



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

When offered a choice, mosquitoes preferred to take bloodmeals from membrane feeders filled with human red blood cells combined with the supernatant from cultured trophozoite and gametocyte-stage parasites over blood cells alone. Amazingly, they found that they could get a similar increase in the level of attraction to red blood cells when the cells were spiked with HMBPP alone. When the volatiles produced by red blood cells alone, in combination with the supernatant from gametocyte-infected cells, or combined with HMBPP, were measured, Emami *et al.* observed an increase in CO<sub>2</sub> emissions, aldehydes, and monoterpenes. When these volatiles were combined with CO<sub>2</sub> they were able to reproduce the attraction response. These results indicate that the HMBPP produced by the parasite during blood-stage infection in the vertebrate may increase the attraction of mosquitoes to infectious hosts.

Once mosquitoes reached the feeders, further effects on mosquito feeding and engorgement were observed. A female approaching an HMBPP-spiked bloodmeal was more likely to engorge compared with females approaching feeders containing only red blood cells. This increase in engorgement rates was similar to those found in females offered bloodmeals containing blood-stage malaria parasites. Convincingly, the proportion of females engorging could be manipulated by altering either the concentration of gametocyte-stage parasites in the blood meal or the concentration of HMBPP alone. Females feeding on HMBPP feeders took larger bloodmeals and were more likely to be successfully infected with a higher titer of malaria parasites at both the oocyst and sporozoite stages. These changes in susceptibility to parasites may be related to changes in the transcription of several immune factors measured in these females.

While these changes in attraction preference and blood-feeding behaviour would greatly benefit the parasites by getting

mosquitoes to feed on infectious hosts, their effects on the mosquito seemed to be neutral. While only a single clutch of eggs was measured, there was no effect of HMBPP on the number of eggs laid by females or their subsequent survival.

This study is the first to implicate a specific parasite factor responsible for causing increased attraction to infectious hosts. Many of the assays executed in this study were made possible by using an artificial membrane system. It will be important going forward to confirm that HMBPP has similar effects when circulating in entire hosts. Encouragingly, the membrane system used here did replicate some aspects of work with living hosts. For example, work in mice [1] has shown that the increased attraction to infected mice was also correlated with periods of infection with higher gametocyte intensity. The effect of these changes in bloodmeal preference feeding behaviour in mosquitoes needs to be further investigated. While fecundity and survival were not affected, these related parameters were measured in separate individuals. Utilizing more complete measures of mosquito fitness may clarify the effects of altered feeding and immune gene expression on females [8]. As always is the case with laboratory-based studies, it will be important to confirm that these results are true in field-derived strains under natural conditions.

Despite these remaining questions, this study contributes an important piece of the puzzle of how malaria may maintain transmission against seemingly unlikely odds. While recent work on how parasites may alter mosquito feeding behaviour after infection has cast the parasite in a more passive role, this study indicates that when it comes to infecting mosquitoes in the first place, malaria parasites are playing an active role.

<sup>1</sup>Grand Challenges in Ecosystems and Environment, Department of Life Sciences, Imperial College London, Silwood Park, Ascot, UK

\*Correspondence: l.cator@imperial.ac.uk (L. Cator).

<http://dx.doi.org/10.1016/j.pt.2017.03.003>

#### References

1. De Moraes, C. *et al.* (2014) Malaria induced changes in host odors enhance mosquito attraction. *PNAS* 111, 11079–11084
2. Cornet, S. *et al.* (2013) Both infected and uninfected mosquitoes are attracted toward malaria infected birds. *Malaria J.* 12, 179
3. Lacroix, R. *et al.* (2005) Malaria infection increases attractiveness of humans to mosquitoes. *PLoS Biol.* 3, e298
4. Batista, E.P. *et al.* (2014) *Anopheles darlingi* (Diptera: Culicidae) displays increased attractiveness to infected individuals with *Plasmodium vivax* gametocytes. *Parasit. Vectors* 7, 251
5. Cator, L.J. *et al.* (2012) Do malaria parasites manipulate mosquitoes? *Trends Parasitol.* 28, 466–470
6. Emami, S.N. *et al.* (2017) A key malaria metabolite modulates vector blood seeking, feeding, and susceptibility to infection. *Science* Published online February 9, 2017. <http://dx.doi.org/10.1126/science.aah4563>
7. Lindberg, B.G. *et al.* (2013) Immunogenic and antioxidant effects of a pathogen-associated prenyl pyrophosphate in *Anopheles gambiae*. *PLoS One* 8, e73868
8. Ohm, J.R. *et al.* (2016) Fitness consequences of altered feeding behavior in immune-challenged mosquitoes. *Parasit. Vectors* 9, 113

