



Kindness to the Final Host and Vice Versa: A Trend for Parasites Providing Easy Prey?

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Traditionally the “extended phenotype” concept refers to parasites that manipulate host phenotype to increase parasite fitness. This includes parasites that render intermediate hosts more susceptible to predation by final hosts. We explore here the proposition that an evolutionary driver in such cases is the energetic benefit to the final host, in addition to increased parasite fitness. We will review some well-established host-manipulation models, where such a scenario seems likely. One example is provided by the protozoan *Toxoplasma gondii*, which conspicuously impairs predator avoidance in rodents. Pathologies in humans that acquire *T. gondii* are known, but infection in adult feline definitive hosts are most commonly asymptomatic and apparently innocuous. In another well-documented case of parasite-mediated trophic transmission, trematode (*Euhaplorchis californiensis*) infected killifish (*Fundulus parvipinnis*) abandon normal caution and exhibit a range of behaviors which makes them more conspicuous to predatory birds. The birds get a free meal, but the presence of adult trematodes in the gut would seem to incur few if any negative consequences for the birds. There are exceptions to this pattern also among cases of parasite mediated trophic transmission, but major pathology in definitive hosts seems for the most part restricted to cases where manipulated intermediate hosts are of minor energetic importance. Current theories for the evolution of reduced pathogenicity in predatory final hosts primarily focus on parasites minimizing pathogenicity to increase their own reproductive output and/or avoid selection on host preference for non-infected prey types. Here we advocate another alternative: If or when the benefit of increased prey acquisition outweighs pathogenicity or resource drain, there should be little or no selection on final hosts to minimize parasite infections. This means that not only will host avoidance of infection not develop, but the molecular arms race for increased immunological defense will also likely be halted in such cases.

Keywords: arms race, coevolution, cost-benefit, extended phenotype, immunity, parasite manipulation, trophic transmission

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INTRODUCTION: PARASITES AND THE EVOLVING IMMUNE SYSTEM

Multicellular animals achieve defense against other, disease-causing organisms by means of a range of complex immune responses. Analogously as to how the highly complex vertebrate nervous system evolved from much simpler signaling systems, the immune system evolved from simpler defense mechanisms. The evolutionary mechanisms involved are a topic of intense study

(Kaufman, 2010; Rich and Chaplin, 2019). This quest reflects the fundamental interest in long-term co-evolutionary arms races between parasites and pathogens and their hosts (Decaestecker et al., 2007; Brockhurst et al., 2014), as well as the need to understand the rapidly developing multitude of immune related diseases in the human population (Dunne and Cooke, 2005; Allen and Maizels, 2011; Levine et al., 2011). For the most part, interest has been directed into how the immune system detects and fights invaders, and how these invaders in turn develop infectivity by avoiding detection and attack (Woolhouse et al., 2002; Paterson et al., 2010; Hall et al., 2011; Laanto et al., 2017). In a majority of studies, focus is placed on the conflict between hosts and their parasites and pathogens, and the resulting evolutionary arms race. In an ecological context, however, roles of different interacting species cannot be strictly limited to the traditional definitions of parasitic or mutualistic (Betts et al., 2016).

Species of parasites, which inhabit and utilize different host species for different purposes during their life cycle, will have contrasting effects on hosts depending on both transmission stage and host as well as parasite developmental stage (Parker et al., 2009; Dianne et al., 2011; Weinreich et al., 2013). Parasites occupying multiple sequential host species appear as appropriate model systems for variable nature of host-parasite relationship. Parasites may be beneficial in certain contexts (Thomas et al., 2000), for instance protecting their hosts from either predation or disease (Methot and Alizon, 2014; Gopko et al., 2015), and recent publications analyze how parasites may evolve to protect their hosts (Ashby and King, 2017). Here we will suggest that the ability of parasites to potentiate host fitness also by indirect extended phenotype effects could be an overlooked but potent evolutionary driver in shaping the host immune response.

We focus in this review on cases of co-existence without fierce resistance, in other words when an organism reside in the body of another species without apparent negative consequences. Understanding the biology behind such conditions could potentially provide clues to combatting over-activation and resulting immunopathologies.

