EVOLUTION

How the Malaria Parasite Manipulates Its Hosts

Looking at the malaria parasite through an evolutionary biologist's lens could yield better ways to fight the disease. That was the take-home message from two groups of researchers at the recent biennial meeting of the European Society of Evolutionary Biology in Arnhem, the Netherlands (24 to 28 August). These scientists' studies suggest that in its mosquito and mammalian hosts, the parasite, like all living things, behaves according to the rules of evolutionary theory—and its adaptations have consequences for human health.

Contradicting the long-standing belief that malaria doesn't harm its mosquito hosts, Jacob Koella from the University of Aarhus in Denmark and his colleagues showed that the parasite has evolved the ability to turn them into the insect equivalents of bloodthirsty Count Draculas. The mosquitoes—à la Bela Lugosi, vanting to suck your blood—aggressively seek more and more encounters, boosting the parasite's chances of being transmitted, but also increasing the insects' chances of dying in action.

In a mammalian host, too, the parasite is responding to evolutionary pressures, suggests Margaret Mackinnon of the University of Edinburgh in the United Kingdom, leader of the second team. Her findings fit largely untested theoretical models claiming that pathogens face an evolutionary trade-off that affects their virulence. The faster they replicate in the early stages of the disease, the more readily they can be transmitted. Too fast, however, and the host will die first.

Together, the studies show how evolutionary biology can open a new window on one of the oldest and most common of human diseases. "[Koella and Mackinnon are] taking the point of view of the disease organism—that it's something that evolves and has its own ecology," says Marlene Zuk, an evolutionary biologist at the University of California, Riverside. "And that's what's usually missing" in other approaches to malaria.

Until Koella's study, for example, researchers generally studied malaria-bearing mosquitoes only in the lab. There, the female *Anopheles* mosquito can survive for several months with the *Plasmodium* parasite living in her salivary glands and being transmitted. That lengthy period led scientists to believe that *Plasmodia* don't harm their insect hosts.

But Koella found otherwise. Studying mosquitoes in the wild in Tanzania with collaborators, including Edith Lyimo of the Ifakara Centre for medical research, he discovered that the infected insects have a shorter life-span than their caged counterparts. "Most mosquitoes die when they bite someone and are squashed [in response]," Koella says. It thus makes sense for a mosquito to keep its biting to a minimum.

It might also seem smart for the malaria parasite to want its insect host to behave with some restraint, as the longer the insect is alive, the more opportunities the parasite would have to be transmitted. But in fact, says Koella, the *Plasmodium* "wants the mosquito to bite as often as possible, in order [for the parasite] to be transmitted to as many hosts as possible."

To test this counterintuitive idea, Koella asked human volunteers (who had been screened for distinct genetic differences) to spend a night in a house in an area where malaria is rampant. In the morning, he collected 173 mosquitoes that had fed on the volunteers. Using the polymerase chain reaction technique, which distinguished the genetic patterns of each volunteer, his team was able to identify which sleepers each mosquito had bitten. Only 18% of the 111 uninfected mosquitoes had feasted on more than one person, compared to 34% of the 62 infected mosquitoes. "That suggests the mosquitoes are moving around much more when they are infected, something that epidemiologists should be taking into account," notes Andrew Read, an evolutionary biologist at the University of Edinburgh who is also working on malaria.

R. A. ANDERSON/UNIV. OF AARHUS

Pity the mosquito. Malaria makes it bite recklessly.

Koella speculates that the parasite alters the neurochemistry controlling the mosquito's abdominal stretch receptors, so that it bites insatiably. "If Koella is right," Read says, "then this is a fantastic demonstration of a parasite manipulating its host." Adds Kevin Lafferty, a parasitologist at the University of California, Santa Barbara, "He has broken that old paradigm about malaria not causing any pathology to the mosquito. And that's exciting, but it's also shocking to find such a big gap in our knowledge at this stage."

Another gap in understanding malaria is that there's no predicting how virulent the disease may be. "That variation has always been a puzzle," says Read, who works with Mackinnon. "You see kids who have been infected with the disease at the same time and with the same dose, and some are very ill, while others aren't." Clinicians often attribute such variation to the differences in human immune systems, say Mackinnon and Read. But the variation may also stem from genetic differences within the parasite that cause some strains to replicate at a higher rate and an earlier stage, possibly producing a more virulent—and more transmissible—form of malaria.

Such genetic differences could mean that natural selection controls the level of virulence, says Mackinnon, making "the parasite sufficiently nasty to its host to reproduce and get transmitted, but not enough to kill its host." The malaria parasite—like other pathogens—should thus evolve to an intermediate level of virulence. "It's one of the basic tenets of Darwinian medicine," says Read, "but there is little experimental data to back it up."

To see if malaria fits the model, Mackinnon infected lab mice with eight distinct, cloned strains of the parasite. She then checked to see which mice were suffering highly virulent infections by measuring a variety of classic symptoms. The results showed "large and consistent differences" between the strains, says Mackinnon. Those that had high replication rates early in infection were the most virulent, making the mice extremely ill; these strains also had slightly higher transmission rates, suggesting that there is a "genetic relationship" among the three traits.

The finding suggests that the parasite does indeed face an evolutionary trade-off between being transmitted quickly and killing the host. Thus, the researchers say, it's possible that control measures such as vaccines or mosquito nets could actually lead to the development of more virulent strains of the disease. For instance, explains Mackinnon, a vaccine is likely to cause the parasite to replicate earlier and faster so that it can be transmitted before the host's enhanced immune response wins out. "It's an important issue," says Zuk. "How will the disease organism respond to different ecological conditions?"

"That's the big question," agrees Mackinnon, and it's one she hopes her research will eventually answer. "We know now that the parasite has the capacity to change genetically. Will it become more virulent if we start curbing its transmission?" Evolutionary theory predicts that it could.

–Virginia Morell