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Pleiotropic Action of Parasites: How to be Good for the Host

Yannis Michalakis, Isabelle Olivieri, François Renaud and Michel Raymond

Parasites reduce the reproductive output of their hosts, limit their growth, and sometimes even castrate or kill them. Under certain conditions however, a parasitized host may be better off than an uninfected one. Such 'nice' parasites have a 'pleiotropic' action on their hosts. Parasites can be pleiotropic either in space (in which case they have a beneficial effect on the host in one environment while being detrimental in another) or in time (the parasite is beneficial at one stage of the host's development and 'costly' at another stage). Such pleiotropic parasites may constitute the intermediate stage between parasitism and mutualism.

Parasites, by definition, live at the expense of a host organism. Some parasites, such as parasitoids (which always kill their hosts), affect only host survivorship. Others, such as trematodes and certain crustaceans, exploit the reproductive organs of their host, and therefore alter only their fecundity[1]. Interspecific brood parasites, such as cuckoos or parasitic ants, exploit their hosts by making them spend time and energy raising offspring that are of no value to them[2]. The outcome of the host–parasite interaction (evolutionary arms race, intermediate virulence, commensalism or mutualism) depends on the relationships between parasite-induced host mortality, parasite transmission, host recovery and host resistance to the parasites (see Refs 3 and 4 for a review).

In most models, however, these parameters are not allowed to vary. In nature, the outcome of the host–parasite interaction can in fact be very different where these factors differ in hosts of different ages, or where the effects depend on environmental conditions.

The case of the chestnut blight

The causal agent of chestnut blight is a fungus, *Cryphonectria parasitica* (see Ref. 5 for a review). This fungus attacks chestnut species in the USA (*Castanea dentata*) and in Europe (*C. sativa*), whereas trees from Asia (*C. crenata*), where the genus originated, seem to be resistant to the fungus. The fungus enters the chestnut through the bark. Hyphae spread through the cambium, while the disease is manifested externally as sunken cankers. These cankers eventually kill the host by blocking the exchange of water and nutrients between roots and leaves. The fungus reproduces both sexually (by ascospores, scattered by the wind) and asexually (by conidia, secreted in a sticky matrix and dispersed by insects, birds and possibly rain). Chestnut blight was probably introduced into both the USA and Europe by imported Asian specimens, at the beginning of the century. By 1950 it occupied the entire natural range of chestnut in the USA, decimating natural populations (most mature trees were killed during this period). The disease progressed more slowly in Europe, because of greater resistance to the fungus and a more patchy tree distribution. Nevertheless, *C. sativa* was decimated in Italy within 25 years of the introduction of the fungus, and French trees were also coming under attack.

In 1953, it was reported that some European trees appeared to be resisting the pathogen[6]. Later, it was found that this resistance was due to infection by hypovirulent fungus strains[7]. Hypovirulent strains were also discovered in America in 1976[5]. These strains cause cankers that develop very slowly and do not kill the host; they also form many fewer spores than virulent strains[8]. The hypovirulence trait is horizontally transmissible: when hypovirulent and virulent fungus strains come in contact, the virulent strain becomes hypovirulent[8].

The factor responsible for hypovirulence is a double-stranded RNA (dsRNA) found in the cytoplasm[9,10]. The mechanism by which it causes

Yannis Michalakis and Isabelle Olivieri are at INRA, Station de Génétique et d'Amélioration des Plantes, Centre de Montpellier, Domaine de Melgueil, 34130 Mauguio, France; François Renaud is at the Laboratoire de Parasitologie Comparée, CP 105, Université Montpellier II, Pl. E. Bataillon, 34095 Montpellier Cedex 5, France; Michel Raymond is at the Laboratoire de Génétique et Environnement, Institut des Sciences de l'Evolution, URA 327, Université de Montpellier II, Pl. E. Bataillon, 34095 Montpellier Cedex 5, France.

hypovirulence is still unknown, but transmission of hypovirulence always involves the transfer of dsRNA, while the removal of dsRNA always causes a reversion to virulence[11]. It is believed that dsRNA represents the genome of a defective virus that is unable to produce a capsid or a protein coat[11]. It passes from one strain to another during hyphal anastomosis. Hyphal anastomosis is controlled by vegetative compatibility between the anastomosing fungal strains. However, vegetative incompatibility is not a perfect barrier to dsRNA transmission[12,13].

