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Mosquito Biology: How a Quest for Water Spawned a Thirst for Blood

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The invasive yellow-fever mosquito *Aedes aegypti* preferentially feeds on human blood. A new study finds that human-biting in this important disease vector might just be an unfortunate side effect of breeding in human-stored water.

The triangle trade between Europe, Africa, and the New World during the 16–19th centuries is one of the most abhorrent events in recorded history, resulting in the enslavement of an estimated 12.5 million native Africans. The repercussions from this grim trade are still vivid today. 400 years after the first slaves arrived at Point Comfort and 150 years after emancipation, America is still a nation deeply divided along racial lines, with Black Americans disproportionately subjected to police brutality, poverty, and poor health. Institutionalized racism is, however, not the only legacy. As the vessels set off across the region, with countless dead — were performed by questionable experiments — involving inoculation of human volunteers with yellow fever to flourish on the island. Their studies caught the interest of the Cuban ophthalmologist Carlos Finlay, who later recalled: “It occurred to me that to inoculate yellow fever it would be necessary to pick out the inoculable material from within the blood vessels of a yellow fever patient and to carry it likewise into the interior of a blood vessel of a person who was to be inoculated. All of which conditions the mosquito satisfied most admirably through its bite” [3]. From this insight followed a series of experimental observations — involving inoculation of human volunteers with yellow fever through bites of infected mosquitoes — that led Finlay in 1881 to conclude that mosquitoes could transfer this *inoculable material* between humans [4]. The mosquito-vector theory was, however, initially met with skepticism and it would take another 20 years before Finlay’s observations were generally accepted. The conclusive experiments — this time leaving three people dead [5] — were performed by U.S. army surgeon Major Walter Reed; mosquitoes, and more specifically *Aedes aegypti*, indeed transmit the dreaded yellow fever [6].

These African mosquitoes had arrived in the New World as stowaways on slave ships, carrying with them the causative flavivirus. In the New World, *Ae. aegypti* found all that it needed, a favorable climate, a bounty of humans providing easy blood meals, and ample supplies of stagnant water in which to lay eggs. Whereas the issue of how the mosquitoes escaped Africa can be satisfactorily explained, the questions of *when*, *where*, *how*, and *why* this species acquired an appetite for human blood have remained more difficult to answer. The ancestral form, known as *Aedes aegypti formosus*, is found in forests, breeds in water-filled tree holes, and (presumably) draws blood from non-human primates. At some point in time and space, a population of these mosquitoes switched to almost exclusively biting humans, over time turning into *Aedes aegypti*, the subspecies that went on the transatlantic voyage.

A study published in this issue of Current Biology by Rose and co-workers [7] now sheds light on the *why* and *where* questions. The authors argue that human-biting might simply have evolved as a byproduct of breeding in human-stored water. To arrive at this conclusion, the international team behind the study — led by Carolyn McBride — first embarked on a pan-African odyssey to sample mosquitoes. In the end, the team managed to establish laboratory colonies of mosquitoes collected from 27 sites across sub-Saharan Africa. Having established colonies, the authors then examined 17,856 females for host-odor preference; this analysis revealed that mosquitoes from east Africa mostly prefer animal smells, whereas mosquitoes from west Africa, and especially those from Senegal, show strong preference for humans. The authors then used modelling to identify variables associated with human preference and identified two specific factors. The first one is fairly obvious, namely regional human
population density; that is, the more humans around, the more likely the mosquitoes are to bite humans. The second predictor — precipitation seasonality — is perhaps not as obvious at first. A high degree of precipitation seasonality — meaning that rainfall comes with long intervals in between — poses a major hurdle for mosquitoes, which need water for reproduction. In areas with extended dry seasons, a lack of water, argue the authors, would have driven the mosquitoes out of their native forests and into human settlements in search of stored water, and once in human habitats, the mosquitoes would have shifted to biting the prevailing mammal — us. *Aedes* would hence join the ranks of many other animals that have found a living in our dwellings, not because of an initial liking to us *per se*, but because our artificial ecosystem provides shelter, food, and breeding opportunities. Whereas most of these house guests are merely a nuisance, content with feeding from our scraps, *Ae. aegypti* not only moved in with us, it even evolved an appetite for our blood. A possible confounding issue though is that the authors use present day climate conditions to model an event that happened a long time ago. To address the issue of why, it is necessary to also have a grasp of when. Although no dating attempt was made in the present study, previous work has estimated that the transition took place between 10,000 and 5,000 years ago [8,9]. The earlier date would, however, be hard to reconcile with the proposed hypothesis, as it would place the shift in the middle of the African humid period (~14,500 to 5,000 years ago), when the Sahara and the Sahel were covered in lush grasslands, intercrossed by rivers and lakes. During this period, access to water would not have been a limiting factor for the mosquitoes. Moreover, an early date would also be hard to reconcile with the West African archeological record, where traces of (more or less) sedentary humans — and with them villages and stored water — first showed up ~6,000 years ago [10].