HOST AND PARASITE PERSPECTIVES

Pinnacles for the evolution and ontogenetic unfolding of virulence and pathogenicity vs. benign interactions has been addressed previously by multiple authors (Ewald, 1987, 1995; May and Anderson, 1990; Anderson and May, 1992; Nowak and May, 1994; Combes, 2001). A parasite infection will generally evoke an immune response in the host, and parasite species with complicated life cycles need to overcome a variety of immune defenses from multiple hosts, often of both vertebrate and invertebrate origin (Auld and Tinsley, 2015). For example, if completion of the life cycle requires sickening or conspicuousness of an intermediate host, but health and longevity of the final host, pathogenicity needs to be adjusted accordingly. To complicate things further, a parasite might have different purposes even in the same host depending on its developmental stage. For example, a parasite awaiting trophic transmission but is not yet infective for its next host, could be

expected to minimize damage and seek to extend the life span of an intermediate host. When the parasite matures and becomes infective for the next host, however, its infection mechanism may change with adverse consequences for the host (Parker et al., 2009; Dianne et al., 2011; Weinreich et al., 2013). Thus, parasites may adjust their virulence to match their life history strategy and stage. An example of such a strategy is provided by the cestode *Schistocephalus solidus*, plerocercoids of which reduce anti-predator behavior of sticklebacks (*Gasterosteus aculeatus*) only when infective to the final host, piscivorous birds (Tierney et al., 1993).

Parasites may reduce or even enhance longevity and survival of the host depending on what is the most adaptive outcome for them (Hammerschmidt et al., 2009; Dianne et al., 2012). Hosts, in turn will adjust their response to maximize expected life time fitness. Hence, hosts may have very different degrees of incentives for fighting off the parasite and accordingly invest in immunity.

From the perspective of the host, in particular regarding parasites manipulating host phenotype, the evolutionary pressures for parasite resistance may be highly variable (Poulin et al., 1994). In short, a host that suffers from manipulation by the parasite in a way that only benefits the parasite could be expected to develop a strong immune response compared to a host that do not suffer considerably. But even in hosts that do not directly benefit or even that severely suffer from infection, there is a trade-off between keeping the parasite infection in check and avoiding potential immunopathological costs and even mortality associated with immune reactivity (i.e., autoimmunity) (Graham et al., 2005; Maizels, 2016). Of note, heavy investment in immune responses obviously also goes at the expense of investment in other imperative traits, such as growth (Soler et al., 2003; Brommer, 2004) and reproduction (Gustafsson et al., 1994; Nordling et al., 1998; Siva-Jothy et al., 1998).

In the following we introduce a hitherto overlooked factor that may limit the immune response of end hosts, namely the energetic/nutritional benefit of prey rendered easily captured because of infections. By now, a multitude of examples have been described where parasite-associated changes in the phenotype of intermediate hosts appear to facilitate trophic transmission. In many cases it would appear that the final host indeed benefits from the presence of a certain parasite, and would gain little from eliminating it. A close scrutiny of current literature reveals few reports of apparent pathology or other negative fitness effects on the end host in such systems (see **Table 1**).

PARASITES PROVIDING EASY PREY

Many parasite life cycles include a stage at which successful transmission requires that an infected host must be ingested by a predator, which then becomes host for the next -and often final- life stage of the parasite. Specifically regarding such trophically transmitted parasites, it can be predicted that pathology should be low in the final predatory host, otherwise a negative fitness effect would select for avoidance of parasitized prey (Lafferty, 1992; Kuris, 2003). Scenarios where different hosts in a trophically transmitted life cycle is impacted differently

TABLE 1 | Parasites providing easy prey.

