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REVIEW

An overview of parasite-induced behavioral alterations – and some lessons from bats

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Summary

An animal with a parasite is not likely to behave like a similar animal without that parasite. This is a simple enough concept, one that is now widely recognized as true, but if we move beyond that statement, the light that it casts on behavior fades quickly: the world of parasites, hosts and behavior is shadowy, and boundaries are ill-defined. For instance, at first glance, the growing list of altered behaviors tells us very little about how those alterations happen, much less how they evolved. Some cases of parasite-induced behavioral change are truly manipulative, with the parasite standing to benefit from the changed behavior. In other cases, the altered behavior has an almost curative, if not prophylactic, effect; in those cases, the host benefits. This paper will provide an overview of the conflicting (and coinciding) demands on parasite and host, using examples from a wide range of taxa and posing questions for the future. In particular, what does the larger world of animal behavior tell us about how to go about seeking insights – or at least, what not to do? By asking questions about the sensory–perceptual world of hosts, we can identify those associations that hold the greatest promise for neuroethological studies of parasite-induced behavioral alterations, and those studies can, in turn, help guide our understanding of how parasite-induced alterations evolved, and how they are maintained.

Key words: pathology, defense, Umwelt, behavior, parasite manipulation.

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Introduction

The contest between parasites and their hosts began well before the evolution of mitochondria and will end only with the end of evolution itself. Host behavior is one manifestation of that contest. Using broad brushstrokes, we can create the general outline of the strategies employed by both sides; I have been asked to provide an overview of parasite-induced behavioral alterations for this issue and I will use that broad approach to review those strategies here. The details are harder to come by. They are clouded not only by what we do not understand but also by what we do not imagine.

Parasites and their hosts have some clear evolutionary assignments. In the case of parasites, they are under strong selection to get to a host, and once there, to use that host in a way that promotes the parasites' survival and reproduction. Likewise, we expect hosts to be under strong selection to avoid colonization by parasites; if they fail at this, they are under equally strong selection to minimize the negative fitness effects of parasites. All of these assignments can have behavioral consequences for hosts.

Host manipulation and behavior

Within this broad description we can find a wealth of detail; I reviewed much of that detail in a 2002 book (Moore, 2002), and will describe a fraction of it here. When we think of manipulative parasites, the challenge of getting to the host occupies much of our attention, although enhancing parasite survival and reproduction does not lag far behind. Indeed, what seems to be the earliest suggestion of parasite manipulation of a host was tied to possible trophic consequences. I hesitate to call this suggestion one about transmission, because in 1853, when Siebold [cited in Kagan (Kagan, 1951); see also Ahrens (1810), cited in Lewis (Lewis, 1977)] wondered whether the pulsating tentacles of snails infected with *Leucochloridium* might attract predators, the first trematode life cycle had yet to be discovered. Of course, *Leucochloridium* in snails is highly visible – the snails are said to crawl out into lighted areas, and the striped broodsacs pulsate; this visibility is something to keep in mind as I continue my brief review. *Leucochloridium* and its snail hosts can be difficult to keep in the laboratory and are patchily distributed in nature, so in the almost 200 years since its description by C. G. Carus in 1835 (see Kagan, 1952), both the ecological influence of the parasite and the mechanism by which it accomplishes its visibility have remained more of a puzzle than one might expect (see Casey et al., 2003).

There are many other examples of parasites manipulating intermediate hosts to take advantage of final host foraging behavior in transmission, and these have received more careful scrutiny. Indeed, this area of research has expanded from classic studies such as those of van Dobben (van Dobben, 1952), showing that in the field, cormorants were more likely to capture *Ligula*-infected roach, and those of Bethel and Holmes (Bethel and Holmes, 1977) (and references therein) on acanthocephalans, gammarids and ducks in the laboratory. It now encompasses a wide range of parasites and intermediate hosts, and poses a wide variety of questions, many of which are addressed in this volume.

