Opinion piece

Parasites—the new frontier: celebrating Darwin 200

To Darwin, parasites were fascinating examples of adaptation but their significance as selective factors for a wide range of phenomena has only been studied in depth over the last few decades. This work has had its roots in behavioural/evolutionary ecology on the one hand, and in population biology/ecology on the other, thus shaping a new comprehensive field of ‘evolutionary parasitology’. Taking parasites into account has been a success story and has shed new light on several old questions such as sexual selection, the evolution of sex and recombination, changes in behaviour, adaptive life histories, and so forth. In the process, the topic of ecological immunology has emerged, which analyses immune defences in a framework of costs and benefits. Throughout, a recurrent theme is how to appropriately integrate the underlying mechanisms as evolved boundary conditions into a framework of studying the adaptive value of traits. On the conceptual side, major questions remain and await further study.

Keywords: parasitism; evolution; virulence; ecological immunology

1. INTRODUCTION

For Darwin, the sometimes strange and spectacular lives of parasites were good examples to illustrate the powers of natural selection. But it remained by and large with J. B. S. Haldane (Haldane 1949) and W. D. Hamilton (Hamilton 1980) to bring parasites back as a key to many problems that Darwin and his followers could not solve satisfactorily. Over the last two or three decades, the study of how parasitism selects for very diverse host traits has been one of the most active areas in evolution and ecology (table 1).

Even though not all outstanding questions have and can be solved by invoking parasites, why should parasites be so important as selective factors? A number of points have been raised. Parasites are numerous and typically have shorter generation times than their hosts, they interact at close range physiologically, genetic variation in both parties has a strong effect, and the arms race is asymmetric. These factors contribute to the strength of selection by parasites but might also pertain to predators. Perhaps more importantly, parasites cut deep into the problem of self versus non-self identities, as parasites need to be accepted or tolerated as ‘self’ by the host to extract resources. Distinguishing self from (dangerous) non-self can be non-trivial, such as when dealing with a virus. Indeed, a wide range of parasite tactics to gain acceptance as host self, from mimicry and subversion of the defences, to coercion of the host that lacks any

alternatives is known. The self versus non-self distinction is certainly one of the deepest divides in the organismic world and one that characterizes life more generally. Not surprisingly, host defences against parasites through the immune system, are among the most complex molecular-biochemical machineries known, probably selected for robustness against parasite manipulation (Bergstrom & Antia 2006).

2. WHAT HAVE WE LEARNED?

A large number of insights would not have been gained without explicit consideration of parasites (table 1). Interestingly enough, parasitologists were not really at the cradle of this modern field of evolutionary parasitology (if we may call it that way). For example, illustrations of absurdly complex parasite life cycles are not lacking in any textbook of parasitology (Cheng 1986), but these cycles are taken as provided. It remained for behavioural ecologists borrowing concepts from life-history theory to develop a deeper understanding of their adaptive value—adding hosts to your life cycle allows growing further and becoming more fecund (Parker *et al.* 2003). This might also explain why such life cycles are found in parasites that can grow as individuals and not in organisms such as viruses and bacteria.

A good part of evolutionary parasitology therefore has grown from questions in behavioural and evolutionary ecology (table 1). In the process, the study of immune-defence strategies has become a field of its own, starting from questions about trade-offs to modern ecological immunology (Sheldon & Verhulst 1996; Schmid-Hempel 2003). A second major input has its origin in the work of ecologists, population biologists and geneticists wondering, for example, about parasite virulence (Anderson & May 1982) or community organization (Burdon & Leather 1990). Querying the adaptive value of sexual reproduction, something that Darwin considered in a different framework (Darwin 1868), is an instructive example of how a long-standing question is reconsidered in the new light of parasitism and where the different origins motivating the study of parasitism still leave their mark in today’s discussions. Epitomized by the Red Queen hypothesis, sexual reproduction (and meiotic recombination that goes along with it) is considered an adaptive strategy to genetically outrun rapidly coevolving parasites (Hamilton 1980). Although behavioural/evolutionary ecologists rapidly endorsed this idea (Peters & Lively 1999), population geneticists remained sceptical or at least advocated a plurality of mechanisms (Otto & Nuismer 2004). The topic also shows that empirical evidence to settle the questions is often hard to come by and—compared with the burgeoning theories—still much too scarce for most major questions.