An explanation for the establishment of hypovirulence can be advanced, by viewing the dsRNA as a parasite of *Cryphonectria parasitica* clones acting 'pleiotropically' in time. (The term 'pleiotropic gene' is used to characterize any gene that acts on different characters in different ways. The characters can be, for example, fecundities or survivorships at different ages or in different environments.) A clone infected by dsRNA in the first phase of infection of a population of trees would have a very low fitness, since virulent clones grow faster. As infection of trees by the fungus advances, each tree carries more and more fungi. As a consequence, (1) tree population density decreases, and (2) virulent strains are more likely to co-occur with avirulent clones. On each tree, there is still individual selection for virulence (since virulent clones grow faster than avirulent ones). A process similar to the one involved in the interaction between myxoma virus and rabbits may then take place (see Ref. 14 for a review): clones not infected by dsRNA (virulent clones) are likely to kill their hosts before they have been transmitted to another tree (because tree density is low). Conversely, avirulent clones have much more time to disperse to another tree, since they do not kill the host (a mechanism similar to that proposed by Levin and Pimentel[15] to explain the evolution of intermediate virulence). Therefore, overall, avirulent clones would have a higher selective value than uninfected clones, or clones resistant to dsRNA.

This explanation is compatible with the natural establishment of hypovirulence in relatively small areas (Europe, Michigan[11]) where the conditions for selection of hypovirulence (i.e. low tree density) are met faster. Once the hypovirulent strains are established, the system is in theory temporarily invasible by any fungal strain resistant to dsRNA. If such a resistant mutant appeared, the fungus populations would increase until tree density decreased and the cycle would begin again. An equilibrium between susceptible and resistant strains could be maintained in theory, if the chestnut–fungus–dsRNA system behaved as a set of metapopulations[16], with selection acting in favor of virulent clones in young populations and in favor of hypovirulent clones in old populations.

However, the maintenance of a polymorphism between strains of different degrees of virulence is an open theoretical issue. Similar scenarios have been proposed to explain the existence of temperate bacteriophage[17–19] in phage–bacteria interactions, as well as the evolution of apathogenicity in newt trypanosomes[20]. Indeed, Stewart and Levin[19] suggest that coexistence of temperate and virulent bacteriophage is possible over a broad range of conditions, and Levin and Pimentel[15] too report cases where such polymorphisms are possible. Virulence polymorphisms have also been reported for the leishmaniasis of the great gerbil (*Rhombomys opymus*)[21]. On the other hand, models of the myxoma-virus–rabbit system show that such polymorphisms should not exist: a single strain of intermediate virulence is ultimately fixed, although the process of fixation may be very long[14,22,23].

The system would therefore behave like a three-level trophic web, with a host (the chestnut), a parasite (the fungus) and a hyperparasite (the dsRNA). In the above scenario, the dsRNA acts as a fungal gene that is pleiotropic in time, being detrimental to the fungus in the beginning of an infection but beneficial once the infection is well established.

Pleiotropy in time

Pleiotropy in time has mainly been studied as an explanation for the evolution of senescence. Among the various evolutionary theories that have been put forward to account for senescence, the pleiotropic theory is the only one that is well corroborated (see Refs 24 and 25 for a review). For senescence to evolve, there must be genes with positive effects at some early age and antagonistic effects at a later age. These genes would affect either fertility or survivorship, or both.

The pleiotropic theory of senescence was clearly expressed by Medawar[26] and Williams[27]. Subsequently, several authors developed mathematical models to explore and assess their verbal arguments[28,29]. They showed that there is an inherent selection pressure favoring genes ('senescence genes') that are pleiotropic in the sense of improving reproduction (or survival) at early ages at the expense of reproduction (or survival) in old age; this tendency is enhanced in rapidly growing populations. Experimental results are in good agreement with this theory[24,25], and a direct test provided evidence for it[30]. Moreover, the first senescence gene identified in *Caenorhabditis elegans*[31] has exactly the pleiotropic properties predicted by Williams[27]: it increases early reproductive value and decreases late survival.

This theory could apply to any transmissible character that causes pleiotropy in time, in particular a character that is not encoded by the organism's own genes, for example a parasite. Obviously, host genes act physiologically in a very different way from parasites. Whenever we compare them, we refer only to their respective effects on the fitness of the host.

