

1 **Review**

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3 **Manipulative parasites in the world of veterinary science: Implications for epidemiology**
4 **and pathology**

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16

17 **Abstract**

18 One of the most complex and least understood transmission strategies displayed by
19 pathogenic parasites is that of manipulation of host behaviour. A wide variety of pathogens
20 alter their host's behaviour, including species of medical and veterinary importance, such as
21 *Diplostomum spathaceum*, *Echinococcus* spp. and *Toxoplasma gondii*. The manipulative
22 ability of these parasites has implications for pathology and transmission dynamics. Domestic
23 animals are hosts for manipulative pathogens, either by being the target host and acquiring the
24 parasite as a result of vector-host manipulation, or by having their behaviour changed by
25 manipulative parasites. This review uses several well-known pathogens to demonstrate how
26 host manipulation by parasites is potentially important in epidemiology.

27

28 *Keywords:* Parasite manipulation; Host behaviour; Transmission; *Diplostomum spathaceum*;
29 *Echinococcus* spp.; *Toxoplasma gondii*

30

31 **Introduction**

32 Parasites face considerable odds against the successful completion of their life cycle, since
33 most hosts represent isolated and patchy resources that are capable of self-defence. This is
34 especially true for parasite species that rely on a vector host coming in contact with or being
35 eaten by a specific target host in which the parasite must continue its development (Choisy et
36 al., 2003; Parker et al., 2003; Poulin, 2007). The parasite and its host must be at the right
37 place at the right time to be transmitted to the next appropriate host. As a result, in some
38 situations, natural selection has favoured parasites capable of manipulating their host's
39 behaviour.

40

41 Parasites may use chemical secretions or other means to alter a variety of host behaviours
42 in a way that benefits the parasites by increasing their chances of transmission to the next host
43 (Moore, 2002; Thomas et al., 2005; Poulin, 2007). Some of these examples involve changes
44 in host phenotype, including the acquisition of new behaviours, and they provide strong
45 evidence for the concept of the extended phenotype, i.e. genes in one organism having
46 phenotypic expression in another organism (Dawkins, 1982).

47

48 Here, we provide an overview of ways in which parasites can alter some aspects of their
49 host's behaviour to increase their own transmission success. In particular, we highlight some
50 parasites of veterinary significance that are known to alter host behaviour, demonstrating that
51 host manipulation is tightly linked to the parasite's epidemiology.

52

53 **Classical examples of parasitic 'manipulation'**

54 The scientific literature contains many reports of modified behaviours in parasitised
55 animals. Three spined sticklebacks harbouring the larval cestode *Schistocephalus solidus*

56 swim closer to the water surface and become less aware of the presence of predatory birds
57 that serve as the parasite's definitive hosts (DHs) (Barber et al., 2004). Rodents infested by
58 the nematode *Trichinella spiralis* or the protozoan *Sarcocystis cernae* are less wary of
59 predators, thus facilitating the parasites' transmission to DHs (Rau, 1983; Hoogenboom and
60 Dijkstra, 1987).

61

62 In some cases, completely new behaviours are observed in infested hosts. For instance, an
63 orb-weaving spider infested by a parasitic wasp larva builds an unusual web designed to
64 protect the emerging larva after the host spider's death (Eberhard, 2000). Another parasitic
65 wasp induces its caterpillar host to remain near the parasite after the latter emerges from its
66 body, thus protecting the pupating wasps from potential predators by acting as a 'bodyguard'
67 (Grosman et al., 2008).

68

69 Ants infested by a nematode that must be transmitted to fruit-eating birds not only look
70 like fruit, by developing a swollen, red abdomen, but also 'behave' like fruits, perching
71 among berries of similar colour, with the abdomen held in an elevated position, motionless,
72 waiting for predation by birds (Yanoviak et al., 2008).

73

74 Nematomorphs (hairworms) and mermithid nematode larvae are parasitic and develop
75 inside terrestrial arthropods, but must reach the aquatic environment in which the adult worms
76 live after maturation. They induce their arthropod hosts to commit 'suicide' by forcing them
77 to seek and jump into water (Thomas et al., 2002, 2003; Penney and Bennett, 2006). Again,
78 such manipulation involves the sudden appearance of new host behaviours induced by the
79 parasite for its own needs (Thomas et al., 2003; Biron et al., 2005).