## Forum

# Stress Hormones Bring Birds, Pathogens and Mosquitoes Together

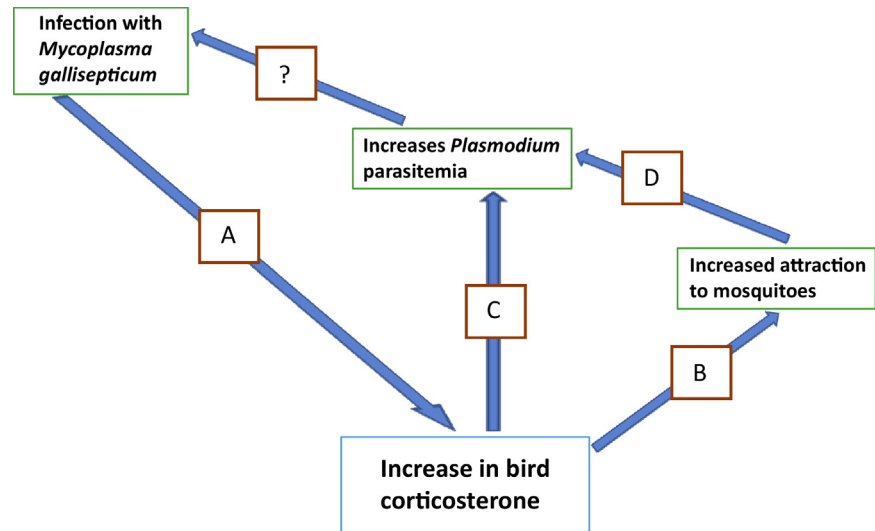
André A. Dhondt<sup>1,\*</sup> and Andrew P. Dobson<sup>2</sup>

**Do stress hormones, such as corticosterone, enhance bird susceptibility to mosquitoes in ways that enhance rates of co-infection? Does this then enhance pathogen emergence?**

Interactions between pathogens are often mediated by the immune system of the host [1]. Two recent experimental papers suggest that interactions between the immune system and corticosterone are important in mediating synergistic interactions between pathogens that enhance rates of co-infection

in birds. As part of a long-term study of the effect of the bacterial pathogen *Mycoplasma gallisepticum* on the house finch *Haemorrhous mexicanus*, Dana Hawley and her team investigated the extent to which stress hormones that are important for energy mobilization and regulation of the immune system are influenced by experimental infection with *M. gallisepticum* [2]. They found that corticosterone levels increased after house finches were infected with *M. gallisepticum*, decreased again to pre-infection levels once the infection was cleared, and that individuals with greater disease severity had the highest corticosterone concentrations. Trying to identify factors that influence West Nile virus transmission, Lynn Martin and his team started from the premise that stress hormones might represent a key link between individual levels of infection, population levels of parasite transmission, and zoonotic disease risk. They experimentally manipulated zebra finch *Taeniopygia guttata* stress hormones by implanting corticosterone-filled silastic tubules and examined subsequent feeding preferences, feeding success, and productivity of mosquito vectors [3]. Despite performing more frequent defensive behaviors against mosquitoes, birds with elevated stress hormone concentrations were approximately twice as likely to be fed on by mosquitoes compared with control birds.