Genus	Intermediate host, phenotypic change	Parasite effects on final host
ACANTOCEPHALA		
<i>Moniliformis moniliformis</i>	Insecta; Blattidae (<i>Periplaneta americana</i>) Behavior (Moore, 1983a; Wilson and Edwards, 1986; Libersat and Moore, 2000)	Mammalia; Muridae (<i>Rattus norvegicus</i>) Local intestinal histopathological changes (Teimoori et al., 2011).
<i>Acanthocephalus dirus</i>	Crustacea; Isopoda (<i>Caecidotea intermedius</i> , <i>Asellus intermedius</i>) Behavior and appearance (Camp and Huizinga, 1979; Hechtel et al., 1993)	Actinopterygii; Cyprinidae (<i>Semotilus atromaculatus</i>) No reports on <i>S. atromaculatus</i> , but see (Bullock, 1963; Schmidt et al., 1974; Sakthivel et al., 2016)
<i>Acanthocephalus lucii</i>	Crustacea; Isopoda (<i>Asellus aquaticus</i>) Behavior, increased predation rate (Benesh et al., 2008)	Actinopterygii; Percidae No reports on pathology, but see (Sures, 2002)
<i>Polymorphus paradoxus</i>	Crustacea; Amphipoda (<i>Gammarus lacustris</i>) Behavior, increased predation rate (Holmes and Bethel, 1972; Bethel and Holmes, 1973, 1977)	Aves and Mammalia No reports
<i>Polymorphus laevis</i>	Crustacea; Amphipoda (<i>Gammarus lacustris</i>) Behavior, increased predation rate (Bakker et al., 1997)	Actinopterygii; Gasterosteidae (<i>Gasterosteus aculeatus</i>) Survival cost proportional to severity of infection (Mazzi and Bakker, 2003)
<i>Corynosoma constrictum</i>	Crustacea; Amphipoda (<i>Hyalella azteca</i>) Behavior, increased predation rate (Bethel and Holmes, 1973, 1977)	Aves No reports
<i>Plagiorhynchus cylindraceus</i>	Crustacea; Isopoda (<i>Armadillidium vulgare</i>) Behavior, increased predation rate (Moore, 1983b)	Aves, Sturnidae (<i>Sturnus vulgaris</i>) Both reported to be of little or no histopathological consequence (Moore and Bell, 1983a) and to negatively affect energy metabolism (Connors and Nickol, 1991).
<i>Profilicollis</i> spp	Crustacea; Decapoda (<i>Macrophthalmus hirtipes</i> , <i>Hemigrapsus crenulatus</i>) Behavior (Latham and Poulin, 2002)	Aves Local intestinal damage and inflammation, potentially lethal in young chicks (La Sala et al., 2013).
<i>Pomphorhynchus laevis</i>	Crustacea; Amphipoda (<i>Gammarus pulex</i>) Behavior, increased predation rate (Kennedy et al., 1978; Kaldonski et al., 2007; Dianne et al., 2012)	Actinopterygii Local intestinal damage and inflammation and reduced condition factor in <i>Cottus gobio</i> (Sheath, 2016). No effect on growth or mortality in salmonids (Pippy, 1969; Wanstall et al., 1986) or cyprinidae, recognized as preferred hosts (Hine and Kennedy, 1974)
TREMATODA (DIGENEA)		
<i>Curtuteria australis</i>	Mollusca; Bivalvia (<i>Austrovenus stutchburyi</i>) Behavior, increased predation rate (Thomas and Poulin, 1998)	Aves; Haematopodidae (<i>Haematopus palliatus</i>) No reports
<i>Euhaplorchis californiensis</i>	Actinopterygii; Fundulidae (<i>Fundulus californiensis</i>) Behavior, increased predation rate (Lafferty and Morris, 1996)	Aves No reports
<i>Microphallus turgidus</i>	Crustacea; Decapoda (<i>Palaemonetes pugio</i>) Behavior, increased predation rate by non-final host (Kunz and Pung, 2004; Gonzalez, 2016)	Aves No reports
<i>Brachylecithum mosquensi</i>	Insecta; Formicidae (<i>Camponotus herculeanus</i>) Behavior (Carney, 1969)	Aves; Turdidae (<i>Turdus migratorius</i>) No reports
<i>Ascocotyle (Phagicola) pindoramensis</i>	Actinopterygii; Poeciliidae (<i>Poecilia vivipara</i>) Behavior (Santos and Santos, 2013)	Aves and Mammalia No reports
<i>Telogaster opisthorchis</i>	Actinopterygii; Galaxiidae (<i>Galaxias anomalus</i>) Behavior (Poulin, 1993)	Actinopterygii; Anguilliformes No reports
<i>Ribeiroia ondatrae</i>	Amphibia Morphology, presumed increased predation rate (Sessions and Ruth, 1990; Johnson et al., 1999, 2010)	Aves and Mammalia Local moderate inflammation (El-Dakhly et al., 2018)
<i>Plagiorchis noblei</i> Park	Insecta; Culicidae (<i>Aedes aegypti</i>) Behavior, increased predation rate (Webber et al., 1987a,b)	Aves and Mammalia No reports
<i>Plagioporus</i> sp.	Anthozoa; Poritidae (<i>Porites compressa</i>) Appearance, increased predation rate (Aeby, 1991)	actinopterygii No reports
<i>Crassiphiala bulboglossa</i>	Actinopterygii; Fundulidae (<i>Fundulus diaphanous</i>) Behavior (Krause and Godin, 1994)	Aves No reports
<i>Diplostomum spathaceum</i>	Actinopterygii Behavior (Crowden and Broom, 1980; Seppälä et al., 2004, 2008)	Aves No reports
<i>Gymnophallus fossarum</i>	Mollusca; Bivalvia (<i>Venerupis aurea</i>) Positioning, increased predation rate (Combes, 2001)	Aves; Haematopodidae (<i>Haematopus ostralegus</i>) No reports
<i>Gynaecotyla adunca</i>	Crustacea; Amphipoda (<i>Corophium volutator</i>) Behavior (Damsgaard et al., 2005)	Aves; Scolopacidae (<i>Calidris pusilla</i>) No reports