Classical host–parasite theory considers the parameters determining the outcome of the host–parasite interaction (i.e. parasite-induced host mortality, transmission, host recovery and host resistance to the parasites) as constant for a given genotype (in the sense that they are not subject to deterministic phenotypic variation). Recently Lundberg[32] showed that the host might, under certain conditions, develop an increased susceptibility at young ages for infections producing a lifelong immunity and having a detrimental effect

on adult reproduction when contracted by adults. In this way, increased mortality in the young can be compensated by a lessened detrimental effect on adult reproduction. The process results in a shift of the prevalence curve towards younger ages.

However, there are no well-documented examples of a parasite acting like a true 'senescence gene', i.e. one increasing the early reproductive value of the host and diminishing its later survival. A system composed of such a temporally pleiotropic parasite and a host susceptible to it would be uninvasible by any host resistant to the parasite. Indeed, the parasite–host couple acting in this way would be selected for in all growing or stationary populations, which compose the majority of the populations of any species. The only examples that come close to this situation concern the interactions between snails and schistosomes. Snails of the species *Biomphalaria glabrata* exposed to the schistosome *Schistosoma mansoni*, but not infected, have a higher early reproductive value than unexposed snails[33]. However, snails actually infected by the schistosomes have a lower early reproductive value and die much earlier than the two previous groups. Thus, the reaction of snails exposed to the parasites appears to be a plastic response to infection, rather than due to a pleiotropic action of schistosomes. An increase of early reproductive value is also shown by *Lymnaea stagnalis* individuals infected as subadults by the schistosome *Trichobilharzia ocellata*, although this increase is not shown by snails infected at the adult stage[34]. However, we lack the detailed demographic data on the effect of the schistosome on its host's survival with which to assess whether, in this case, the benefits of early infection in terms of reproductive value overcome the costs of parasitism.

Pleiotropy in space

Pleiotropy in space is caused by genes that confer high fitness in some places and low fitness elsewhere. This notion is similar to the term 'correlated outcomes', proposed by Thompson[35]. In Thompson's terms, 'the distribution of outcome in an interaction can therefore result from constraints and selection arising from other interactions affecting a population'.

By analogy, an arms race between hosts and parasites can also be avoided when parasites have a beneficial effect on their host in some localities while being detrimental in others, i.e. when their action is pleiotropic in space.

Examples of parasites that are beneficial to their host in one environment while being detrimental in a different environment come from the interactions of plasmids with their bacterial hosts. Plasmids often confer resistance to antibiotics and are therefore highly beneficial to their hosts in environments that contain antibiotics, while they are detrimental in antibiotic-free environments[17].

A spectacular illustration of a parasite that can eventually act like a spatially pleiotropic gene is given by the study of Smith[36] on the interaction of cowbirds and their avian hosts in Panama. Cowbirds of the species *Scaphidura oryzivora* are brood parasites of at least three species of oropendolas (*Zarhyncus wagleri, Psarocolius decumanus* and *Gymnostinops montezuma*) and one species of cacique (*Cacicus cela*). The host species nest in colonies. Smith followed numerous colonies for four years and classified them into two categories: (1) colonies in which hosts accepted cowbirds, and (2) colonies in which hosts were discriminating and did not accept alien eggs. In order to understand this difference between colonies, Smith studied the other important factors in host population dynamics and, particularly, mortality. Botflies (*Philornis* sp.), which lay their eggs on the chicks, are the main cause of mortality. The larvae burrow into the chick's body, and a chick with more than seven larvae usually dies. Oropendolas and caciques often cluster their nests near the nests of wasps and stingless but biting bees. This gives them good protection from vertebrate predators and for some unknown reason protects them from botflies as well, since in such nests chicks are rarely parasitized. Host birds nesting in such sites tend to discriminate their eggs from *Scaphidura* eggs.

