensis* infection on the feeding persistence of *Anopheles stephensi* Liston throughout the sporogonic cycle. Proc Biol Sci 266:1729–1733

Anderson RA, Knols BG, Koella JC (2000) *Plasmodium falciparum* sporozoites increase feeding-associated mortality of their mosquito hosts *Anopheles gambiae* s.l. Parasitology 120:329–333

Arling TA, Yolken RH et al (2009) *Toxoplasma gondii* antibody titers and history of suicide attempts in patients with recurrent mood disorders. J Nerv Ment Dis 197:905–908

Baldauf SA, Thünken T, Frommen JG, Bakker TCM, Heupel O, Kullmann H (2007) Infection with an acanthocephalan manipulates an amphipod's reaction to a fish predator's odours. Int J Parasitol 37:61–65

Bauer A, Trouve S, Grégoire A, Bollache L, Cézilly F (2000) Differential influence of *Pomphorhynchus laevis* (Acanthocephala) on the behaviour of native and invader gammarid species. Int J Parasitol 30:1453–1457

Beckage NE, Drezen J-M (2012) Parasitoid viruses: symbionts and pathogens. Academic Press, New York, p 312

H. Mehlhorn (ed.), *Host Manipulations by Parasites and Viruses*,
Parasitology Research Monographs 7, DOI 10.1007/978-3-319-22936-2

Benesh DP, Kitchen J, Pulkkine K, Hakala I, Valtonen ET (2008a) The effect of *Echinorhynchus borealis* (Acanthocephala) infection on the anti-predator behavior of a benthic amphipod. J Parasitol 94:542–545

Benesh D, Valtonen E, Seppälä O (2008b) Multidimensionality and intra-individual variation in host manipulation by an acanthocephalan. Parasitology 135:617–626

Benesh D, Seppälä O, Valtonen E (2009) Acanthocephalan size and sex affect the modification of intermediate host colouration. Parasitology 136:847–854

Bennett KE, Hopper JE, Stuart MA, West M, Drolet BS (2008) Blood-feeding behavior of vesicular stomatitis virus infected *Culicoides sonorensis* (Diptera: Ceratopogonidae). J Med Entomol 45:921–926

Berdoy M, Webster JP et al (1995) Parasite-altered behaviour: is the effect of *Toxoplasma gondii* on *Rattus norvegicus* specific? Parasitology 111:403–409

Berdoy M, Webster JP, Macdonald DW (2000) Fatal attraction in rats infected with *Toxoplasma gondii*. Proc Biol Sci 267:1591–1594

Berenreiterova M, Flegr J et al (2011) The distribution of *Toxoplasma gondii* cysts in the brain of a mouse with latent toxoplasmosis: implications for the behavioral manipulation hypothesis. PLoS One 6:e28925

Biron DG, Marché L, Ponton F, Loxdale HD, Galéotti N, Renault L, Joly C, Thomas F (2005) Behavioural manipulation in a grasshopper harbouring hairworm: a proteomics approach. Proc Biol Sci 272:2117–2126

Biron DG, Ponton F, Marche L, Galeotti N, Renault L et al (2006) 'Suicide' of crickets harbouring hairworms: a proteomics investigation. Inst Mol Biol 15:731–742

Bollache L, Gambade G, Cézilly F (2001) The effects of two acanthocephalan parasites, *Pomphorhynchus laevis* and *Polymorphus minutus*, on pairing success in male *Gammarus pulex* (Crustacea: Amphipoda). Behav Ecol Sociobiol 49:296–303

Bos N, Lefèvre T, Jensen AB, d'Ettorre P (2012) Sick ants become unsociable. J Evol Biol 25:342–351

Breed MD, Moore J (2012) Animal behavior. Academic Press, San Diego

Brodeur J, Vet LEM (1994) Usurpation of host behaviour by a parasitic wasp. Anim Behav 48:187–192

Brown S (1999) Cooperation and conflict in host–manipulating parasites. Proc R Soc Lond B 266:1899–1904

Brown S, Loot G, Grenfell B, Guegan J (2003) Host manipulation by *Ligula intestinalis*: accident or adaptation? Parasitology 123:519–529

Carney WP (1969) Behavioral and morphological changes in carpenter ants harboring dicrocoeliid metacercariae. Am Midl Nat 82:605–611

Carney WP (1970) *Brachylecithum mosquensis*: infection in the vertebrate, molluscan and arthropod hosts. Trans Am Microsc Soc 89:233–250

Carruthers VB, Suzuki Y (2007) Effects of *Toxoplasma gondii* infection on the brain. Schizophr Bull 33:745–751