(Continued)

TABLE 1 | Continued

Genus	Intermediate host, phenotypic change	Parasite effects on final host
<i>Microphallus</i> spp.	Crustacea; Amphipoda (<i>Corophium volutator</i>) and Mollusca; Gastropoda (<i>Potamopyrgus antipodarum</i>) Behavior, increased predation rate by non-final host (Levri and Lively, 1996; Levri, 1998; Damsgaard et al., 2005)	Aves No reports
<i>Microphallus turgidus</i>	Crustacea; Decapoda (<i>Palaemonetes pugi</i>) swimming stamina, increased predation rate by non-final host (Kunz and Pung, 2004)	Aves No reports
<i>Microphallus papillorobustus</i>	Crustacea; Amphipoda (<i>Gammarus insensibilis</i>) Behavior, increased predation rate (Helluy and Thomas, 2010)	Aves No reports
<i>Maritrema oocysta</i>	Mollusca; Gastropoda (<i>Hydrobia ulvae</i>) Behavior (Huxham et al., 1995)	Aves No reports
<i>Ornithodiplostomum</i> sp	Actinopterygii; Percidae (<i>Etheostoma nigrum</i>) Behavior (Krause et al., 2010)	Aves No reports
CESTODA		
<i>Anomotaenia brevis</i>	Insecta; Formicidae (<i>Temnothorax nylanderi</i>) Behavior (Beros et al., 2015)	Aves; Picidae (<i>Dendrocopos major</i> , <i>Dendrocopos minor</i>) No reports
<i>Eubothrium salvelini</i>	Crustacea; Copepoda (<i>Cyclops vernalis</i>) Behavior, increased predation rate (Poulin et al., 1992)	Actinopterygii; Salmonidae Impairs growth rate, survival, sea water adaptation and swimming abilities in sockeye salmon smolt (Smith and Margolis, 1970; Boyce, 1979; Boyce and Clarke, 1983) and associated with chronic haemolytic anemia in Arctic charr (Hoffmann et al., 1986)
<i>Hymenolepis diminuta</i>	Insecta, Coleoptera (<i>Tenebrio molitor</i>) Behavior, increased predation rate (*) (Pasternak et al., 1995; Blankespoor et al., 1997; Webster et al., 2000)	Mammalia; Muridae (<i>Rattus norvegicus</i>) Local histopathological changes (Hindsbo et al., 1982)
<i>Ligula intestinalis</i>	Actinopterygii; Cyprinidae Behavior (Barber and Huntingford, 1996; Loot et al., 2001, 2002)	Aves No reports
<i>Polyocephalus</i> spp.	Crustacea; Decapoda (<i>Litopenaeus setiferus</i>) Behavior (Carreon et al., 2011)	Chondrichthyes No reports
<i>Taenia crassiceps</i>	Mammalia; Muridae (<i>Mus musculus</i>) Physiology (Gourbal et al., 2001)	Mammalia; felidae No reports
<i>Schistocephalus solidus</i>	Actinopterygii; Gasterosteidae (<i>Gasterosteus aculeatus</i>) Anti-predator behavior, presumed increased predation rate (Tierney et al., 1993; Barber et al., 2004)	Aves No reports
<i>Echinococcus granulosus</i>	Mammalia; Ungulata Debilitation, increased predation rate	Mammalia; Canidae No pathological response (Lafferty and Kuris, 2012)
NEMATODA		
<i>Dispharynx nasuta</i>	Isopods (<i>Armadillidium vulgare</i>) Altered light-dark preference, decreased shelter use (Moore and Lasswell, 1986)	Aves Associated with morbidity and mortality in wild and domestic birds (Goble and Kutz, 1945; Lindquist and Straffuss, 1980; Blasdel and Lasswell, 1986; Schulman et al., 1992)
<i>Pseudoterranova decipiens</i>	Actinopterygii; Osmeridae (<i>Osmerus eperlanus</i>) Reduced overall condition, presumed increased predation rate (Möller and Klatt, 1990)	Mammalia; Otariidae, Phocidea Local inflammatory reactions observed, but generally nonpathogenic (McClelland, 1980)
<i>Pterygodermatites peromysci</i>	Insecta; Rhaphidophoridae (<i>Ceuthophilus pallidipes</i>) Physical abilities, assumed increased predation rate (Luong et al., 2011)	Mammalia; Cricetidae (<i>Peromyscus</i> spp.) Indications of reduced body condition in individuals co-infected with <i>P. peromysci</i> and <i>P. leucopus</i> (Vandegrift and Hudson, 2009)
<i>Skrjabinoclava morrisoni</i>	Crustacea; Amphipoda (<i>Corophium volutator</i>) Behavior (McCurdy et al., 1999)	Aves; Scolopacidae (<i>Calidris pusilla</i>) No reports
<i>Toxocara canis</i>	Mammalia; Muridae (<i>Mus musculus</i>) Behavior (Holland and Cox, 2001)	Mammalia; Canidae Clinical symptoms are rare in adult dogs (Despommier, 2003).
<i>Trichinella spiralis</i>	Mammalia; Muridae (<i>Mus musculus</i>) Behavior (Rau, 1983; Rau and Putter, 1984)	Mammalia Generally assumed to be asymptomatic in animals, but reduces body weight in pigs (Ribicich et al., 2007)
<i>Trichinella nativa</i>	Mammalia; Cricetidae (<i>Peromyscus maniculatus</i>) Activity deficits (Poirier et al., 1995)	Mammalia; Canidae and Ursidae Highly pathogenic in humans, but no apparent pathology or energy drain in dogs (Schanbacher et al., 1978) and foxes (Prestrud et al., 1993). No reports of pathology in bear