Not surprisingly, given its implications for human health, one of the earliest clear demonstrations of the role of altered behavior in parasite transmission came from an arthropod vector, the flea. Bacot and Martin noticed that fleas harboring plague exhibited blocked proventriculi that limited their success in blood feeding (Bacot and Martin, 1914). By watching individual fleas, Bacot and Martin demonstrated that this blockage led to plague transmission. Since then, many arthropod vectors have been shown to suffer from parasite interference in hematophagy that could well increase

parasite transmission to vertebrate hosts; the parasites include a number of viruses, protists (including malaria), and filariid nematodes using a range of mosquitoes, sandflies, triatomids, tsetse flies, mites and more flies (reviewed in Moore, 1993; Moore, 2002; Lefèvre and Thomas, 2008). There seems to have been quite a bit of convergence across parasite taxa as they manipulated hematophagy across vector taxa. Mechanisms underlying this manipulation vary, ranging from interference with specific enzymes to mechanical blockage, but the resulting phenomenon is compromised vector feeding (e.g. Rogers and Bates, 2007). This may be a mixed blessing for the parasite. While the multiple probes that usually result from impaired feeding often mean that the vector feeds on more than one host, and might therefore infect more than one host, the impaired feeding may also mean that the inocula are small. This could compromise successful establishment of the parasite in the new host (Burkot et al., 1988). Substantially less is known about behavioral modifications involved in the return trip – that is, vertebrate-to-arthropod transmission – although outcomes such as altered blood characteristics, decreased defensiveness and even increased appeal of infected hosts have been studied (reviewed in Moore, 2002). The impaired defensive behavior in malarial mice may be seen as pathology, or it may be seen with at least equal sensibility as an adaptive strategy, because it occurs when the gametocytes are most infective and available to the vector (Day and Edman, 1983). Even that possibility can prove complicated; defensive vertebrate host behavior itself may increase transmission if a squashed vector means the parasite can enter the feeding wound [e.g. *Leishmania Mexicana* (Strangways-Dixon and Lainson, 1966)].

Finally, the successful dispersal of parasite propagules frequently involves host behavior; eggs and spores are not randomly strewn across the landscape. Thus, insect hosts to viral and fungal parasites frequently move to places where those propagules find favorable conditions for development and dispersal (see Moore, 2002), insect hosts of protists and mermithids undergo ‘false oviposition’ and deposit parasites in breeding areas (Egerter et al., 1986; Vance and Peckarsky, 1996), and intertidal gastropods liberating cercariae may move to areas that allow easier access to beach-dwelling second-intermediate hosts (Curtis, 1993). Horsehair worms compel their terrestrial hosts to enter water, and fungus-infected flies are fatally attractive to mates (Biron et al., 2005; Moller, 1993). One of the most spectacular dispersal mechanisms involves a fungal parasite of the 17 year cicada; the hyphae take over the abdomen, leaving the head and thorax functional and flying [Peck (1878), cited in Goldstein (Goldstein, 1929)]. The fact that hosts of fungal parasites often display a periodicity in their time of death raises questions about the potential adaptive consequences of time of day for some of the behaviors surrounding that event (Krasnoff et al., 1995).

Given the ubiquity of parasite-induced behavior, questions inevitably arise about the effects of these parasites on human behavior. Flegr (Flegr, 2013) and others (see also Webster et al., 2013) have made major inroads in this area using the *Toxoplasma gondii* complex, but as with most human behavioral research, we are hampered by our (reasonable!) inability to do experimental infections. Indeed, the absence of experimental infection plagues many studies, because natural variation in behavior may predispose some hosts to infection; these hosts will have behaved differently from other hosts prior to infection, and the fact that they behave differently afterward should not be attributed to parasites.

Considering the problem of experimental infection of humans, it occurred to Chris Reiber and me that the human immune system might well mediate at least some behavioral changes in humans, and therefore vaccination might be used as a proxy for infection. Following up on this idea, we found that participants in flu vaccination clinics were significantly more social in the 48 h following exposure than during 48 h pre-exposure; this increased social behavior was reflected in interactions with more people and participation in significantly larger groups (Reiber et al., 2010). Although we used the best interview methods available to gather these data, confirmation of the suggestion of increased sociability awaits the placebo study that we are currently proposing.

