Are there Pros as well as Cons to being Parasitized?

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The diversity of ways in which parasites reduce the fitness of their hosts has been documented during the past decades, and clearly indicates that parasites can often be considered as direct agents of selection. In natural systems, however, the outcome of a host–parasite interaction might be strongly determined by other ecological factors. Parasites can be detrimental to host fitness in one environment, whereas they can be beneficial to it in another. From an evolutionary perspective, this phenomenon is of considerable importance for understanding the dynamics of coevolution among geographically structured populations evolving under different ecological pressures. Here, Frédéric Thomas and colleagues review several ecological situations in which parasitized individuals enjoy a selective advantage over unparasitized conspecifics.

Parasites are, by definition, detrimental for their hosts in that they divert resources that could otherwise be used for host growth, maintenance or reproduction[1]. In ecosystems, however, host species are confronted with numerous selection pressures in addition to those imposed by parasites (eg. competition, predation and sexual selection). Disentangling the relative importance of parasitism compared with other selective factors and how parasites interact with other ecological constraints are essential for understanding the direction of the selection and, ultimately, the long-term adaptive responses of populations (eg. life-history traits, morphology and behaviour of individuals).

When observed outside their ecological context (eg. in the laboratory), the fitness reduction of infected individuals might be a poor approximation of that incurred by the same hosts in a natural ecosystem. For instance, there are numerous reports of reduced fecundity among parasitized animals as a result of depleted energy reserves (direct cost; Fig. 1a). In the ecosystem, however, such individuals in poor condition often incur an additional and more drastic fitness reduction by becoming preferential prey for predators[2] or by suffering from other side effects[3] (indirect consequences; Fig. 1a). In this example, the direct cost and the indirect consequences act in the same direction (ie. to decrease host fitness) with the consequences having a bigger impact on host fitness than the immediate (or direct) costs.

Under particular circumstances, however, direct costs and indirect consequences can act in opposite directions so that the net fitness of infected individuals might be similar to or even greater than that of uninfected ones[4] (Fig. 1b). Such situations are of considerable importance from an evolutionary perspective because natural selection does not act on punctual fitness reductions (ie. direct costs) but on the net fitness value of individuals. In addition, a geographic view of host–parasite interactions is undoubtedly needed for a more comprehensive understanding of the different ways in which interactions coevolve[5].

Protection

Against predators and cannibals. Although parasites impose a cost on their hosts, they do not systematically reduce host fitness to zero. In contrast, ingestion by a predator or by a conspecific (ie. cannibalism) is a radical way of decreasing the fitness of an individual to zero. From a predator or a cannibal perspective, the presence of transmissible parasite stages within a prey or a conspecific might result in future energetic costs[6–8]. In this context, and when the risk of being eaten is high, it is expected that infection by a parasite that induces avoidance by predators or cannibals would be advantageous. For instance, bivalve molluscs such as cockles are important intermediate hosts for helminth parasites, for which oystercatchers are the definitive hosts. To maximize energy intake, birds should selectively consume the largest size classes of cockles, but to minimize their ingestion rate of parasite larvae they should consume the smallest size classes, because helminth intensity in cockles increases significantly with cockle size[9]. In the wild, birds selectively consume intermediate size classes, which represent a compromise between these conflicting demands[9] (but see Ref. 10 for an example of infected cockles being preferred by oystercatchers). In this case, it can be argued that, despite the cost of being infected, cockles benefit from parasites in that they allow them to reach a large size (and, probably, a high fecundity) without being eaten by predators (Fig. 1b). Whether advantages are beneficial to infected cockles only, or beneficial to all large cockles (infected or not) is not clear in this case. Further investigations would be necessary to determine whether size is the only criterion used by oystercatchers to avoid infected prey.

Pathogen transmission has also been proposed recently as a general explanation for why cannibalism is infrequent or absent in most species[11]. Indeed, although cannibalism can confer important nutritional and competitive advantages to the cannibal, it is an obvious way to acquire pathogens owing to the greater genetic similarity among conspecifics and selection for host specificity and resistance to host immune defences among pathogens[11]. However, once anti-cannibalistic genes are fixed in a population (ie. no cannibals), the advantage of being parasitized disappears because there is no need for protection.