Whenever colonies lack protection from bees and wasps, however, oropendolas and caciques do not discriminate alien eggs from their own. Nests with *Scaphidura* chicks are significantly less parasitized by botflies and produce the great majority of fledglings in such sites, while nests without parasitic chicks are very heavily infested by botflies. Evidently, *Scaphidura* chicks preen their nest mates and eat botfly larvae and eggs, while host chicks never show this particular behaviour. Thus, clutches without cowbirds do much better in colonies with bees and wasps, while all clutches with cowbirds have a much better fledgling production in colonies without bees and wasps. Not surprisingly, there is an optimum number of parasitic cowbirds that a host should accept. Thus, parasitic cowbirds are acting like pleiotropic genes, in that they benefit their hosts in colonies without bees and wasps by providing protection against parasitic botflies, while they are detrimental to their hosts' fitness in colonies with bees and wasps since protection against botflies is already available for the host. However, they do not act pleiotropically in time, as a 'senescence gene' would; rather, they act in space. This can explain why at a given time it is possible to find localities where the hosts have developed resistance against the brood parasite (i.e. discriminating colonies).

This example also illustrates that a causal link between performance in different environments is not necessary to avoid an antagonistic interaction between the host and the parasite. Cowbirds do not alter their behaviour; they have the same action whether the colony of their hosts is associated with bees and wasps or not. However, the hosts modify their behaviour and accept cowbirds in colonies without bees and wasps, leading to this 'correlated outcome' (*sensu* Thompson[35]).

Parasites can be useful to their hosts

In these ways (pleiotropic action in space or time) parasites can actually be useful to their hosts. Hence, parasites can avoid the evolution of resistance strategies by their host and escalation in an 'evolutionary arms race'.

However, one may wonder whether such situations are stable. Why are oropendola and cacique chicks unable to remove botflies from their nest mates, whereas cowbirds are? What would happen if this behaviour appeared some day in oropendolas?

A host's gene that could replace the beneficial action of the parasite without diminishing the host's fitness (e.g. a gene for preening behaviour in oropendolas and caciques, hypovirulence of *C. parasitica* in declining populations of chestnuts) would be strongly selected for. Such supergenes may not exist because of evolutionary constraints (*sensu* Antonovics and van Tienderen[37]). It should also be noted that systems with pleiotropic parasites are stable against resistant genes of the host (genes that would cause the host always to resist the parasite, without restoring the advantages brought by the parasite).

Certain biological systems are more prone to reveal pleiotropic parasites. Systems functioning as metapopulations[16] are potential candidates for polymorphism in virulence, since virulent genotypes are selected for in rapidly growing populations while moderately virulent genotypes are selected for in aged populations. On the other hand, systems in which the host and the parasite have recently come in contact and where the parasite is initially very virulent to its new host are likely to evolve towards a monomorphic state of moderate virulence. This moderate virulence may be due either to the establishment of resistant host genotypes or to the fixation of moderate parasite genotypes. This case is illustrated by the examples of the myxomatosis virus and the chestnut blight.

We need more studies on the effects of parasites on hosts of different ages. The examples available on the interaction of snails and schistosomes[33,34] are promising, since in both cases parasites increase the reproductive output of their hosts in early stages of the infection, even though these examples do not demonstrate that the parasites' effect is pleiotropic in time.

In conclusion, the pleiotropic effect of parasites can have a large influence on the outcome of the host–parasite interaction. It has been proposed that mutualisms have evolved from parasitism[35,38]. Pleiotropic parasites could well play the role of an intermediate stage in this process. This hypothesis has been confirmed by Bouma and Lenski[39], who studied a bacterium–plasmid interaction. The parasite (i.e. the plasmid, which in this case confers antibiotic resistance) has a pleiotropic-in-space action on its host (the bacterium). Indeed, the interaction is mutualistic in environments with the antibiotic and antagonistic in antibiotic-free environments. After 500 generations of experimental association, the relationship became mutualistic in both environments. It is thus conceivable that most mutualisms may have evolved from pleiotropic parasitisms, as illustrated by this last example.

Acknowledgements

Although for brevity there are only four authors, this paper is really the result of interactions with Thierry de Meeûs and Michael Hochberg. We would like to thank Judy Bronstein who overcame our spatial pleiotropy and helped us to clarify many of the ideas presented in this paper. We would also like to thank Mrs Berthelay-Sauret for help with the chestnut blight example. Richard Lenski and two anonymous reviewers made valuable suggestions. This work was supported by MEN (Ministère de l'Education Nationale) grant 90.76. YM was the recipient of an MRT (Ministère de la Recherche et Technologie) fellowship.

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