Cézilly F, Grégoire A, Bertin A (2000) Conflict between co-occurring manipulative parasites? An experimental study of the joint influence of two acanthocephalan parasites on the behaviour of *Gammarus pulex*. Parasitology 120:625–630

Cézilly F, Favrat A, Perrot-Minnot MJ (2013) Multidimensionality in parasite-induced phenotypic alterations: ultimate versus proximate aspects. J Exp Biol 216:27–35

Dass SA, Vasudevan A et al (2011) Protozoan parasite *Toxoplasma gondii* manipulates mate choice in rats by enhancing attractiveness of males. PLoS One 6:e27229

Day JF, Edman JD (1983) Malaria renders mice susceptible to mosquito feeding when gametocytes are most infective. J Parasitol 69:163–170

De Jong-Brink M (1995) How schistosomes profit from the stress responses they elicit in their hosts. Adv Parasitol 35:177–256

Dheilly NM (2014) Holobiont–Holobiont interactions: redefining host–parasite interactions. PLoS Pathog 10:e1004093

Dheilly NM, Maure F, Ravallec M, Galinier R, Doyon J, Duval D, Leger L, Volkoff AN, Missé D, Nidelet S, Demolombe V, Brodeur J, Gourbal B, Thomas F, Mitta G (2015) Who is the puppet

master? Replication of a parasitic wasp-associated virus correlates with host behaviour manipulation. Proc Biol Sci. doi:10.1098/rspb.2014.2773
Dianne L, Rigaud T, Léger E, Motreuil S, Bauer A, Perrot-Minnot MJ (2010) Intraspecific conflict over host manipulation between different larval stages of an acanthocephalan parasite. J Evol Biol 23:2648–2655
Dianne L, Perrot-Minnot MJ, Bauer A, Gaillard M, Léger E, Rigaud T (2011) Protection first then facilitation: a manipulative parasite modulates the vulnerability to predation of its intermediate host according to its own developmental stage. Evolution 65:2692–2698
Dickerson F, Boronow J et al (2007) *Toxoplasma gondii* in individuals with schizophrenia: association with clinical and demographic factors and with mortality. Schizophr Bull 33:737–740
Dielenberg RA, Hunt GE et al (2001) "When a rat smells a cat": the distribution of Fos immunoreactivity in rat brain following exposure to a predatory odor. Neuroscience 104:1085–1097
Eberhard WG (2010a) Recovery of spiders from the effects of parasitic wasps: implications for fine-tuned mechanisms of manipulation. Anim Behav 79:375–383
Eberhard WG (2010b) New types of behavioral manipulation of host spiders by a parasitoid wasp. Psyche. 2010:Article ID 950614. doi:10.1155/2010/950614
Engelstädter J, Hurst G (2009) The ecology and evolution of microbes that manipulate host reproduction. Ann Rev Ecol Evol Syst 40:127–149
Ezenwa VO, Gerardo NM, Inouye DW, Medina M, Xavier JB (2012) Microbiology. Animal behavior and the microbiome. Science 338:198–199
Fiore M, Alleva E et al (1998) Infection with *Schistosoma mansoni* in mice induces changes in nociception and exploratory behavior. Physiol Behav 65:347–353
Fiore M, Carere C et al (2002) Passive avoidance response in mice infected with *Schistosoma mansoni*. Physiol Behav 75:449–454
Flegr J (2007) Effects of *Toxoplasma* on human behavior. Schizophr Bull 33:757–760
Flegr J (2013) Influence of latent *Toxoplasma* infection on human personality, physiology and morphology: pros and cons of the *Toxoplasma*–human model in studying the manipulation hypothesis. J Exp Biol 216:127–133
Flegr J, Striz I (2011) Potential immunomodulatory effects of latent toxoplasmosis in humans. BMC Infect Dis 11:274
Flegr J, Zitkova S et al (1996) Induction of changes in human behaviour by the parasitic protozoan *Toxoplasma gondii*. Parasitology 113:49–54
Flegr J, Kodym P et al (2000) Correlation of duration of latent *Toxoplasma gondii* infection with personality changes in women. Biol Psychol 53:57–68
Flegr J, Preiss M et al (2003) Decreased level of psychobiological factor novelty seeking and lower intelligence in men latently infected with the protozoan parasite *Toxoplasma gondii* dopamine, a missing link between schizophrenia and toxoplasmosis? Biol Psychol 63:253–268
Flegr J, Lindova J et al (2008) Sex-dependent toxoplasmosis-associated differences in testosterone concentration in humans. Parasitology 135:427–431
Flegr J, Novotna M et al (2010) The influence of RhD phenotype on toxoplasmosis and age-associated changes in personality profile of blood donors. Folia Parasitol (Praha) 57:143–150
Flegr J, Lenochova P et al (2011) Fatal attraction phenomenon in humans: cat odour attractiveness increased for *Toxoplasma*-infected men while decreased for infected women. PLoS Negl Trop Dis 5:e1389
Fouad K, Libersat F, Rathmayer W (1996) Neuromodulation of the escape behavior of the cockroach *Periplaneta americana* by the venom of the parasitic wasp *Ampulex compressa*. J Comp Physiol A 178:91–100
Franceschi N, Cornet S, Bollache L, Dechaume-Moncharmont F-X, Bauer A, Motreuil S, Rigaud T (2010a) Variation between populations and local adaptation in acanthocephalan-induced parasite manipulation. Evolution 64:2417–2430
Franceschi N, Bollache L, Cornet S, Bauer A, Motreuil S, Rigaud T (2010b) Covariation between the intensity of behavioural manipulation and parasite development time in an acanthocephalan–amphipod system. J Evol Biol 23:2143–2150
Gal R, Libersat F (2008) A parasitoid wasp manipulates the drive for walking of its cockroach prey. Curr Biol 18:877–882