Once contact is made, the second evolutionary obligation of a parasite is to survive in or on the host and reproduce, and this challenge can also involve some modifications to host behavior. These modifications range from post-emergence manipulation by parasitoids (Brodeur and Vet, 1994; Eberhard, 2010) to modification of behavior prior to host death (Müller, 1994; Brodeur and McNeil, 1989). In other cases, a parasite that is using its host for dispersal, nutrients and reproduction is often under selection to minimize negative effects on its host that would interfere with those parasite priorities. In these cases, parasite and host interests can be similar and can produce superficially similar results; that is, these hosts are seemingly healthy and mobile. They are often not particularly fit, however, given the fact that one of the most dramatic and widespread manipulations that seems to favor parasite survival and reproduction in a host is that of reduced host fecundity and in some cases, host castration. There is a vast literature surrounding this topic, and the advantages to the parasite are often thought to be reallocation of host resources and enhanced host longevity (reviewed in Moore, 2002) (see also Kuris, 1974; Baudoin, 1975; Lafferty and Kuris, 2009). This, too, can involve behavior in ways that go beyond reproduction itself; by reducing cockroach (*Periplaneta americana*) male responses to female pheromones, the acanthocephalan *Moniliformis moniliformis* performs a kind of behavioral castration on its host (Carmichael et al., 1993).

Host defense and behavior

In addition to manipulation of hosts, parasites have profound effects on animal behavior in ways that are not manipulative – that is, they do not benefit the parasite. These involve the host viewpoint, evolutionarily speaking, and deserve brief mention here because our understanding of host behavior is remarkably incomplete without this perspective. If the parasite is under selection to find a host, survive and reproduce, then we cannot ignore the fact that the host is under selection to avoid parasites when possible, and if parasitized, to minimize the negative effects. The way that hosts do this often involves behavior. Indeed, Hart emphasized that the first line of defense against parasites is not the immune system, but the behaviors that allow animals to avoid exposure to parasites in the first place (Hart, 1990; Hart, 1994). Although we know that animals alter essential ecological activities under threat from parasitoids (e.g. Feener and Moss, 1990), and although many animals may insulate themselves from parasite propagules through behavioral means such as territoriality/xenophobia (Freeland, 1976), site-specific defecation (Taylor, 1954; Michel, 1955), mate selection and the like (see Moore, 2002), the majority of examples in this area deal with avoidance of ectoparasites, and include such drastic measures as moving away (including avoiding old nests), shifting habitats, adjusting posture, forming selfish herds (good for biting fly avoidance, bad for propagule avoidance) and lethal combat (swatting). The extent to which a given host is defensive may be influenced by size and activity patterns; smaller animals risk losing

a substantial proportion of their blood to hematophagous parasites, and all animals risk disease transmission if they are hosts to blood feeders (for a review, see Moore, 2002). As humans – large hosts with modern medicine and insect repellent at our disposal – we may not fully appreciate the challenge of ectoparasites. A study of howler monkeys puts things into perspective: the monkeys used more than 24% of their metabolic budget (less basal metabolism) to slap at flies or engage in other defensive movements, and executed over 1500 slaps in a 12 h resting period (Dudley and Mitton, 1990). Grooming is another parasite-inspired behavior that is both expensive and difficult to categorize. In some respects, it is avoidance of parasites that would otherwise engage the host; in other respects, it is a post-contact response. Either way, it is costly (Ritter and Epstein, 1974; Hart et al., 1992), but failure to groom is catastrophic (Clayton, 1991).