80

81 Clearly, many parasite species are capable of manipulating their hosts' behaviour in
82 natural systems. However, domestic animals can also be affected by manipulative parasites,
83 either as target hosts or manipulated vector hosts. Rabies is one of the best examples of a
84 pathogen that manipulates the behaviour of the host. The virus infects the central nervous
85 system (CNS) of mammals, particularly regions of the brain controlling aggressive and social
86 behaviours, and the salivary glands. Infected hosts may display aggression, which facilitates
87 transmission of infection through biting (Klein, 2003). Although the fatal outcome of rabies
88 forces the pathogen into a permanent search for new hosts, rabies-induced behavioural
89 changes has ensured the transmission, survival and spread of this pathogen across time, space
90 and host species with extraordinary efficacy.

91

92 **Parasites of veterinary importance**

93 *Dicrocoelium dendriticum*

94 The trematode *Dicrocoelium dendriticum* is present worldwide and is distributed
95 throughout Europe, Asia, North Africa and America (Otranto and Traversa, 2002). Although
96 the pathogenicity of *D. dendriticum* is usually low, dicrocoelosis can lead to weight loss and
97 reduced milk production in domestic ruminants and can sometimes be fatal (Otranto and
98 Traversa, 2002). Reports of the disease are increasing, mostly due to the development of
99 anthelmintic resistance and the geographical expansion of *D. dendriticum* (Otranto and
100 Traversa, 2002; Goater and Colwell, 2007).

101

102 *D. dendriticum* is transmitted to ruminants, including domestic cattle and sheep, when
103 they accidentally ingest infested ants along with their plant food. The parasite larva induces
104 its insect host to climb to the tip of grass blades and remain there, anchored by its mandibles,
105 awaiting ingestion by a grazing herbivore (Carney, 1969; Roming et al., 1980).

106

107 *Diplostomum spathaceum*

108 The common digenean eye fluke *Diplostomum spathaceum* has a complex three host life
109 cycle including lymnaeid snails, fish and fish-eating birds, such as grebes and cormorants
110 (Crowden and Broom, 1980; Karvonen et al., 2004a). Free-swimming cercariae, produced
111 through asexual multiplication within the snail and released into the water, must find a fish,
112 which they penetrate through the gills or skin. They migrate through tissues to the lens of the
113 eye, where they develop into long-lived metacercariae. The cycle is completed when the fish
114 host, along with its metacercariae, is eaten by the DH, a bird.

115

116 By lodging themselves in the host's eyes, metacercariae induce cataracts due to
117 mechanical destruction of the lens and metabolic products excreted by the parasites, thus
118 reducing the host's vision (Karvonen et al., 2004b; Seppälä et al., 2004). *D. spathaceum*
119 infestation in fish is also associated with changes in host behaviour, such as increased activity,
120 migration towards the surface of the water and lack of responsiveness to visual stimuli,
121 although swimming ability is unaffected (Crowden and Broom, 1980; Brassard et al., 1982;
122 Seppälä et al., 2004). Thus, by injuring important sensory organs, *D. spathaceum* is able to
123 alter fundamental fish anti-predator mechanisms, such as crypsis and shoaling behaviour, in a
124 way that is likely to increase the vulnerability of the intermediate host (IH) to predation by the
125 DHs (Krause and Ruxton, 2002; Seppälä et al., 2005, 2006, 2008).

126

127 *D. spathaceum* is a globally distributed parasite that infests a large number of fish species,
128 with high prevalence and intensities recorded in some hosts (Crowden and Broom, 1980;
129 Moody and Gatén, 1982; McKeown and Irwin, 1997; Valtonen and Gibson, 1997; Karvonen
130 et al., 2004b). While pathological effects of diplostomiasis have seldom been documented in

131 wild fish, partly because heavily infested individuals are removed from the population
132 through predation (Pennycuick, 1971), *D. spathaceum* epizootics can be very serious in
133 captive fish, particularly farmed salmonids, such as rainbow trout (*Oncorhynchus mykiss*;
134 Betterton, 1974).