If we combine these apparently unrelated studies with those carried out by Sylvain Gandon's group on avian malaria in domestic canaries *Serinus canaria* [4] and with an older experiment by Applegate on avian malaria in house sparrows (*Passer domesticus*) [5,6] things become quite interesting. Cornet *et al.* [4] asked to what extent variable relapse rates of birds with chronic *Plasmodium* infections would represent a plastic transmission strategy used by the parasite in fluctuating environments. They showed that, in domestic canaries



Trends in Parasitology

**Figure 1.** The Role of Corticosterone When a Bird Is Co-infected with the Bacterium *Mycoplasma gallisepticum* and the Protozoan *Plasmodium*. Arrows show causal relationships proven experimentally. Infection with *M. gallisepticum* causes an increase in corticosterone level (A) [2], making the bird more attractive to mosquitoes (B) [3], and causing an increase in *Plasmodium* parasitemia directly (C) [5,6] and indirectly (D) [4]. The question mark represents the hypothesis that *Plasmodium* infection in a bird increases the disease severity caused by *M. gallisepticum*, which would result in a positive feedback loop.

with chronic *Plasmodium relictum* infections, the parasite responded to the birds being bitten by mosquitoes by increasing its parasitemia and, hence, increasing its transmission probability. By contrast, while various authors have suggested that stress-related hormonal changes would increase hematozoan parasitemia [7,8], the effect of corticosterone on parasitemia had already been tested experimentally by Applegate, 45 years ago! While attempting to understand what drives the spring increase in *P. relictum* infection intensity in house sparrows with a chronic infection, Applegate [6] treated the birds with corticosterone; this resulted in an increase in *Plasmodium* parasitemia: a higher proportion of blood films had demonstrable parasites, and a higher proportion of erythrocytes was infected than in the control group. In a follow-up experiment, Applegate and Beaudoin [6] demonstrated that corticosterone and not gonadotropin caused the spring relapse in avian malaria.

In Figure 1, we summarize these findings by linking the observation that *Mycoplasma gallisepticum* infection causes an increase in corticosterone level (Figure 1A) making the bird more attractive to mosquitoes (Figure 1B), and increasing *Plasmodium* parasitemia directly (Figure 1C) and indirectly (Figure 1D). If the presence of *Plasmodium* in a bird were to increase the disease severity caused by *Mycoplasma gallisepticum*, then we would have a positive feedback loop. If this were confirmed experimentally, this would imply that the transmission success of both pathogens is enhanced by prior infection with the other pathogen. Could co-infection have contributed to the emergence and subsequent evolution of virulence of *M. gallisepticum* [9,10]? At first glance, co-infection cannot be beneficial to either parasite or to the host; if all else is equal, co-infected hosts should die faster than hosts with a single infection because they are experiencing two sources of pathology. Alternatively, the presence of

two pathogens may reduce the immunopathological effects of an overworked immune system and this may allow each pathogen to persist for longer in co-infected hosts. This could enhance either the transmission success of one or both pathogens or the colonization of a new host species by a novel pathogen.

Prior infection with one pathogen (the malaria parasite *Plasmodium*) may facilitate later infection with, and transmission of, another completely unrelated pathogen, the bacterium *M. gallisepticum*. A similar situation is the example of *Babesia microti* (a malaria-like parasite that infects red blood cells and is the cause of babesiosis) and *Borrelia burgdorferi*, a bacterium that causes Lyme disease [11]. Diuk-Wasser and colleagues showed how *Babesia* only successfully establishes in populations in which Lyme disease is already present. More subtly, these examples suggest that prior infections, such as malaria, or parasitic helminths, help facilitate the emergence of pathogens, such as Ebola, Nipah, Hendra, severe acute respiratory syndrome (SARS), or Zika virus. They also underline the previously underexplored potential role that co-infection interacting with host endocrine stress might have in mediating the emergence of novel pathogens. For example, pregnant mothers who are often immunologically stressed and have major upheavals in their endocrine system are more susceptible to mosquito bites [12]. Was this a significant factor in the emergence of Zika virus? To date, the role of endocrine and nutritional processes in the within-host dynamics of pathogens has been essentially ignored. However, it may prove to be an important missing link in many future studies of the emergence and subsequent coevolutionary dynamics of many host–parasite systems.

#### Acknowledgments

This work was supported by NSF grants DEB 0094456 and EF 0622705, and by NIH grant R01GM085232, all part of the Ecology and Evolution

of Infectious Diseases program. We thank Lynn (Marty) Martin and an anonymous referee for helpful comments.

<sup>1</sup>Laboratory of Ornithology, Cornell University, 159

Sapsucker Woods Road, Ithaca, NY 14850, USA

<sup>2</sup>EEB, Eno Hall, Princeton University, NJ 08540, USA

\*Correspondence: aad4@cornell.edu (A.A. Dhondt).