Gal R, Libersat F (2010) A wasp manipulates neuronal activity in the sub-esophageal ganglion to decrease the drive for walking in its cockroach prey. PLoS One 5:e10019

Galvani AP (2003) Epidemiology meets evolutionary ecology. Tr Ecol Evol 18:132–139

Gonzaga MO, Sobczak JF, Penteado-Dias AM, Eberhard WG (2010) Modification of *Nephila clavipes* (Araneae Nephilidae) webs induced by the parasitoids *Hymenoepimecis bicolor* and *H. robertsae* (Hymenoptera Ichneumonidae). Ethol Ecol Evol 22:151–165

Gonzalez LE, Rojnik B, Urdaneta H, Hernandez L (2001) Rats infected with *Toxoplasma gondii* are highly risk-taking. Soc Neurosci Abstr 27 Program no. 955.6

Goulson D (1997) Wipfelkrankheit: modification of host behaviour during baculoviral infection. Oecologia 109:219–228

Grimstad PR, Ross QE, Craig GB (1980) *Aedes triseriatus* (Diptera, Culicidae) and La Crosse Virus 2. Modification of mosquito feeding-behavior by virus infection. J Med Entomol 17:1–7

Grosman AH, Janssen A, de Brito EF, Cordeiro EG, Colares F, Fonseca JO, Lima ER, Pallini A, Sabelis MW (2008) Parasitoid increases survival of its pupae by inducing hosts to fight predators. PLoS One 3:e2276

Haine E, Boucansaud K, Rigaud T (2005) Conflict between parasites with different transmission strategies infecting an amphipod host. Proc R Soc Lond B 272:2505–2510

Hamilton C, Stafford P, Pinelli E, Holland C (2006) A murine model for cerebral toxocariasis: characterization of host susceptibility and behaviour. Parasitology 132:791–801

Hanelt B, Janovy J (1999) The life cycle of a horsehair worm, *Gordius robustus* (Nematomorpha: Gordioidea). J Parasitol 85:139–141

Hart BL (1990) Behavioural adaptations to pathogens and parasites: five strategies. Neurosci Biobehav Rev 14:273–294

Hart BL (2011) Behavioural defences in animals against pathogens and parasites: parallels with the pillars of medicine in humans. Philos Trans R Soc Lond B 366:3406–3417

Harvey J, Kos M, Nakamatsu Y, Tanaka T, Dicke M, Vet L, Brodeur J, Bezemer T (2008) Do parasitized caterpillars protect their parasitoids from hyperparasitoids? A test of the 'usurpation hypothesis'. Anim Behav 76:701–708

Harvey JA, Tanaka T, Kruidhof M, Vet LEM, Gols R (2011) The 'usurpation hypothesis' revisited: dying caterpillar repels attack from a hyperparasitoid wasp. Anim Behav 81:1281–1287

Haspel G, Rosenberg LA, Libersat F (2003) Direct injection of venom by a predatory wasp into cockroach brain. J Neurobiol 56:287–292

Haspel G, Gefen E, Ar A, Glusman JG, Libersat F (2005) Parasitoid wasp affects metabolism of cockroach host to favor food preservation for its offspring. J Comp Physiol A 191:529–534