Against other parasites. In ecosystems, host species are generally challenged by several parasite species (some more harmful than others). When harmful parasites are abundant, being infected by a less-harmful parasite that prevents the establishment of other parasites (ie. competition between parasite taxa) is

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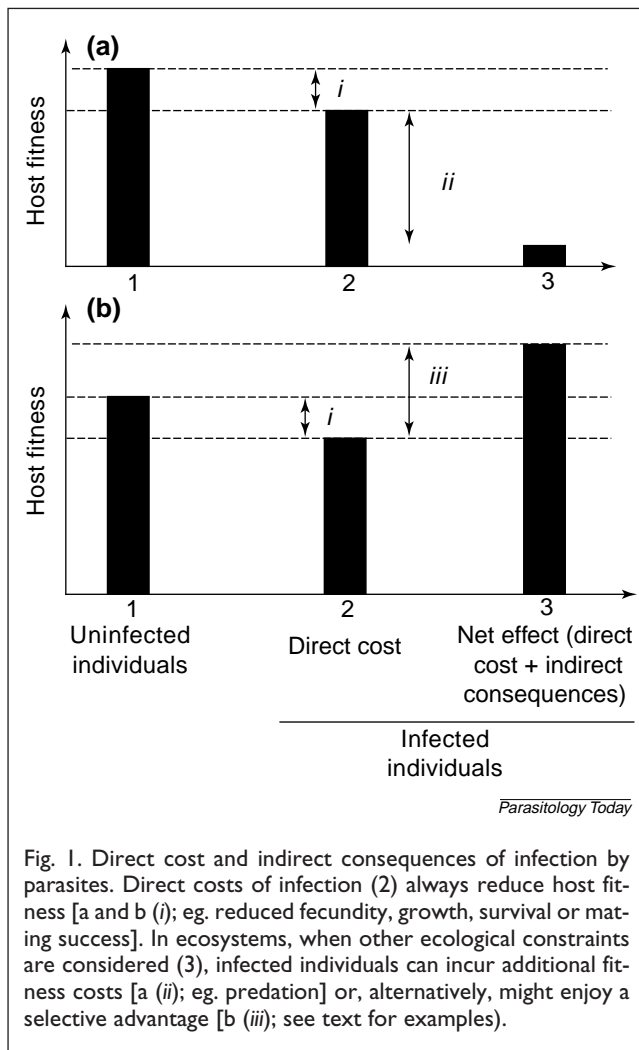
Focus

Fig. 1. Direct cost and indirect consequences of infection by parasites. Direct costs of infection (2) always reduce host fitness [a and b (*i*); eg. reduced fecundity, growth, survival or mating success]. In ecosystems, when other ecological constraints are considered (3), infected individuals can incur additional fitness costs [a (*ii*); eg. predation] or, alternatively, might enjoy a selective advantage [b (*iii*); see text for examples].

probably another advantageous solution. The first evidence (although still contentious) of such a parasitic protection has been proposed in the complex interaction between oropendulas (American orioles), botflies and cowbirds[12]. Botflies are a major mortality source for oropendula chicks. Oropendulas that breed in the presence of adult botflies allow cowbirds to develop in their nest because these brood parasites remove immature stages of botflies by grooming before the young oropendula become infected. Thus, although the cowbirds reduce the fitness of the oropendulas in the absence of botflies, they increase it in the presence of botflies. Another, and less costly, option to accepting cowbirds is sometimes possible: oropendula nests in trees that harbour large wasp nests are relatively free from botflies because wasps chase botflies away. Remarkably, the oropendulas are hostile to cowbirds when they nest in the vicinity of wasps (because there are only direct costs of accepting cowbirds), but tolerant to cowbirds in the absence of wasps (ie. net fitness consequences outweigh direct costs).

Similarly, there is evidence among fungi that less-virulent strains colonizing infection sites on plant surfaces protect plants against closely related, but more-virulent, strains[13]. Other examples of parasitic protection may come from host–parasitoid–pathogen interactions. The diamondback moth *Plutella xylostella* incurs fitness reductions when infected by the bacterial pathogen *Bacillus thuringiensis*. However, this

pathogen has a significant negative effect on a worse enemy, which kills the host: the larvae of the parasitoid *Cotesia plutellae*. Whereas hosts that are susceptible to the bacteria are protected against parasitoid infections, highly resistant hosts constitute a refuge from competition for the parasitoid[14].