(Continued)

TABLE 1 | Continued

PROTOZOA		
<i>Frenkella</i> spp.	Mammalia; Cricetidae Increased predation risk (Vorišek et al., 1998)	Aves; Accipitriformes (<i>Buteo</i> spp.) No reports
<i>Sarcocystis dispersa</i>	Mammalia; Muridae (<i>Mus musculus</i>) Increased predation risk (Vorišek et al., 1998)	Aves; Strigidae (<i>Asio otus</i>) No reports
<i>Sarcocystis rauschorum</i>	Mammalia; Cricetidae Increased exploratory activity (Quinn et al., 1987)	Aves; Strigidae (<i>Nyctea scandiaca</i>) No reports
<i>Toxoplasma gondii</i>	Mammalia; Muridae Anti-predator behavior, presumed increased predation rate (Webster, 2001)	Mammalia; Felidae Infection in adult feline definitive hosts are most commonly asymptomatic and apparently innocuous (Elmore et al., 2010)
APICOMPLEXA		
<i>Sarcocystis cernae</i>	Mammalia; Cricetidae (<i>Microtus arvalis</i>) Increased predation rate (Hoogenboom and Dijkstra, 1987)	Aves; Falconidae (<i>Falco tinnunculus</i>) No reports

Overview of parasite-host systems where the parasite alters the phenotype of its intermediate host in ways that is likely or has been reported to increase predation of the intermediate host by the final host and where the intermediate host is assumed to be energetically significant prey for the final host.

(Kuris, 2003), and in which the host actually benefits from interaction with the parasite have been proposed by several authors (Lafferty, 1992; Thomas et al., 2000). Lafferty (1992) proposed a model that weighed energetic costs of parasitism for a predator against the energetic value of infected prey items, which revealed that there is often no selective pressure to avoid parasitized prey. In other words, predators may actually benefit from their parasites if energetic costs of parasitism are moderate and prey capture is facilitated by parasites. Such hosts are likely to be under strong selection to avoid colonization by some, but not all, parasites.

Numerous reports have documented that parasite infected animals may change their behavior in ways that increase parasite fitness [e.g., Holmes and Bethel, 1972; Barber et al., 2000; Poulin, 2010; Lafferty and Shaw, 2013; Moore, 2013]. Following empirical demonstrations that amphipods harboring larval acanthocephalan parasites display behavior and abnormal coloration making them more susceptible to predation by the parasite's next host (Hindsbo, 1972; Holmes and Bethel, 1972), there has been sustained interest in this phenomenon. As a result, host manipulation by parasites has now been documented in a few hundred distinct host-parasite associations spanning all major phyla of living organisms (see reviews in Moore, 2002, 2013; Dawkins, 2012). Remarkable examples include "suicidal" behavior in rats infected by the protozoan parasite *Toxoplasma gondii*, which become attracted to cat urine (Berdyo et al., 2000), and water-seeking behavior in otherwise terrestrial crickets which allow parasitic hairworms to emerge and reproduce in water (Thomas et al., 2002). Interest in this field has taken a leap as new molecular and systems biology approaches are revealing the potential impact of parasites and pathogens on behavior and neurobiology both in natural ecosystems and in the human society (Biron et al., 2006; Lefèvre et al., 2009; Prandovszky et al., 2011; Biron and Loxdale, 2013; Flegel, 2015; Syn et al., 2018).