135

136 Since *D. spathaceum* cercariae are not actively host seeking and are often patchily
137 distributed, behavioural avoidance of these sources of infestation is the prime defence
138 mechanism displayed by fish hosts (Karvonen et al., 2004c). Captive housing of fish for
139 research, display and large-scale aquaculture is likely, because of spatial confinement and
140 artificially high densities, to constrain fish avoidance behaviours (Barber, 2007). As a result
141 of high and continuous exposure to parasite larvae, *D. spathaceum* frequently is found in large
142 numbers in farmed fish and may cause welfare problems. Anecdotally, rainbow trout heavily
143 infested by *D. spathaceum* are not responsive to anglers' lures, which reduces their suitability
144 for recreational fishing (Moody and Gatlen, 1982).

145

146 *Echinococcus* spp.

147 Hydatid disease (echinococcosis) is due to infestation with cysts (metacestodes) of the
148 cestode parasite *Echinococcus* spp. (Lymbery and Thompson, 1996). These parasites have a
149 life cycle with two hosts, both mammals. The DHs are carnivores, in which the adult cestodes
150 inhabit the small intestine. Eggs released in the faeces and are accidentally ingested by an IH,
151 in which they hatch and develop into hydatid cysts in the lungs, liver and other internal
152 organs. The DH becomes infested when preying on an infested IH.

153

154 Several *Echinococcus* spp. are currently recognised, although numerous intraspecific
155 genetic strains exist (Jenkins et al., 2005). *Echinococcus* spp. have a narrow range of DHs,

156 mainly domestic and wild canids, but a wide geographical distribution, being virtually present
157 on every continent (Eckert and Thompson, 1997). Their metacestodes are generally less host-
158 specific than those of other taeniids and can develop in a wide range of herbivores and
159 omnivores, including humans and, of particular veterinary concern, sheep, cattle and horses
160 (Lymbery and Thompson, 1996; Eckert and Thompson, 1997).

161

162 *E. granulosus* and *E. multilocularis* are the most important species in term of public health
163 implications and geographical distribution (Eckert et al., 2000; Jenkins et al., 2005; Schweiger
164 et al., 2007; Gottstein and Hemphill, 2008). *E. granulosus* infests almost exclusively domestic
165 animals, with dogs as DHs and predominantly sheep as IHs, but is also infectious for humans
166 (Eckert and Thompson, 1997). *E. granulosus* and *E. multilocularis* are responsible for cystic
167 and alveolar echinococcosis, respectively, both resulting, through asexual reproduction, in
168 increasingly large and abundant cysts that eventually become debilitating, if not lethal
169 (Jenkins et al., 2005; Thompson, 2008). Infested IHs may thus become more vulnerable to
170 predators, including the DH of the parasite (Ewald, 1995).

171

172 The hypothesis that echinococcosis could increase host vulnerability to predation came
173 from an anecdotal incident reported by Crisler (1956), in which a caribou cow (*Rangifer*
174 *tarandus*) failed to escape from wolves. Postmortem examination revealed that its lungs were
175 infested with several large cysts of *E. granulosus*. In moose (*Alces alces*), a large proportion
176 of hydatid cysts are found in the lungs and severe infestations reduce the endurance of
177 animals trying to escape from grey wolves (*Canis lupus*), one of the DHs of *E. granulosus*
178 (Messier et al., 1989). Wolves and other carnivores selectively prey on weaker animals and
179 moose with cystic hydatid disease may be more vulnerable to predation (Messier et al., 1989;
180 Joly and Messier, 2004). However, no study to date has empirically shown the direct link

181 between hydatid infestation, increased predation risk and increased transmission rates for the
182 parasite.

183

184 Internal organs, including the lungs, are often among the first to be eaten by large
185 carnivores, such as wolves (Joly and Messier, 2004). Therefore, it is possible that selection
186 has favoured the location of parasite cysts at these sites to ensure rapid consumption by the
187 DHs rather than to enhance transmission probability. Nevertheless, the pathological effects of
188 echinococcosis do modify the escape behaviour of its IHs in a way that could increase
189 predation and parasite transmission.