<http://dx.doi.org/10.1016/j.pt.2017.01.001>

#### References

- Graham, A.L. (2002) When T-helper cells don't help: immunopathology during concomitant infection. *Q. Rev. Biol.* 77, 409–434
- Love, C.L. et al. (2016) Changes in corticosterone concentrations and behavior during *Mycoplasma gallisepticum* infection in house finches (*Haemorrhous mexicanus*). *Gen. Comp. Endocrinol.* 235, 70–77
- Gervasi, S.S. et al. (2016) Host stress hormones alter vector feeding preferences, success, and productivity. *Proc. R. Soc. B* 283, 20161278
- Comet, S. et al. (2014) Evolution of plastic transmission strategies in avian malaria. *PLoS Pathog.* 10, e1004308
- Applegate, J.E. (1970) Population changes in latent avian malaria infections associated with season and corticosterone treatment. *J. Parasitol.* 56, 439–443
- Applegate, J.E. and Beaudoin, L. (1970) Mechanism of spring relapse in avian malaria: effect of gonadotropin and corticosterone. *J. Wildl. Dis.* 6, 443–447
- Valkiūnas, G. et al. (2004) Factors affecting the relapse of *Haemoproteus belopoluskyi* infections and the parasitaemia of *Trypanosoma* spp in a naturally infected European songbird, the blackcap. *Sylvia atricapilla*. *Parasitol. Res.* 93, 218–222
- Pollitt, L.C. et al. (2011) Competition and the evolution of reproductive restraint in malaria parasites. *Am. Nat.* 177, 358–367
- Osnas, E.E. et al. (2015) Evolution of Pathogen virulence across space during an epidemic. *Am. Nat.* 185, 332–342
- Hawley, D.M. et al. (2013) Parallel patterns of increased virulence in a recently emerged wildlife pathogen. *PLoS Biol.* 11, e1001570
- Diuk-Wasser, M.A. et al. (2016) Coinfection by *Ixodes* tick-borne pathogens: ecological, epidemiological, and clinical consequences. *Trends Parasitol.* 32, 30–42
- Ansell, J. et al. (2002) Short-range attractiveness of pregnant women to *Anopheles gambiae* mosquitoes. *Trans. R. Soc. Trop. Med. Hyg.* 96, 113–116

## Forum

# The Expanding World of Human Leishmaniasis

James A. Cotton<sup>1,\*,@</sup>

**New *Leishmania* isolates form a novel group of human parasites related to *Leishmania enrietti*, with cases in Ghana, Thailand, and**

**Martinique; other relatives infect Australian and South American wildlife. These parasites apparently cause both cutaneous and visceral disease, and may have evolved a novel transmission mechanism exploiting blood-feeding midges.**

*Leishmania* is a diverse and widespread genus of human pathogens that cause the neglected tropical disease leishmaniasis in South and Central America, Africa, Asia, and Europe. Their clinical diversity includes asymptomatic infections and symptoms ranging from localised ulcers to fatal infections. Cutaneous leishmaniasis (CL) appears when parasites remain in the skin, causing either localised symptoms at the site of insect vector bites, more widespread cutaneous disease (disseminated CL) or destructive mucocutaneous leishmaniasis (MCL). Systemic infections (visceral leishmaniasis; VL) occur when the parasites spread to other organs, in particular to the liver and spleen where they destroy immune cells. VL is generally fatal if not adequately treated.

One key to this clinical and geographic range is the biological diversity of *Leishmania*. Clinically important parasites are found in two clades – the new world subgenus *Viannia* and the subgenus *Leishmania* found in both the new and old worlds (Figure 1); the parasites largely responsible for VL are in *Leishmania*, while both groups contain parasites causing CL. The *Viannia* and *Leishmania* groups contain all the best known species, but only around 20 out of approximately 53 recognised species of *Leishmania* [1] are known to infect humans, and of these probably only 10 are of major public health importance. Other *Leishmania* species are much less well known: a basal group of *Leishmania* species known as *Paraleishmania* and a species called *Leishmania enrietti* infect wild mammals in South America. An unusual group (subgenus *Sauroleishmania*)