In the following we will focus on trophically transmitted parasites, which are associated with altered behavior, appearance, or general condition of prey hosts in ways that increase their rates of consumption by predatory final hosts (see reviews by Moore, 2002; Lefèvre et al., 2009; Lafferty and Shaw, 2013). In

such cases, increased predation success per effort for the final host may imply a fitness advantage, given that the cost of parasitism is low. Such cases are of particular interest for the evolution of tolerance vs. pathogenicity (Kuris, 2003). To our knowledge, however, no systematic review exists that specifically investigates if parasites that are benign to the predatory host outnumber pathogenic ones among known examples of parasite mediated trophic transmission.

As will be proposed in this review, in such cases there also exists a selection pressure for minimizing the immune response to ward off beneficial infections. This stance is derived from those cases where an energetic benefit to the final host has been either demonstrated or strongly incurred by empirical data on catchability or behavior of infected prey. In an extensive review, Lafferty and Shaw (2013) identified 55 genera of trophically transmitted parasites meeting this criterion distributed among the following taxa: protozoans, acanthocephalans, nematodes, and digenean and cestode species in the plathyhelminthes phylum. In the present paper, we aimed to investigate if any significant pathology has been reported among final hosts in at least one example from each of these genera. In addition, Poulin and Maure (2015) identified 26 host-parasite species combinations for which actual predation tests had been performed, which all were included. We however omit examples involving the ingestion of organisms that cannot be considered as normally occurring energetically significant prey in the diet of the end host.

For example, our criteria exclude some spectacular and well-known examples of host manipulation. The antennae of snails infected with *Leucochloridium* trematodes become abnormally large and conspicuous to avian final hosts of the parasite. Snails do, however, not belong to the final host's normal diet and cannot be considered energetically important to the predatory bird (Moore, 2002). Along the same lines, ants infected by the liver fluke *Dicrocoelium dendriticum* climb and anchor themselves to the top of grass, presumably rendering them more susceptible to ingestion by large herbivorous mammals where the fluke can reach adulthood. Evidently, *Dicrocoelium metacercaria* are associated with a dramatic behavioral change in the ants, but the insects are not of any known nutritional value to the ruminant

host. Interestingly, the *Dicrocoelium* example provides a case where host manipulation is associated with significant pathology in the final host, i.e., the disease known as dicrocoeliosis in ruminants (Otranto and Traversa, 2003). As a contrary example from a by now classical model system, cystacanths of the acantocephalon *Plagiorhynchus cylindraceus* alters sheltering and light-dark preference in isopods rendering them more prone to capture by birds. Effects of adult *P. cylindraceus* on the model host, starlings, are however reported to be typically minor (Moore, 1983b; Moore and Bell, 1983a; Connors and Nickol, 1991). Although some metabolic cost may be incurred (Connors and Nickol, 1991), tissue damage is minimal, and infected birds in the wild exhibit weights comparable to those of uninfected conspecifics (Moore and Bell, 1983a). Pathological reactions are on the other hand common among unintended hosts and in vector borne and direct life cycles. In **Table 1** we list the trophic transmission model systems that we identified as relevant in this context, and whether or not any associated pathology have been reported in the final host.

Of note, host modification does not necessarily need to include only strictly defined behavioral manipulation. The larval tapeworm *Echinococcus granulosus* for instance incapacitate ungulate intermediate hosts, such as moose by lodging in the lungs and other organs making it easier for wolves to attack the debilitated prey (Joly and Messier, 2004). The result for the end host is the same as with behavioral manipulation, the prey becomes easier to catch. In fact, mathematical models has been published which identify potential situations where wolves could not persist on moose as prey without the assistance of the debilitating parasite (Hadelér and Freedman, 1989). At least it seems likely that presence of the tapeworm enables wolves to drive the moose population to lower levels than would otherwise be possible. Canid final hosts, however, show no pathological responses to the adult tapeworm (Lafferty and Kuris, 2012).