Once a parasite becomes established in a host, host behavior is also altered as the infected host reacts to the parasite in ways that minimize damage from the parasite. Again, this is not particularly manipulative – that is, it does not serve the parasite's interests – but it is a crucial part of the behavioral repertoire of a parasitized host. Hart argued that sickness behavior, especially behavior that is almost universal among febrile vertebrates, is an adaptive response to parasitism (Hart, 1988; Hart, 2010). Fever is an effective and almost universal defense; as discussed below, in the case of behavioral fever, this can easily be confused with manipulation because it involves a variety of conspicuous behaviors. Behavioral chills are less well known, but have been demonstrated in host–parasite associations involving trematodes and acanthocephalans, as well as conopid flies (reviewed in Moore, 2002). Self-medicating behavior has also been observed, and can result in unusual foraging bouts; sick animals may consume medicinal plants that are not part of the usual diet. This is well documented for chimpanzees (Huffman, 1997), but even caterpillars may profitably switch host plants if they are hosts to tachinid flies (Karban and English-Loeb, 1997). Plants can also be used as nest fumigants by both birds and mammals (Clark and Mason, 1988; Hemmes et al., 2002). Hart suggests that the pillars of medicine – quarantine, immune-boosting vaccinations, use of medicinal products, and caring or nursing – all have their parallels in the ways that animals behaviorally confront pathogens and parasites (Hart, 2011).

In sum, the field of parasite-induced behavioral alterations has come a long way since its beginnings. It has definitely gained traction since the 1980s, and now borders on 'fashionable' [see Moore for a selective history (Moore, 2012)]. It certainly piques public interest (e.g. McAuliffe, 2012)! However, when we dig below the increasing wealth of information and examples, we find that we are at a tantalizing but frustrating stage that is not uncommon in the process of scientific exploration: we know more than we understand. It is a time of reassessment, and I will address three broad areas among many that are worth considering as we consider the future.

Future considerations

Pathology and adaptation

First, we perhaps should question ideas of pathology and adaptation. Most people studying this phenomenon in the 1980s viewed behavioral outcomes of parasitism as reflections of one of three states: host-adaptive, parasite-adaptive or some 'side-effect' of 'pathology' (e.g. Jones, 1985; Minchella, 1985; Milinski, 1990; Moore and Gotelli, 1990). In an effort to avoid an over-simplified adaptationist approach (see Gould and Lewontin, 1979), there were well-justified calls for increased rigor in our interpretation of the survival value and fitness attributes of these behavioral changes, with more attention to their complexity (Moore and Gotelli, 1990; Horton and Moore, 1993; Poulin, 1995).

It is increasingly unclear whether behavioral effects can be so neatly sorted into three piles. For instance, 'summit disease' (elevation seeking), so common in insects infected with pathogens, is tantalizing in this regard. It can promote behavioral fever, a remarkably effective defense against many parasites, which can have narrower thermal tolerances than their hosts (e.g. Lackie, 1972). It is also commonly thought to lead to increased conspicuousness and predation. But then again, perhaps it helps disperse airborne parasite propagules? Depending on the parasite involved, any of these interpretations could signal benefit to one of the participants. Many, if not most, of the associations in which this alteration appears are not particularly amenable to laboratory work or to transmission studies, and we are left with ambiguity (Horton and Moore, 1993; Moore, 2002).

In addition, for those who study this sort of thing, there can be disturbing variation during the course of infection in an individual host. For example, houseflies (*Musca domestica*) infected with *Entomophthora muscae* can survive and eliminate the fungal parasite if they access warm enough temperatures during the first 3 days of infection, and infected flies seek warmth during this phase. The absence of such a cure changes the beneficiary of altered behavior and promotes fungal success; the fly moves into cool areas where fungal spore formation is favored (Watson et al., 1993).

Clearly, there are some problems with the three explanatory piles of host benefit, parasite benefit and pathology. Even if we consider only behavioral fever and elevation seeking, it is apparent that difficulties abound when assigning host–parasite associations to the appropriate pile; it is often difficult to know which pile reflects the actual outcome, and whether the outcome is stable.