190

191 *Toxoplasma gondii*

192 Alterations in host behaviour following parasitic infection are sometimes exactly what we
193 would expect to see if the host was to start acting in ways that benefit parasite transmission
194 (Poulin, 2007). This is shown by the modifications in host behaviour induced by *Toxoplasma*
195 *gondii* and how they may influence the parasite's transmission to the DH.

196

197 *T. gondii* is a widespread intracellular protozoan capable of infecting all endothermic
198 vertebrates. The parasite has a complex life cycle in which Felidae, mostly cats, are the DHs.
199 Oocysts released in host faeces are persistent in the environment and can remain infectious for
200 more than a year (Webster, 1994a). During that time, they must be ingested by another host,
201 either directly by a cat, in which the parasite invades intestinal cells, matures and sexually
202 produces new oocysts, or by an IH.

203

204 Although a wide range of endotherms (rodents, birds or humans) can be infected, wild
205 rodents are the natural IHs of *T. gondii* (Berdyozov et al., 2000). In the acute phase of infection,

206 the parasite penetrates the intestine, undergoes asexual reproduction and enters macrophages
207 and is transported to preferred encystment sites. The parasite then forms resistant cysts in
208 various organs of its IHs, most commonly the brain (Berdoy et al., 1995); these cysts can
209 persist for the life of an infected host (Webster, 2001). The parasite completes its life cycle
210 when a cat consumes an infected host.

211

212 Although *T. gondii* does not need its DH to survive and can be maintained over time in IH
213 populations by congenital transmission, cannibalism or interspecific predation, its infectivity
214 increases after each episode of sexual reproduction (Webster, 1994a, 2001). Since sexual
215 reproduction of *T. gondii* can be accomplished only in the DH, the parasite is ultimately
216 dependent upon predation of infected prey by cats. As a result, there might be strong selective
217 pressures for transmission to the DH and, therefore, on the parasite to evolve mechanisms to
218 enhance the transmission rate from IHs to cats (Berdoy et al., 2000; Webster, 2001; Webster
219 et al., 2006).

220

221 Latent toxoplasmosis has long been considered to produce inapparent infections in
222 immunocompetent hosts (Webster et al., 1994, 2006; Kankova et al., 2007). However, recent
223 studies have shown that chronic *T. gondii* infection can induce modifications in the behaviour
224 of infected hosts. In rodents, *T. gondii* causes increased levels of activity, along with
225 decreases in neophobic (i.e. fear of novelty) and anxiety behaviours, all of which could
226 potentially enhance transmission to DHs (Webster, 1994b; Webster et al., 1994, Gonzalez et
227 al., 2007). Since *T. gondii* mostly invades and encysts in the brain of its IHs, behavioural
228 alterations (i.e. increased activity and lost of neophobia) observed in infected wild rats were
229 initially attributed to encephalitis (Webster, 1994b; Skallova et al., 2006). However, other

230 directly transmitted brain parasites (i.e. parasites that do not rely on the predation of the host)
231 of wild rats do not appear to induce changes in behaviour (Webster, 1994b).

232

233 Rats are strongly neophobic and display a strong innate aversive reaction to cat odour,
234 even after several hundred generations with no exposition to the predator (Berdoy et al., 2000;
235 Webster, 2001; Vyas et al., 2007b). Such anti-predator behaviour is an obvious obstacle
236 against *T. gondii* transmission and could be a prime target for parasite manipulation. *T. gondii*
237 infected rats not only lose their innate aversive reaction to cat odour, but appear to be
238 specifically attracted to the odour, even though other behavioural traits, such as social status
239 and mating success, are unaltered (Webster, 1994b; Berdoy et al., 1995, 2000; Vyas et al.,
240 2007a, b; Lamberton et al., 2008).