Hedges LM, Brownlie JC, O'Neill SL, Johnson KN (2008) *Wolbachia* and virus protection in insects. Science 322:702

Helluy S (1983) Relations hôtes-parasites du trématode *Microphallus papillorobustus* (Rankin, 1940) II –modifications du comportement des *Gammarus*, hôtes intermédiaires et localisation des métacercaries. Ann Parasitol Hum Comp 58:1–17

Hinaidy HK (1983) *Dicrocoelium suppereri* nomen novum (syn. *D. orientalis* Sudarikov et Ryjikov 1951), ein neuer Trematode für die Parasitenfauna Österreichs. Zentralbl Veterinarmed B 30:576–589

Hohorst W (1962) Die Rolle der Ameisen im Entwicklungsgang des Lanzettegels (*Dicrocoelium dendriticum*). Parasitol Res 22:105

Hohorst W, Graefe G (1961) Ameisenobligatorische Zwischenwirte des Lanzettegels (*Dicrocoelium dendriticum*). Naturwissenschaften (Berlin) 48:229–230

Hohorst W, Lämmler G (1962) Experimentelle Dicrocoeliose-Studien. Tropenmed Parasitol 13:377–397

Holt RD, Dobson AP, Begon M, Bowers RG, Schauber EM (2003) Parasite establishment in host communities. Ecol Lett 6:837–842

Horwitz P, Wilcox BA (2005) Parasites, ecosystems and sustainability: an ecological and complex system perspective. Int J Parasitol 35:725–732

Hughes DP, Brodeur J, Thomas F (2012) Host manipulation by parasites. Oxford University Press, Oxford

Hurd H, Warr E, Polwart A (2001) A parasite that increases host lifespan. Proc Biol Sci 268:1749–1753

Kagan IG (1951) Aspects in the life history of *Neoleucochloridium problematicum* (Magath, 1920) new comb, and *Leucochloridium cyanocittae* McIntosh, 1932 (Trematoda: Brachylaemidae). Trans Am Microsc Soc 70:281–318

Kaushik M, Lamberton PHL, Webster JP (2012) The role of parasites and pathogens in influencing generalized anxiety and predation-related fear in the mammalian central nervous system. Horm Behav 62:191–201

Kavaliers M, Colwell DD (1995) Decreased predator avoidance in parasitized mice: neuromodulatory correlates. Parasitology 111:257–263

Keasar T, Sheffer N, Glusman G, Libersat F (2006) Host handling: an innate component of foraging behavior in the parasitoid wasp *Ampulex compressa*. Ethology 112:699–706

Klein SL (2003) Parasite manipulation of the proximate mechanisms that mediate social behavior in vertebrates. Physiol Behav 79:441–449

Klein SL, Zink MC et al (2004) Seoul virus infection increases aggressive behaviour in male Norway rats. Anim Behav 67:421–429

Klimpel S, Mehlhorn H (eds) (2014) Bats (Chiroptera) as vectors of diseases and parasites, vol 5. Parasitol Res Monographs. Springer, Berlin

Knox DP, Skuce PJ (2005) SAGE and the quantitative analysis of gene expression in parasites. Trends Parasitol 21:322–326

Koella JC, Packer MJ (1996) Malaria parasites enhance blood-feeding of their naturally infected vector *Anopheles punctulatus*. Parasitology 113:105–109

Koella JC, Sörensen FL, Anderson RA (1998) The malaria parasite, *Plasmodium falciparum*, increases the frequency of multiple feeding of its mosquito vector, *Anopheles gambiae*. Proc Biol Sci 265:763–768

Koella JC, Rieu L, Paul REL (2002) Stage-specific manipulation of a mosquito's host-seeking behavior by the malaria parasite *Plasmodium gallinaceum*. Behav Ecol 13:816–820

Koks S, Planken A et al (2002) Cat odour exposure increases the expression of wolframin gene in the amygdaloid area of rat. Neurosci Lett 322:116–120

Krasnoff SB, Watson DW, Gibson DM, Kwan EC (1995) Behavioral effects of the entomopathogenic fungus, *Entomophthora muscae* on its host *Musca domestica*: postural changes in dying hosts and gated pattern of mortality. J Insect Physiol 41:895–903

Lafferty KD, Kuris AM (1999) How environmental stress affects the impacts of parasites. Limnol Ocean 44:564–590

Lafferty K, Thomas F, Poulin R (2000) Evolution of host phenotypemanipulation by parasites and its consequences. In: Poulin R, Morand S, Skorping A (eds) Evolutionary biology of host–parasite relationships: theory meets reality. Elsevier Science, Amsterdam, pp 117–127