I wish to take this trichotomy one step further and shrink one of those piles considerably. The idea that altered behaviors are 'side-effects' of 'pathology' is a questionable explanation and should probably be discarded in the absence of clear evidence; that is, it should not be the default explanation for behavior, as it seems to be so often when other explanations are elusive. To illustrate, one of my favorite cautionary notes about invoking pathology as an explanation for altered behavior comes from the substantial literature surrounding the cestode *Hymenolepis diminuta* and the beetle intermediate host *Tenebrio molitor* (Webb and Hurd, 1999). Female beetles experience reduced fecundity when infected with the cestode. This could easily be seen as a pathological side effect were it not for the fact that Webb and Hurd discovered that the metacestode produces a substance that inhibits vitellogenin uptake (Webb and Hurd, 1999). Of course, perhaps the production of that 10–50 kDa molecule is itself some sort of side effect, but telescoping and extending the side-effect explanation in that way is not obviously productive.

It is possible that we inherit this idea of pathology-as-side-effect – the idea of pathology as something that is even unnatural – from historical biomedical thinking. In the days before Anderson and May (Anderson and May, 1978), the notion that parasites evolve toward avirulence was widespread and almost unquestioned (but see Ball, 1943). Anderson and May [(Anderson and May, 1992) and references therein] caused a sea change in the way we think about the evolution of virulence when they explicitly linked the outcomes of infectious disease to evolutionary theory: the outcomes of infection by parasites are subject to natural selection, and

whether a host–parasite association becomes more or less virulent depends largely on fitness outcomes for participants in that association. If we see parasite-induced behavioral alterations as among those outcomes, then those alterations are also subject to natural selection, and only rarely may be mere side effects of infection [a major point made by Moore; see especially pp. 57–62 (Moore, 2002)] (see also Lefèvre and Thomas, 2008). Of course, any evolution textbook will acknowledge the limits of natural selection – limits ranging from phylogenetic constraints to the very real inability to optimize everything in a heterogeneous environment! – but we are still left with a strong message: we ignore natural selection at our peril. In many respects, and certainly in the realm of behavior, host–parasite associations are neither host nor parasite – they are an amalgam that is profoundly different from what the host might have been in the absence of the infection (Combes, 2001; Moore, 1995; Moore, 2002), and the phenotype that they jointly present to the world, however shifting and conflicted, is subject to natural selection. Such a fluid, dynamic relationship is anything but the static list of characters that we often associate with 'phenotypes', and in many cases may not fit any default explanation.

Genetics and variation

Second, to invoke natural selection is to invoke some level of genetic contribution to the phenomena we study. Evidence for that is thin on the ground (but see Hinnebusch et al., 1996; Hoover et al., 2011), although not for lack of trying. I speculate that some of the reluctance to fund studies that address the genetic basis of parasite-induced behavioral change may reflect the widely held (and erroneous) notion that these changes are 'abnormal' and 'pathological'.

Most of the evidence that exists for a genetic contribution to parasite-induced behavioral changes comes from strain differences (e.g. Yan et al., 1994; Franceschi et al., 2010) (see also Leung et al., 2010). Indeed, strain formation itself is a bugaboo for experimenters who maintain animals in the laboratory. For instance, mosquitoes brought into the laboratory often undergo a severe bottleneck, with early mortality reaching 95%. In addition, although some systems exhibit little variation in parasite effects on a given host behavior (see Bethel and Holmes, 1973), others may exhibit considerable variation (see Thomas et al., 2011). This is reasonable: if uninfected hosts vary in their behaviors, which is frequently the case, the way in which they are modified by parasites could also vary (Moore, 2002). As with all behaviors, some of the variation is probably due to genetic variation and some may come from environmental sources. Learning more about the relative contributions of genetics and environment to parasite manipulation will reveal much about the variation that is inherent in many of the systems that we study. In the meantime, we know that a parasite's effect on behavior can be influenced by such diverse attributes as host sex (Gotelli and Moore, 1992), method of exposure (Draski et al., 1987), and the age of the parasite or the host (Dolinsky et al., 1985; Poulin, 1993). Geographic variation has also been documented (e.g. Seidenberg, 1973; Pilecka-Rapacz, 1986; Lobue and Bell, 1993). In addition, host physiology itself will set limits on what can be modified. For instance, *Plasmodium berghei* does not alter probing in *Anopheles stephensi*, quite possibly because the mosquito has naturally low levels of salivary apyrase that are not amenable to further diminution by a parasite (Li et al., 1992). Variation in host–parasite interactions comes from many sources, underlining the importance of understanding more about the genetic basis of these interactions.