241

242 While these studies provide convincing evidence that *T. gondii* is capable of manipulating
243 the behaviour of its IHs, two fundamental questions remain unanswered. First, actual
244 predation rates by the appropriate DH on infected and uninfected rats in the wild are currently
245 unknown and require further investigation (Berdoy et al., 2000; Webster, 2001). Testing the
246 real link between host manipulation and increased transmission (i.e. increased predation) in
247 the wild is a cornerstone of the manipulation hypothesis (Poulin, 1995). Secondly, the
248 mechanisms by which *T. gondii* affects the CNS of its host and achieves such behavioural
249 manipulation have yet to be elucidated (Webster, 2001, 2007). The harmful effects of latent
250 toxoplasmosis on human health and behaviour include meningoencephalitis, personality
251 changes, decreased intelligence quotient, reduced psychomotor performance and
252 neuropsychiatric disorders, such as schizophrenia (Webster et al., 2006; Flegr, 2007).

253

254 Secretion of chemicals by *T. gondii* and/or manipulation of neurotransmitter secretion are
255 likely to be required to induce alterations in behaviour, since the physical presence of cysts in
256 the brain is unlikely to be sufficient to cause such complex and specific changes in IH innate
257 behaviours (Carruthers and Suzuki, 2007; Vyas et al., 2007b). Hosts infected with *T. gondii*
258 exhibit changes in expression of dopaminergic and anxiogenic brain receptors, in levels of
259 neurotransmitters, such as dopamine, and in concentrations of noradrenaline (norepinephrine)
260 and testosterone (Skallova et al., 2006; Flegr, 2007; Webster, 2007; Flegr et al., 2008).

261

262 Although the effects of toxoplasmosis on the brain have been investigated in detail, the
263 pathways by which *T. gondii* manipulates host behaviour remain unclear. For example,
264 preferential invasion sites of different strains of *T. gondii* in the brain could also affect the
265 severity of the disease (Klein, 2003; Carruthers and Suzuki, 2007; Gonzalez et al., 2007; Vyas
266 et al., 2007a). In addition, the outcome of infection is strongly influenced by both parasite and
267 host properties; in humans and laboratory rodents, different genetic strains of *T. gondii* may
268 vary in virulence (Carruthers and Suzuki, 2007; Webster, 2007). A combination of
269 neurochemical and behavioural studies, controlling for both host and parasite genetic strains,
270 are still essential to our understanding of the physiological mechanisms underlying *T. gondii*-
271 induced alterations in animal behaviour (Skallova et al., 2006).

272

273 **Conclusions**

274 Since van Dobben (1952) reported that fish harbouring larvae of the cestode *Ligula*
275 *intestinalis* were significantly more likely to be captured by cormorants (their DHs) than
276 uninfected counterparts, it has been suspected that parasites could manipulate their hosts.
277 Since then, examples of parasite-induced modifications of host behaviour have been
278 documented in a wide range of parasite-host associations, including species of medical and

279 veterinary importance. Some diseases, such as rabies and echinococcosis, are of concern due
280 to their recent re-emergence, wide spatial distribution and human health implications.

281

282 Parasite-induced alterations are often considered to be adaptive parasitic manipulations
283 that increase the transmission rates of the pathogens. However, the mechanisms, particularly
284 neurological pathways, underlying these behavioural changes are only now coming to light
285 (Thomas et al., 2003). How a pathogen alters its host's phenotype remains a central topic in
286 parasite-induced behavioural manipulation. Understanding such mechanisms is vital for
287 solving fundamental evolutionary questions. Moreover, understanding parasite transmission
288 strategies is also at the heart of applied aspects of parasitology, such as the treatment of
289 associated disease.

290

291 The use of proteomics to study the proteins produced by manipulative parasites and the
292 associated host behavioural alterations offers new opportunities for the study of manipulation
293 by parasites (Biron et al., 2005, Thomas et al., 2005). Future studies would therefore benefit
294 from a focus on the molecular cross-talk, particularly the neurochemical pathways, between
295 hosts and their manipulative parasites.

296

297 **Conflict of interest statement**

298 None of the authors of this paper has a financial or personal relationship with other
299 people or organisations that could inappropriately influence or bias the content of the paper.

300

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