Lagrue C, Kaldonski N, Perrot-Minnot M, Motreuil S, Bollache L (2007) Modification of hosts' behaviour by a parasite: field evidence for adaptive manipulation. Ecology 88:2839–2847

Lee JH, Rowley WA, Platt KB (2000) Longevity and spontaneous flight activity of *Culex tarsalis* (Diptera: Culicidae) infected with western equine encephalomyelitis virus. J Med Entomol 37:187–193

Lefèvre T, Thomas F (2008) Behind the scene, something else is pulling the strings: emphasizing parasitic manipulation in vector-borne diseases. Infect Genetics Evol 8:504–519

Lefèvre T, Koella JC, Renaud F, Hurd H, Biron DG, Thomas F (2006) New prospects for research on manipulation of insect vectors by pathogens. PLoS Pathog 2:e72

Lefèvre T, Thomas F, Ravel S et al (2007) *Trypanosoma brucei brucei* induces alteration in the head proteome of the tsetse fly vector *Glossina palpalis gambiensis*. Insect Mol Biol 16:651–660

Lefèvre T, Roche B, Poulin R, Hurd H, Renaud F, Thomas F (2008) Exploiting host compensatory responses: the 'must' of manipulation? Trends Parasitol 24:435–439

Lefèvre T, Adamo SA, Biron DG et al (2009a) Invasion of the body snatchers: the diversity and evolution of manipulative strategies in host–parasite interactions. Adv Parasitol 68:45–83
Lefèvre T, Lebarbenchon C, Gauthier-Clerc M, Missé D, Poulin R, Thomas F (2009b) The ecological significance of manipulative parasites. Trends Ecol Evol 24:41–48
Leung TLF, Keeney DB, Poulin R (2010) Genetics, intensitydependence, and host manipulation in the trematode *Curtuteria australis*: following the strategies of others? Oikos 119:393–400
Libersat F, Delago A, Gal R (2009) Manipulation of host behavior by parasitic insects and insect parasites. Annu Rev Entomol 54:189–207
Ling VJ, Lester D et al (2011) *Toxoplasma gondii* seropositivity and suicide rates in women. J Nerv Ment Dis 199:440–444
Loos-Frank B, Zimmermann G (1976) Über eine dem Dicrocoelien-Befall analoge Verhaltensänderung bei Ameisen der Gattung *Formica* durch einen Pilz der Gattung *Entomophthora*. Parasitol Res 49:281–289
Maeyama T, Terayama M, Matsumoto T (1994) The abnormal behavior of *Colobopsis* sp. (Hymenoptera, Formicidae) parasitized by *Mermis* (Nematoda) in Papua New Guinea. Sociobiology 24:115–119
Manga-Gonzalez MY, Gonzalez-Lanza C, Cabanas E, Campo R (2001) Contributions to and review of dicrocoeliosis, with special reference to the intermediate hosts of *Dicrocoelium dendriticum*. Parasitology 123:S91–S114
Marcogliese DJ (2005) Parasites of the superorganism: are they indicators of ecosystem health? Int J Parasitol 35:705–716
Maure F, Brodeur J, Ponlet N, Doyon J, Firlej A, Elguero É, Thomas F (2011) The cost of a bodyguard. Biol Lett 7:843–846
Maure F, Brodeur J, Hughes D, Thomas F (2013a) How much energy should manipulate parasites leve to their hosts to ensure altered behaviours? J Exp Biol 216:43–46
Maure F, Daoust SP, Brodeur J, Mitta G, Thomas F (2013b) Diversity and evolution of bodyguard manipulation. J Exp Biol 216:36–42
Maure F, Doyon J, Thomas F, Brodeur J (2014) Host behavior manipulation as an evolutionary route toward attenuation of parasitoid virulence. J Evol Biol 27:2871–2875
McConkey GA, Martin HL, Bristow GC, Webster JP (2012) *Toxoplasma gondii* infection and behaviour – Location, location, location? J Exp Biol doi:http://dx.doi.org/10.1242/jeb.074153
Mehlhorn H (ed) (2016) Encyclopedia of parasitology, 4th edn. Springer, New York/Berlin
Mehlhorn H (ed) (2011) Nature helps… vol 1, Parasitol Res Monographs. Springer, Berlin
Mehlhorn H (ed) (2011) Progess in parasitology. vol 2, Parasitol Res Monographs. Springer, Berlin
Mehlhorn H (ed) (2012) Arthropods as vectors of emerging diseases. vol 3, Parasitol Res Monographs. Springer, Berlin
Mehlhorn H, Tan KS (eds) (2012) *Blastocystis*: pathogen or passenger? vol 4, Parasitol Res Monographs. Springer, Berlin
Mehlhorn H, Wu Z, Ye B (eds) (2014) Treatment of human parasitosis in traditional Chinese medicine. vol 6, Parasitol Res Monographs. Springer, Berlin
Milinski M (1985) Risk of predation of parasitized sticklebacks (*Gasterosteus aculeatus* L.) under competition for food. Behaviour 93:203–216
Moller AP (1993) A fungus infecting domestic flies manipulates sexual behaviour of its host. Behav Ecol Sociobiol 33:403–407
Moore J (1993) Parasites and the behavior of biting flies. J Parasitol 79:1–16
Moore J (2002) Parasites and the behavior of animals. Oxford University Press, Oxford
Moore J (2012) A history of parasites and hosts, science and fashion. In: Hughes DP, Brodeur J, Thomas F (eds) Host manipulation by parasites. Oxford University Press, Oxford, pp 1–13
Moore J (2013) An overview of parasite-induced behavioral alterations – and some lessons from bats. J Exp Biol 216:11–17
Moore EL, Haspel G, Libersat F, Adams ME (2006) Parasitoid wasp sting: A cocktail of GABA, taurine and β-alanine opens chloride channels for transient synaptic block and paralysis of a cockroach host. J Neurobiol 66:811–820