Another advantage of being infected is likely to occur when naturally acquired immunity exists and when the detrimental effects of an infection increase with host age, such as for mumps in humans. In such a case, early exposure to parasites allows hosts to build up an effective immunity that will give them a selective advantage if the risk of future infections is high. In addition, the phenomenon of heterologous immunity occurs frequently and is a long-term benefit of many infections. Long before the causes of disease and the processes of recovery were known, humans were aware of this long-term positive effect on the subsequent risk of infection. For example, in the 16th century some Chinese prevented smallpox by exposing uninfected individuals to material from smallpox lesions, a practice known as 'variolation'. Although the effects of variolation were variable, the mortality and morbidity rates as a result of smallpox were certainly lower in populations that used variolation than in those that did not[15].

Advantages

In interspecific competition. A host can sometimes enjoy freedom from competitors because of its parasites. Indeed, some host species can invade new areas only because the parasites they carry are more pathogenic to endemic hosts than they are to their original hosts. The case of the nematode *Parelaphostrongylus tenuis* in North American cervids is a good example of a host (white-tailed deer) using its parasites as biological weapons against other Cervidae (moose)[16] (see Refs 17–21 for other examples of apparent competition). In these situations, however, there is no direct correlation between the parasitic status of individuals and their selective advantage; that is, all the individuals (infected or not) of the tolerant host species benefit from the presence of parasites.

In sexual selection processes. Resistance to parasites might play a role in female mate choice, especially if males that have survived parasitism can be discriminated from males that have not been exposed to parasites[22]. In this context, sexual selection should favour, among males having the genes to survive parasitism, those having experienced parasitic infection, because it allows them to provide undeniable evidence of genes for parasite resistance (ie. an honest signal). Several studies have addressed this problem, although they have yielded contradictory results. Early instar larvae of *Drosophila* species are frequently attacked by a variety of parasitoid wasps. In resistant individuals, the melanized capsule enclosing the parasitoid remains intact throughout the life of the adult fly and can be seen clearly through the abdominal wall. Although males harbouring a melanized capsule have proved their ability to survive parasitoid attack, they do not enjoy a higher mating success[22]. In guppies[23] and sticklebacks[24,25], however, the higher attractiveness of resistant males compared with non-resistant ones is revealed once they have been challenged by parasites. Because of the direct costs of building up an effective immunity (Fig. 1b), it seems likely that during the process of infection itself, any observer would

have concluded a negative impact of parasites on fitness. However, in these cases, infection is likely to be beneficial for resistant males later in life, because it allows them to increase their fitness through enhancing reproductive success (Fig. 1b).

In adverse environments. It has recently been suggested that parasites could have a beneficial impact on their hosts when they act as 'internal sinks' for heavy metals in polluted habitats[26]. Various studies have shown that the concentrations of heavy metals in the tissues of intestinal parasites (especially acanthocephalans and cestodes) are many orders of magnitude higher than in the tissues of their fish hosts[27]. The direct cost of parasitism could be compensated by the benefits of using the parasites as accumulators of harmful toxins. Of course, because anthropogenic pollution is of recent origin, using parasites in this way might not be a host adaptation, but hosts might still obtain proximate benefits if they are parasitized and if their habitat is polluted.

Surprisingly, under deficient trophic conditions, parasites can also be beneficial for their hosts. In experimental conditions, the ground squirrels *Spermophilus richardsonii* parasitized with the protozoan *Trypanosoma otospermophili* are negatively affected by the infection when they receive a normal diet, but survive better and grow faster than uninfected controls when they receive a diet deficient in pyridoxine (vitamin B6)[28]. Lincicome[29] also found increased weight gains in rats infected with the protozoan *Trypanosoma lewisi* or the nematode *Trichinella spiralis* under particular conditions. However, under normal circumstances, *T. lewisi* and *T. spiralis* can cause severe fitness reductions[8] (eg. arthritis, abortion, decreased fecundity and death). Therefore, in Nature, *T. lewisi* and *T. spiralis* should not be considered beneficial to their rodent hosts[8].

Finally, another example of how environmental conditions might be crucial in determining the outcome of a host–parasite interaction comes from plasmids and their bacterial hosts. In antibiotic-free environments, plasmids are detrimental to their hosts, whereas in environments containing antibiotics, they often confer bacterial resistance to antibiotics and are consequently highly beneficial to their hosts[30,31].

Conclusion and perspective

A full understanding of the role of parasites as selective agents in the evolution of host species requires a precise knowledge of the net selective pressures they really exert. Direct costs of being infected may be unreliable for estimating the net fitness of infected individuals simply because the consequences of being infected are strongly influenced by environmental conditions. To understand these processes, it is clearly necessary to analyse the long-term effects of parasites on their hosts, and also to consider the other ecological constraints experienced by hosts in the ecosystem. Examples of 'beneficial' parasites remain relatively scarce at the moment, but probably only because of a lack of appropriate studies. However, all apparent indirect positive effects of being parasitized need to be examined critically.