In general, going through the literature on model systems where parasites presumably provide an easy meal to their final host by manipulating their prey (**Table 1**), it is curious to note the lack of reports on pathology in final hosts. In examples where reports on pathology do exist, local and moderate histopathological changes are described. In a very few cases parasitism appears to affect growth and condition of the final host (Boyce, 1979; Vandegrift and Hudson, 2009; Sheath, 2016). Even in these cases pathological effects are primarily reported in either non-preferred (Sheath, 2016) or very young (Boyce, 1979) final hosts, or with co-infections of other parasites so that causality between parasite species and host effects cannot easily be established (Vandegrift and Hudson, 2009). There are also cases in our literature review where parasitism is potentially lethal. For example, the nematode *Dispharynx nasuta* is associated with morbidity and mortality in several bird species that can serve as final hosts for the parasite (Goble and Kutz, 1945; Lindquist and Straffuss, 1980; Blasdel and Lasswell, 1986). It can, however, be debated whether the intermediate host in this case, the isopod *Armadillidium vulgare*, represent an energetically important food item for these birds. Nonetheless, there are exceptions to the rule that parasites

providing easy prey are non-pathogenic to and not fiercely resisted by the final host, but the general trend appears to be one of benign tolerance.

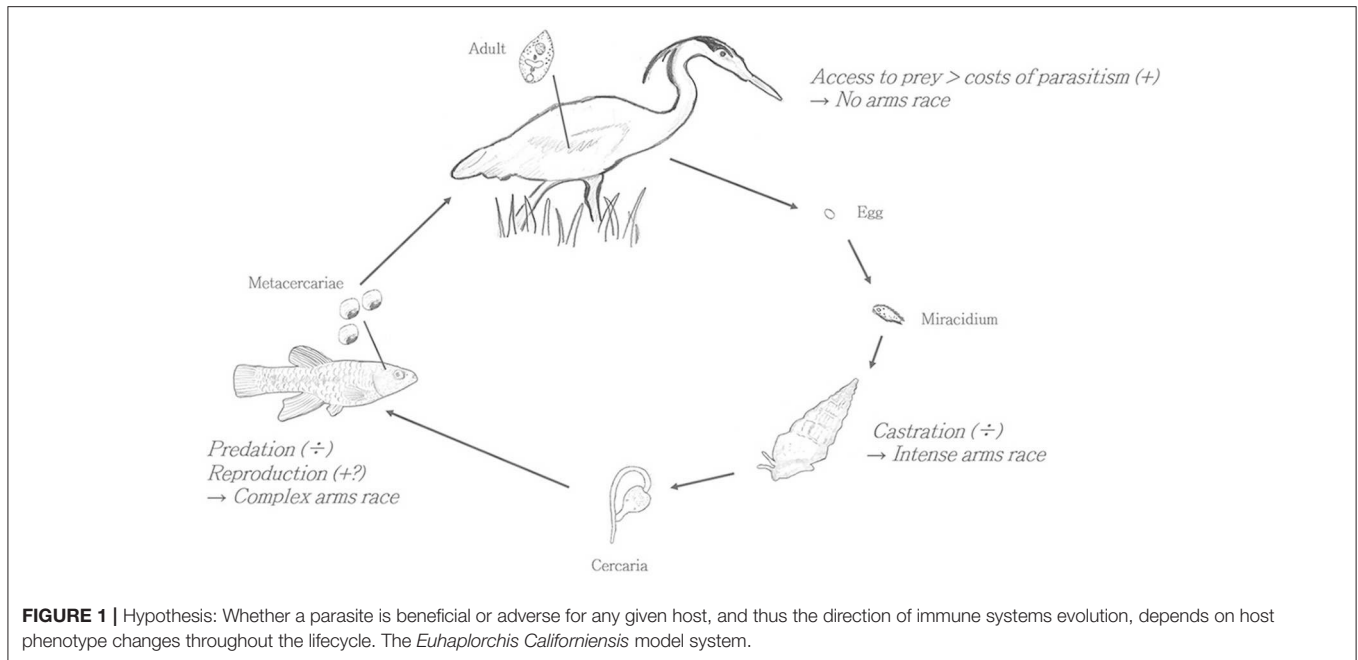
Also of note, severity of pathology and mortality appears to be highly parasite density-dependent. Often, pathology is only observed with heavy infection load and moderate infections appears to be of little pathological consequence (Mazzi and Bakker, 2003; Teimoori et al., 2011). For instance, Hindsbo et al. (1982) found that immunological responses of rats to the cestode *Hymenolepis diminuta* are dose-dependent, indicating that the rodents tolerate a certain number of adult cestodes (up to 100 worms) before they mount an immune response. The underlying mechanisms behind such dose-dependent infection tolerance are unknown, but in the context of this review, it is tempting to point out that *H. diminuta* apparently provide easy to capture beetle prey for the rat final hosts. Said hosts may therefore have evolved to tolerate moderate or even substantial infection loads, ensuring survival of prey-providing parasites.