Moret Y, Schmid-Hempel P (2001) Immune defence in bumble-bee offspring. Nature 414:506
Mouritsen KN, Poulin R (2003) Parasite-induced trophic facilitation exploited by a non-host predator: a manipulator's nightmare. Int J Parasitol 33:1043–1050
Müller CB (1994) Parasitoid induced digging behaviour in bumblebee workers. Anim Behav 48:961–966
Novotna M, Havlicek J et al (2008) *Toxoplasma* and reaction time: role of toxoplasmosis in the origin, preservation and geographical distribution of Rh blood group polymorphism. Parasitology 135:1253–1261
Overli O, Pall M, Borg B, Jobling M, Winberg S (2001) Effects of *Schistocephalus solidus* infection on brain monoaminergic activity in female three-spined sticklebacks *Gasterosteus aculeatus*. Proc R Soc London Sci Ser B 268:1411–1415
Parker GA, Ball MA, Chubb JC, Hammerschmidt K, Milinski M (2009) When should a trophically transmitted parasite manipulate its host? Evolution 63:448–458
Patot S, Lepetit D, Charif D, Varaldi J, Fleury F (2009) Molecular detection, penetrance, and transmission of an inherited virus responsible for behavioral manipulation of an insect parasitoid. Appl Environ Microbiol 75:703–710
Peng Y, Nielsen JE, Cunningham JP, McGraw EA (2008) *Wolbachia* infection alters olfactory-cued locomotion in *Drosophila* spp. Appl Environ Microbiol 74:3943–3948
Perrot-Minnot MJ (2004) Larval morphology, genetic divergence, and contrasting levels of host manipulation between forms of *Pomphorhynchus laevis* (Acanthocephala). Int J Parasitol 34:45–54
Perrot-Minnot M-J, Cézilly F (2013) Investigating candidate neuromodulatory systems underlying parasitic manipulation: concepts, limitations and prospects. J Exp Biol 216:134–141
Piekarski G (1981) Behavioral alterations caused by parasitic infection in case of latent *Toxoplasma* infection. Zentralbl Bakteriol Mikrobiol Hyg A 250:403–406
Pilecka-Rapacz M (1986) On the development of acanthocephalans of the genus *Acanthocephalus* Koereuther, 1771, with special attention to their influence on intermediate host, *Asellus aquaticus* L. Acta Parasitol 30:233–250
Ponton F, Lefèvre T, Lebarbenchon C et al (2006) Do distantly related parasites rely on the same proximate factors to alter the behaviour of their hosts? Proc Royal Soc B-Biol Sci 273:2869–2877
Ponton F, Otalora-Luna F, Lefèvre T et al (2011) Water-seeking behavior in worm-infected crickets and reversibility of parasitic manipulation. Behav Ecol 22:392–400
Poulin R (2010) Parasite manipulation of host behavior: an update and frequently asked questions. Adv Stud Behav 41:151–186
Poulin R, Curtis MA et al (1992) Effects of *Eubothrium salvelini* (Cestoda) on the behavior of *Cyclops vernalis* (Copepoda) and its susceptibility to fish predators. Parasitology 105:265–271
Prenter J, MacNeil C, Dick JTA, Dunn AM (2004) Roles of parasites in animal invasions. Tr Ecol Evol 19:385–390
Ridley M (1995) Animal behaviour. Blackwell Scientific Publications, Oxford
Rogers ME, Bates PA (2007) *Leishmania* manipulation of sand fly feeding behavior results in enhanced transmission. PLoS Pathog 3:e91
Romig T (1980) *Dicrocoelium hospes* and *Dicrocoelium dendriticum* infesting the supraesophageal ganglion of ants. Prakt Tierarzt 61:354
Romig T, Lucius R, Frank W (1980) Cerebral larvae in the second intermediate host of *Dicrocoelium dendriticum* (Rudolphi, 1819) and *Dicrocoelium hospes* Looss, 1907 (Trematodes, Dicrocoeliidae). Parasitol Res 63:277–286
Rosenberg LA, Pfluüger HJ, Wegener G, Libersat F (2006) Wasp venom injected into the prey's brain modulates thoracic identified monoaminergic neurons. J Neurobiol 66: 155–168
Roy HE, Steinkraus DC, Eilenberg J, Hajek AE, Pell JK (2006) Bizarre interactions and endgames: entomopathogenic fungi and their arthropod hosts. Annu Rev Entomol 51:331–357