The examples presented here also suggest that the same parasite, depending on the ecological context, can be detrimental or, conversely, beneficial to host fitness. From an evolutionary perspective, this phenomenon is of considerable importance for understanding the dynamics of co-evolution among geographically structured populations evolving under different ecological pressures[32]. When parasites are only detrimental to host fitness (Fig. 1a), selection should favour individual hosts possessing genes reducing the encounter rate with parasites as well as individuals possessing genes reducing the possibility for parasites to establish and to exploit the host. However, when being parasitized results in net fitness advantages (Fig. 1b), the reverse selection is expected. These situations may constitute the intermediate stage between parasitism and mutualism[4]. Rather than just studying a simple interaction between one host and its parasites, we need to explore the kinds of intimate connections that could exist between the symbiotic systems and their ecosystem as a whole. We clearly need empirical evidence from comparative field studies showing the detrimental versus beneficial effect of a parasite in relation to the ecological context. Furthermore, we should explore the evolutionary consequences for host and parasite populations.

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Molecular Crosstalk in Host–Parasite Relationships:
Schistosome– and Leech–Host Interactions

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The host–parasite relationship is based on subtle interplay between parasite survival strategies and host defense mechanisms. In this context, parasites often use the same or similar immune signaling molecules and/or molecular mimicry to escape host immunosurveillance. Both processes represent an adaptive strategy to ensure host immunocompatibility. This bidirectional communication between parasites and their hosts includes the renin–angiotensin, opioid and opiate systems. Here, Michel Salzet, André Capron and George Stefano review recent work on the interaction of common signaling mechanisms in schistosomes, leeches and their host.

The host–parasite relationship represents an intimate interaction between at least two genetic systems, the host and the parasite. Among the parasites used as models by immunologists, schistosomes, in particular, exhibit an amazing diversity of ingenuous mechanisms regulating their interactions with their intermediate and definitive host[1–4]. In immunocompetent hosts, parasites evade the immune response mainly through two mechanisms: (1) expression of appropriate antigens, either by changing the expressed antigens fast enough to prevent any efficient immune response (antigenic variation) or by expressing epitopes similar, if not identical, to host molecules (antigen mimicry); and (2) modification of the host immune response (via autoimmunoregulatory similarities), either directly by its own molecules, or indirectly by disregulating the host effector cells[1–4]. Parasites may also use host signaling molecules for growth and developmental control; for example, interleukin 7 (IL-7), steroids or thyroid hormone (TH).

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Molecular mimicry

The discovery in schistosomes of antigens common to both vertebrate and invertebrate hosts, followed by the extension of these observations to numerous parasites[1–5], has led to the concept of molecular mimicry (Box 1). The expression by parasites of host proteins such as α-2-macroglobulin, immunoglobulin receptors, major histocompatibility complex (MHC) class I and II antigens, blood group glycolipids or well-preserved oligosaccharides, such as keyhole limpet hemocyanin (KLH) glycan[6,7] or Lewis^x trisaccharide[8], illustrates the diversity of the structures involved in this mimicry. In many cases, such mimicry avoids immune detection. The presence, notably on the surface of the parasite, of structures that are common with the host raises the question of whether their acquisition was active or passive[9]. In certain cases, the passive acquisition of host molecules such as antigens from A, B, H blood groups or MHC molecules simulating parasite structure seems to have been validated.

More recently, the molecular cloning of hundreds of parasite genes has, in many cases, revealed high degrees of identity between the nucleotide sequences of parasite and mammalian genes. For example, there is identity over the whole sequence of certain structural proteins, such as myosin or tropomyosin[6,10] and enzymes or regulatory proteins[11], and, over limited functional sequences, of receptors or growth factors[12,13]. The existence of such widespread and diverse molecular mimicry raises important questions as to the evolutionary origin of parasite molecular mimicry. More specifically, is it evolutionary convergence or an appropriation of sequences?

Free-living invertebrates contain mammalian-like integrative signaling molecules, which exhibit extremely high sequence identity with their counterparts found in mammals[14], suggesting that these molecules originally evolved in simpler animals. However, in regard to parasites, tropomyosin analysis[6,10] has revealed analogies between schistosomes and snails far closer than those between other phylogenetically related

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