Trapped in Umwelt

Finally, consider the fact that the vast majority of what we perceive as behavioral alterations are highly visible changes (e.g. *Leucochloridium*). These include changes in color, the addition of stripes and spots, changes in elevation (usually more exposed locations), changes in activity levels (mixed), changes in size (usually bigger) and the like (Moore, 2002). Parasite-induced changes that are not primarily visual are uncommonly reported, and for good reason: humans are highly visual animals, and most of the things we notice are things that we see. Most animals, however, do not depend so much on vision, or if they do, the ways in which their visual systems work may not resemble ours. If we want to appreciate the full scope of how parasites change their hosts, and in the case of manipulation, if we want to understand the kind of information they put out into the world, we need to do that impossible thing of crawling into the skin of another species and – here we resort to visual terminology again – seeing the world through another species' eyes.

It may be impossible to overstate the extent to which humans are visual. Our use of words, at least in English, is revealing. We say, 'Oh, I see', when we mean, 'Oh, I understand'. We claim to see (or not see) differences in political philosophies. We chat about vacation plans with friends and then ask (about a plan that has no concrete representation), 'How does that plan look to you?' And yes, seeing the world through another's eyes is our ultimate statement of empathy and understanding.

Our discoveries of parasite-induced changes that are not related to the visible light spectrum are few in number. They include the fact that parasites alter the sounds that some flying insects make (e.g. Lundberg and Svensson, 1975; Wulker, 1985) and alter the odors emitted by game birds (Hudson et al., 1992). Sometimes these discoveries are serendipitous. For instance, the cecal nematode *Trichostrongylus tenius* is famous among ecologists and parasitologists as the parasite involved in population cycles in its host, the red grouse, *Lagopus lagopus* (Hudson et al., 1992). This was first noticed during attempts to control predators; as predator pressure decreased, *T. tenuis* burden increased. Hudson and co-workers found that dogs could find infected birds more rapidly than they could locate uninfected ones. The dogs were much more sensitive to odor than the human scientists were, and their discriminatory ability revealed that heavier infections of *T. tenuis* are associated with an inability of the host to control cecal odors and a concomitant inability to avoid predators with keen olfaction. It is interesting to note that if the grouse served as an intermediate host, this odor might be viewed as manipulation. The grouse is not an intermediate host, the life cycle is direct, and manipulation has not been suggested. Because the condition occurs most notably in high-intensity infections, and because high-intensity infections come about when too many near-microscopic (and passive) *T. tenuis* dauerlarvae are consumed in too short a time period, there may be few pathways by which natural selection on the parasite or host can moderate this result. This example reminds us that although thoughtless acceptance of pathology as an explanation of parasite-induced behavioral change is ill advised, an automatic lurch into adaptationism is equally fraught.

One exception to our general disregard for parasite manipulation of chemical signals can be found in work with aquatic intermediate hosts; in these systems, altered reactions of parasitized intermediate hosts to predator-conditioned water are widespread (e.g. Thünken et al., 2010; Perrot-Minnot, 2007; Benesh et al., 2008; Baldauf et al., 2007); there are terrestrial examples of this fearlessness, and even attraction to predators, as well (Kavaliers and Colwell, 1995;

Berdoy et al., 2000). This is not, however, the same phenomenon as one involving parasites that alter host odor itself.