Sanchez M, Ponton F, Schmidt-Rhaesa A, Hughes D, Misse D, Thomas F (2008) Two steps to suicide in crickets harbouring hairworms. Anim Behav 76:1621–1624

Schneider G (1971) Die Wanderung der Metacercarie von *Dicrocoelium dendriticum* (Rud., 1819), Looss, 1899 (Digenea, Trematoda) im Ameisenzwischenwirt und ihre Steuerung durch physiolgisch-ökologische Faktoren. Dissertation, Frankfurt/Main

Seppälä O, Karvonen A, Valtonen E (2005) Manipulation of fish host by eye flukes in relation to cataract formation and parasite infectivity. Anim Behav 70:889–894

Shostak A, Walsh J, Wong Y (2008) Manipulation of host food availability and use of multiple exposures to assess the crowding effect on *Hymenolepis diminuta* in *Tribolium confusum*. Parasitology 135:1019–1033

Sparkes T, Weil K, Renwick D, Talkington J (2006) Development-related effects of an acanthocephalan parasite on pairing success of its intermediate host. Anim Behav 71:439–448

Svensson EI, Raberg L (2010) Resistance and tolerance in animal enemy–victim coevolution. Trends Ecol Evol 25:267–274

Szidat L (1962) Über eine ungewöhnliche Form parthenogenetischer Vermehrung bei Metacercarien einer *Gymnopallus*-Art aus *Mytilus platensis*, *Gymnopallus australis* n. sp. des Südatlantiks. Parasitol Res 22:196–213

Tain L, Perrot-Minnot MJ, Cézilly F (2006) Altered host behaviour and brain serotonergic activity caused by acanthocephalans: evidence for specificity. Proc R Soc B Biol Sci 273:3039–3045

Tain L, Perrot-Minnot M, Cézilly F (2007) Differential influence of *Pomphorhynchus laevis* (Acanthocephala) on brain serotonergic activity in two congeneric host species. Biol Lett 3:69

Takahashi LK, Nakashima BR et al (2005) The smell of danger: a behavioral and neural analysis of predator odor-induced fear. Neurosci Biobehav Rev 29:1157–1167

Thomas F, Poulin R, Guegan J-F, Michalakis Y, Renaud F (2000) Are there pros as well as cons to being parasitised? Parasitol Today 16:533–536

Thomas F, Brown S, Sukhdeo M, Renaud F (2002a) Understanding parasite strategies: a state-dependent approach? Trends Parasitol 18:387–390

Thomas F, Fauchier J, Lafferty KD (2002b) Conflict of interest between a nematode and a trematode in an amphipod host: test of the 'sabotage' hypothesis. Behav Ecol Sociobiol 51:296–301

Thomas F, Schmidt Rhaesa A, Martin G, Manu C, Durand P, Renaud F (2002c) Do hairworms (Nematomorpha) manipulate the water seeking behaviour of their terrestrial hosts? J Evol Biol 15:356–361

Thomas JA, Knapp JJ, Akino T, Gerty S, Wakamura S et al (2002d) Parasitoid secretions provoke ant warfare. Nature 417:505–506

Thomas F, Ulitsky P, Augier R, Dusticier N, Samuel D et al (2003) Biochemical and histological changes in the brain of the cricket *Nemobius sylvestris* infected by the manipulative parasite *Paragordius tricuspidatus* (Nematomorpha). Int J Parasitol 33:435–443