Of note, one parasite taxon appears to provoke more harm to their final host than the other taxa investigated here. In general, acanthocephalans only cause localized pathology in the gut of their hosts, but there are some reports of severe pathology. The severity of damage acanthocephalans cause to their hosts and intensity of host reactions appears to depend on the depth of proboscis penetration, the density of worm burdens and even on the systematic affiliation of the parasites and hosts (Taraschewski, 2000). Of note, those acantocephalan species that are reported to be most intensely pathogenic to their final host are not among the prey providers identified in **Table 1** (for extensive review on pathogenicity of acantacephalans see Taraschewski, 2000).

EXTENDING THE EXTENDED PHENOTYPE CONCEPT

The “extended phenotype” concept promoted by Richard Dawkins implies that parasites have evolved means to alter host phenotype in ways that benefit the parasite. Increased parasite fitness has been seen as the main evolutionary driver. For instance, Poulin (2010) states “In a nutshell, host manipulation by parasite can be defined as any alteration in host phenotype, induced by a parasite that has fitness benefits for the parasite.” Even Dawkins (in the editorial introduction to the 2012 book “Host Manipulation by Parasites”) proclaims that the parasite is “... manipulating the behavior of its host-subverting it to the benefit of the parasite in ways that arouse admiration for the subtlety, and horror at the ruthlessness, in equal measure” (Dawkins, 2012). Presently, we will raise the proposition that in cases of parasite-mediated trophic transmission the possibility that the energetic benefit of the final host (e.g., a fish eating bird) is an equally or perhaps more important evolutionary driver (see **Figure 1**).

As seen above, compared to parasitized intermediate hosts that suffer increased morbidity, such as parasitic castration (Baudoin, 1975), or mortality [e.g., by predation Lafferty and Morris, 1996], reports on negative effects on intended



definitive hosts are suspiciously absent. Previous authors have also suggested that this appears to be a general trend in trophic transmission (Bailey, 1975; Geraci and St. Aubin, 1987). Moreover, definitive hosts of many trophically transmitted parasites do not appear to avoid parasitized prey (Bairagi and Adak, 2015). On the contrary, predatory definitive hosts often consume disproportionately larger numbers of infected vs. uninfected individuals (Hudson et al., 1992, 1998; Lafferty and Morris, 1996; McCallum et al., 2005). For example, *F. parvipinnis* infected with *E. californiensis* display conspicuous swimming behaviors, rendering them up to 30 times more likely to be eaten by a final bird host where the parasite completes its life cycle and sexually reproduce (Lafferty and Morris, 1996). Similarly, loss of the innate aversion to cat odor in rodents infected with *Toxoplasma gondii*, presumably makes them more susceptible to predation by the parasite's final feline host (Webster, 2001). Whereas, *T. gondii* infection in adult cats is most commonly asymptomatic and considered innocuous (Elmore et al., 2010), preliminary data from our lab indicate no energetic or physiological cost of *E. californiensis* in bird hosts (unpublished data). In conclusion, decreased anti-predator behavior of parasitized intermediate hosts/prey, or even pro-predator behavior in some cases can fulfill the extended phenotype not only of the parasite but that of the predatory definite host.

PREY PROVIDERS REVOKE THE EVOLUTIONARY ARMS RACE

Common for the end hosts in these examples is that they do not appear to suffer the same deleterious consequences of the parasite infection as the intermediate hosts. Seen from the parasite's perspective, kindness to the final host vs. aggressive utilization of host resources could be advantageous for several

reasons, in that enhanced host longevity would maximize parasite lifetime accumulated fitness. It is therefore reasonable to assume that trophically transmitted parasites could have a selective benefit from reducing their negative impact on the final host. But on the other hand, parasite mediated trophic transmission of energetically important prey is also likely to prevent the development of potentially destructive immune responses in the host, in addition to avoiding that the predatory final host evolves a tendency to avoid parasitized prey. If easily captured parasitized prey in this way fulfills the extended phenotype of not only the parasite awaiting transmission, but also that of the predator, there should be little or no selection on final hosts to minimize parasite infections. We have by no means covered an extensive list of all parasite-mediated trophic transmissions in this review, but the picture that emerges is that some predators employ parasites as a weapon in biological warfare against their prey, rather than suffering from infection in the traditional sense. This raises a pertinent question: How does the continuously developing immune system of a predatory host acquire and maintain the ability to distinguish useful helpers from pure plague? Apart from novel understanding of evolutionary drivers of host-parasite relationships, proximate understanding of these principles could potentially provide clues to combatting over-activation and resulting immunopathologies.

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