Upon reflection, altered host odor seems a likely effect of parasites. After all, evidence is mounting that animals with strong olfactory sensibility can detect a variety of human diseases (e.g. Ehmann et al., 2012; Willis et al., 2004). The vertebrate major histocompatibility complex (MHC) provides a logical connection between the immune system and odor (Kwak et al., 2010). If one avenue of manipulation is the co-option by parasites of host defenses, then the immune system itself may prove to be fertile ground for future explorations of manipulation, including manipulations that are not immediately apparent to highly visual mammals.

This brings us to the idea of Umwelt, a central concept in animal behavior. Umwelt is a word suggested by Jakob von Uexkull over 100 years ago that has come to mean the sensory–perceptual world of an animal (see Breed and Moore, 2012; Ruting, 2004). Uexkull used the example of questing ticks to illustrate his concept. He noted that the ticks used three cues to guide them to their food – butyric acid, warmth and hair, in that order. Other surrounding environmental features may not even be perceived. We may be sitting next to a tick, we may be hosting one for its dinner, but the tick and the human do not inhabit the same sensory–perceptual world.

If we apply this concept to our work with parasite manipulation, then our first task may be to penetrate, as much as possible, the Umwelt of the hosts that we are studying. For instance, if manipulation is an adaptation for transmission in predator–prey life cycles, then understanding (as much as possible) the Umwelt of the predator–host that is likely to consume the manipulated host may well suggest manipulations that differ from those that humans normally notice. This may seem obvious (and near hopeless), but it is in the arena of Umwelt that mechanism may have a remarkably predictive role to play. Consider that in our brief history as students of manipulation, the search for underlying mechanisms has followed a description of manipulative phenomena; these discoveries and descriptions have been centered on our own visual skills and bias. However, an understanding of the sensory capabilities of a potential final host may help us predict what traits of the intermediate host are likely to be manipulated, and in so doing, may cause us to explore behavioral nooks and crannies that could be otherwise ignored.

A lesson from bats

The history of what we know about bat echolocation, while not addressing manipulative parasites, can perhaps reinforce this suggestion. It is an excellent example of reaching (or in some cases, refusing to reach) beyond what humans can sense. A refusal to consider the possibility that the Umwelt of bats is vastly different from our own caused some of the most famous biologists of their day to discard evidence in favor of their own imaginings. This story is clearly recorded, and it stretches across hundreds of years. It demands that we wonder about the vast array of changes in hosts, induced by parasites, that we do not sense. It demands that we consider host Umwelt in our exploration of parasite manipulation of behavior.

Most of the history that I report here is from an account by Robert Galambos (Galambos, 1942), who, along with Donald Griffin, discovered how bats avoid obstacles while flying. As part of his doctoral dissertation on this subject, Galambos translated the letters of Lazzaro Spallanzani into English. Spallanzani was an 18th century Italian Catholic priest and biologist who discovered that bats use their ears while navigating. The letters record his experiments, and those of others, as they do a variety of experiments with bats – blinding them, covering their heads with hoods, sealing their ears – and observe the outcomes, often including differences between treated and control animals. When Spallanzani observed the flight of blinded bats, it was clear to him that vision was not essential to their dexterity in the air. What sensory system the bats did use was much less clear to him. The first candidate was tactile sensation. Spallanzani did several experiments that showed that a sense of touch was not an adequate explanation for the bats' behavior. Perhaps the most unusual was his decision to coat the blind bat with varnish – and later with flour paste! – neither of which interfered with the bat's ability to avoid silk threads, much less larger obstacles.

Galambos (Galambos, 1942) quotes Spallanzani: '…in the absence of sight there is substituted some new organ or sense which we do not have and of which, consequently, we can never have any idea'. Galambos [see p. 135 of Galambos (Galambos, 1942)] surmises, 'He [Spallanzani] apparently could not believe hearing was involved since he himself heard no sounds as the bats flew'. Mystified, Spallanzani proposed a sixth sense, as yet undiscovered and not found in humans. Meanwhile, Louis Jurine repeated some of Spallanzani's experiments and concluded that bats needed to use their ears if they were to avoid obstacles. His was the first clear statement of what became 'the ear hypothesis', a hypothesis that Spallanzani himself quickly and clearly embraced, abandoning his briefly held sixth-sense suggestion.