Thomas F, Adamo S, Moore J (2005) Parasitic manipulation: where are we and where should we go? Behav Proc 68:185–199

Thomas F, Poulin R, Brodeur J (2010a) Host manipulation by parasites: a multidimensional phenomenon. Oikos 119:1217–1223

Thomas F, Poulin R, Brodeur J (2010b) Infection syndrome and multidimensionality: two terms for two different issues. Oikos 119:1230

Thomas F, Brodeur J, Maure F, Francesci N, Blanchet S, Rigaud T (2011) Intraspecific variability in host manipulations by parasites. Infect Genetics Evol 11:262–269

Thomas F, Rigaud T, Brodeur J (2012) Evolutionary routes leading to host manipulation by parasites. In: Hughes DP, Brodeur J, Thomas F (eds) Host manipulation by parasites. Oxford University Press, Oxford, pp 16–35

Torrey EF, Yolken RH (2007) Schizophrenia and toxoplasmosis. Schizophr Bull 33:727–728

Vala F, Egas M, Breeuwer JAJ, Sabelis MW (2004) *Wolbachia* affects oviposition and mating behaviour of its spider mite host. J Evol Biol 17:692–700

van den Abbeele J, Caljon G, de Ridder K, de Baetselier P, Coosemans M (2010) *Trypanosoma brucei* modifies the tsetse salivary composition, altering the fly feeding behavior that favors parasite transmission. Plos Pathogens 6:e1000926

Van Houten S, Ros VID, van Oers MM (2013) Walking with insects: molecular mechanisms behind parasitic manipulation of host behavior. Mol Ecol 22:3458–3475
Vance S (1996) Morphological and behavioural sex reversal in mermithid-infected mayflies. Proc R Soc Lond B 263:907–912
Varaldi J, Petit S, Bouletreau M, Fleury F (2006) The virus infecting the parasitoid *Leptopilina boulardi* exerts a specific action on superparasitism behaviour. Parasitology 132:747–756
Varaldi J, Patot S, Nardin M, Gandon S (2009) A virus-shaping reproductive strategy in a *Drosophila* parasitoid. Adv Parasitol 70:333–363
Vyas A, Kim SK et al (2007) Behavioral changes induced by *Toxoplasma* infection of rodents are highly specific to aversion of cat odors. Proc Natl Acad Sci U S A 104:6442–6447
Webb TJ, Hurd H (1999) Direct manipulation of insect reproduction by agents of parasite origin. Proc Biol Sci 266:1537–1541
Webster JP (2007) The effect of *Toxoplasma gondii* on animal behavior: playing cat and mouse. Schizophr Bull 33:752–756
Webster JP, McConkey GA (2010) *Toxoplasma gondii*-altered host behaviour: clues as to mechanism of action. Folia Parasitol (Praha) 57:95–104
Webster JP, Kaushik M, Bristow GC, McConkey GA (2013) *Toxoplasma gondii* infection, from predation to schizophrenia: can animal behaviour help us understand human behaviour? J Exp Biol 216:99–112
Weisel-Eichler A, Haspel G, Libersat F (1999) Venom of a parasitoid wasp induces prolonged grooming in the cockroach. J Exp Biol 202:957–964
Werren JH, Baldo L, Clark ME (2008) *Wolbachia*: master manipulators of invertebrate biology. Nature Rev Microbiol 6:741–751
Whitfield JB, Asgari S (2003) Virus or not? Phylogenetics of poly-dna-viruses and their wasp carriers. J Insect Physiol 49:397–405
Wickler W (1976) Evolution-oriented ethology, kin selection and altruistic parasites. Z Tierpsychol 42:205–214
Wilson DS (1977a) How nepotistic is the brain worm? Behav Ecol Sociobiol 2:421–425
Wilson DS (1977b) Structured demes and the evolution of group-advantageous traits. Amer Nat 111:157–185
Wolinska J, King K (2009) Environment can alter selection in host–parasite interactions. Trends Parasitol 25:236–244
Yan G, Stevens L, Schall JJ (1994) Behavioral changes in *Tribolium* beetles infected with a tapeworm: variation in effects between beetle species and among genetic strains. Am Nat 143:830–847
Yanoviak SP, Kaspari M, Dudley R, Poinar G Jr (2008) Parasite-induced fruit mimicry in a tropical canopy ant. Am Nat 171:536–544
Zangrossi H Jr, File SE (1992) Behavioral consequences in animal tests of anxiety and exploration of exposure to cat odor. Brain Res Bull 29:381–388

Index

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