3. A RECURRENT THEME: MECHANISMS AND FUNCTIONS

Classical parasitology assumed that a well-adapted parasite does not kill its host so as to preserve its own resource basis—a concept that still seems to dominate thinking in some quarters (Zinkernagel & Hengartner 2001). The evolutionary theory of

Table 1. An increasing focus on parasitism.

research field	topic in focus	reference, example
ecological immunology	immune defence is costly and traded off against other fitness components	(Schmid-Hempel 2003)
animal behaviour	host behaviour is rigged by parasites in own favour; host behaviour as defence	(Moore 2002)
sexual selection	female choice by selection through parasites	(Hamilton & Zuk 1982)
reproductive systems: sex	sex and meiotic recombination as strategies to escape coevolving parasites	(Hamilton 1980)
reproductive systems: polyandry	female multiple mating to genetically diversify offspring as defence against parasites	(Baer & Schmid-Hempel 1999)
life history	changes in life history owing to parasite manipulation or to limit fitness loss for host	(Sorensen & Minchella 2001)
population biology: regulation	parasitism determines population dynamics	(Hudson <i>et al.</i> 1998)
population biology: sex ratios	sex ratios manipulated by vertically transmitted parasites	
invasion biology	invasion success affected by presence of parasites	(Prenter <i>et al.</i> 2004)
community ecology	parasites as factors that structure ecological communities	(Price <i>et al.</i> 1986)

virulence (Anderson & May 1982; Ewald 1983), by contrast, is focusing on different elements of parasite fitness, such as growth and survival within the host (affected by virulence, which is a side effect of resource extraction) and fecundity (given by transmission probability). In this way, virulence affects parasite fitness and should be under selection. Furthermore, virulence can neither decrease nor increase without bound, since too little virulence would waste opportunities to grow and too much virulence would curtail the survival of the parasite by killing the host prematurely. Such evolutionary trade-off concepts have become a key to understanding variation in parasite virulence but typically ignore the underlying mechanisms.

Indeed, the theory has been successful in only a subset of all problems, notably those where a change in the external conditions occurs (e.g. a change in transmission opportunities) and where the parasite responds by changing its virulence. But why are closely related parasites of vastly different virulence (e.g. *Bacillus anthracis* versus *Bacillus cereus*), or why is a newly invading parasite sometimes virulent and sometimes not (Frank & Schmid-Hempel 2008)? Taking into account the mechanisms underlying 'virulence'—the mechanisms of pathogenesis—enables a more comprehensive theory. In particular, parasite immune evasion—which causes pathogenic effects—embedded in a life-history framework suggests that evasion to extend the lifespan of the infection (avoiding clearance) is under stronger selection than evasion to increase transmission, and thus the evolution of virulence should primarily be shaped by the former (Frank & Schmid-Hempel 2008).

The example illustrates that in a field asking questions about adaptive traits, the underlying mechanisms will sooner or later become important. A lot of such work has been generated already, for example, with the immuno-competence handicap hypothesis of sexual selection (Folstad & Karter 1992). A problem that immediately arises is that a good deal of multi-disciplinary work is needed for such a research agenda, i.e. knowledge not only from

evolutionary biology and ecology but also from physiology, biochemistry, molecular biology or immunology. This requirement remains a major challenge for the future of the field and one that does not go away easily, since collaboration with researchers in other fields is always a rough ride and the more integrative thinking characteristic for evolutionary biology is not always favoured by modern funding schemes and research programmes.

4. ISSUES UNTOUCHED

Evolutionary parasitology has been a success story of the last two decades but major issues are still untouched. For example, we might wonder, if the immune system is so complex and can recognize almost anything, why are there still so incredibly many different parasites? Many studies have given evidence for specific interactions and in many cases the molecular details of the interaction are understood. But what limits the range of evolved possibilities in each case? For example, new influenza epidemics may occur when the novel viral strain hits a 'hole' in the immune space of the host (Wikramaratna & Gupta 2009), but what determines these 'holes'? Similarly, the past years have seen an enormous advance in our understanding of the innate immune system of invertebrates, suggesting that it is capable of mounting complex defences similar to the more charismatic adaptive immune system (Du Pasquier 2005). So, why did the latter evolve at all? More generally, why are there so many different systems of defence? It is indeed a striking observation that in some host–parasite systems only a few major genes are important, whereas many genes are involved in another. Moreover, different combinations of host lines and parasite strains, even of the same species, leave their marks in apparently different genes being recruited for the interaction (Wilfert & Schmid-Hempel 2008). Why all this diversity in the genetic architecture of the interaction? Furthermore, might variation in gene expression rather than the variation in the genes themselves be the key to

the outcome of a host–parasite interaction (Xu *et al.* 2005)? When would an expression-based system evolve and what would be its evolutionary consequences for the host–parasite interaction? Vice versa, one might wonder what limits the range of strategies that parasites have? For example, why do not all parasites use different transmission routes? Also, given that parasites are so ubiquitous, why do long-lived, large-bodied hosts even persist without being completely eliminated by parasites (Hamilton *et al.* 1990)? Would such constraints tell us something about the distribution of body sizes in living organisms? Can we understand the architecture of individuals better with parasitism in mind, i.e. the complexities of living organisms? What does it need to maintain a coherent individual, how complex and dynamic should the population of cells be that make up the body? Also the same questions could be asked for tightly knit societies like ants or corals. Even though the answers are still unknown, the questions at least suggest that parasitism structures our world much more than was appreciated even a few decades ago. Darwin would have been more than pleased with these developments.

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