Unfortunately, the rest of the world did not embrace this shift, or perhaps did not even know about it – in part quite possibly because none other than Georges Cuvier, in rejecting the sixth sense, revived the touch hypothesis. He supported this idea with a combination of sarcasm and the weight of his own reputation; he did no experiments. The result was that throughout the 19th century, bats were said to navigate by touch, a result of wing membranes that were richly supplied with nerve endings capable of sensing many attributes of air that would be disturbed during flight. Galambos suggests several reasons for this intellectual detour, ranging from Cuvier's fame to some unusual aspects of bat anatomy, but notes that ignorance of the nature of sound – especially the sound that humans cannot hear – played a big role in scientists' stubborn refusal to consider the evidence before them: blinded bats could avoid obstacles with as much dexterity as seeing bats could, deaf bats crashed into almost everything.

Galambos goes on to catalog the increasing, if largely unrecognized, evidence for the ear hypothesis during the 19th and early 20th century (Galambos, 1942), but our current understanding awaited two technological advances that would take scientists beyond normal human Umwelt. G. W. Pierce invented a parabolic ultrasonic detector that he and Donald Griffin, then a Harvard undergraduate with an interest in bats, used to show that bats could emit ultrasound. In graduate school, Griffin met Robert Galambos, who was recording cochlear microphonics from guinea pigs. They collaborated to show that bats emitted ultrasonic sounds and avoided obstacles by hearing the echoes of their own cries. According to Griffin [cited in Gross (Gross, 2005)], 'Radar and sonar were still highly classified developments in military technology, and the notion that bats might do anything even remotely analogous to the latest triumphs of electronic engineering struck most people as not only implausible but emotionally repugnant'. Both Griffin and Galambos went on to stellar careers and demonstrated similar courage in stepping forth with other suggestions that initially aroused strong skepticism but that were later accepted: Galambos (Galambos, 1996; Galambos, 2007) in his

emphasis of the importance of glial cells, and Griffin (Griffin, 1976; Griffin, 1998) in his foundation of the field of animal cognition.

The reason that I include the account of the discovery of bat echolocation here is not merely because it is a fascinating story, and not because both Griffin and Galambos were such good writers that I could hardly tear myself away from their tale, although both are true. What matters about this story in the context of parasites and behavior is that it epitomizes what I suspect is an unavoidable conflict between science as we see it and Umwelt. For 150 years, experimental evidence about bat echolocation was no match for human refusal to accept what could not be heard. More than that, what could not be heard turned out to be everything that mattered, everything that was necessary to understand bat navigation.

It is true that we have discovered truckloads of manipulative parasites, changing everything from host color to host activity, altering host elevation, modifying host responses to light, heat, and predators themselves, to name a few targets of manipulation. Yet, for many animals involved in these life cycles, color perception differs from ours, flicker-fusion differences and retinal organization may alter the perception of activity, and for that matter, circadian rhythms and nocturnal activity may make our own observations irrelevant. It is widely hypothesized that chemosensation was the first stimulus–receptor sensory ability to evolve, simply because the earliest metabolic activity had to result in chemical signals, a potential boon for early heterotrophs. Given the antiquity of the parasitic habit, altered host odor is an obvious candidate for manipulation. Altered sound is another target. Sound can be perceived in the absence of light and amid physical obstacles, as can odor.

Given these possibilities, how can we fail to wonder what manipulations we are missing in this wide world of information that lies just beyond our own senses? Such exploration could require some creativity and patience, but it is not doomed, any more than our understanding of bee vision, infrasonic elephant communication, or red grouse cecal odor was doomed. Without such exploration, however, we are likely to miss the majority of parasite manipulation. To borrow from a book title by Donald Griffin (Griffin, 1959), we could do worse than learn to listen in the dark.

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