Settling the issue of when should be a priority.

As for the question of where the transition to human-biting took place, clues can be gleaned from the behavioral experiments [7]. Mosquitoes from the Sahel ecoregion in westernmost Africa showed a strong preference for humans, suggesting this region as the origin of the human-biting behavior, echoing previous findings from genetic studies [8,9]. Behavior would hence indicate that mosquitoes from the Western Sahel are the source population from where the Yellow fever is one of the diseases transmitted by the *Aedes aegypti* mosquito. Both virus and vector stem from Africa and were introduced into the Americas with the transatlantic slave trade. As depicted in this illustration from 1876, advanced stage yellow fever results in jaundice and hemorrhage. Photo courtesy of the Louisiana State University Health Sciences Center Libraries - New Orleans, LA. Copyright © 2011 LSUHSC-New Orleans.
invasive human specialists stem. Rose and colleagues next sequenced and analyzed an impressive 366 mosquito genomes, which revealed that human-biting behavior indeed has a single, shared genomic origin that can be traced to mosquitoes living in Northern Senegal. It should be noted, however, that some important locations are missing in the study, notably Angola. Mosquitoes from this West-Central African country have previously been shown to have an ancestry composition similar to mosquitoes from Senegal [8]. Moreover, parts of Angola have climate conditions similar to the Sahel. Lastly, Angola was until the beginning of the 1640s the primary shipping point for the Portuguese slave trade and could, accordingly, have been the location where the ancestors of the invasive subspecies boarded [11]. That said, placing the origin in Angola is not straightforward. A reasonable assumption is that the arrival of yellow fever and the establishment of a permanent population of human-biting Ae. aegypti in the New World more or less coincide. However, given that there are no well-documented outbreaks of yellow fever in the New World prior to the 1647–1649 epidemic, Angola would be an unlikely port of embarkment for the mosquitoes, since from that period onwards most of the slave vessels destined for the Caribbean used harbors in West rather than West-Central Africa [11]. Moreover, even though climate conditions fit, Angola was until 500 BC inhabited by the San, an ancient group of nomadic hunter-gatherers [12]. With such a lifestyle follows, per definition, a lack of permanent residents, and most certainly villages, and with that also a lack of human-stored water. Nevertheless, including reference genomes from West-Central Africa is needed before any firm conclusions can be drawn as to where human-biting first arose.

The genomes also offer an excellent opportunity to address the question as to how the mosquitoes became human specialists; which molecular modifications underlie the shift in preference? To pinpoint genomic regions involved, Rose et al. performed a population branch statistical analysis, a method used to detect natural selection through pairwise comparisons of allele-frequency changes between two focal populations and an outgroup. The analysis revealed a number of divergent chromosomal regions in the human-biting populations, including a large part of the distal end of the first chromosome, which includes an odorant receptor previously implicated in human preference [13]. Although the present study does not provide any clues as to which genes might be involved, the study highlights genomic hotspots that can be mined in the future. Clear from the analysis, though, is that deciphering the molecular basis of human preference will be complicated.

The same economic factors that unleashed yellow fever onto the world in the 17th century are still at play today. Globalization has turned large swathes of Asia into industrial wastelands, and as mega factories have grown ever larger, humans have been pushed deeper into wildlife habitats, increasing chances of zoonotic transfers of deadly diseases. With an estimated 1.7 million undiscovered viruses in wildlife of the type that could potentially infect humans [14], there is an overwhelming risk that we will see the release of something far worse than SARS-CoV-2 in the future. Our interconnected world also means that local disease outbreaks do not stay local for long, of which the aforementioned coronavirus is a timely example. Mosquitoes have a remarkable capacity to both host and transmit a plethora of diseases, ranging from unpleasant to outright deadly. Although many of these diseases are currently endemic to remote parts of Africa and southeast Asia, short-sighted human activities and climate change create a community that these diseases will find their way out of the jungles. The 2015 Zika virus epidemic in the Americas is a prime case in point of an obscure African mosquito-borne disease becoming a global health threat. Encroaching into wilderness areas and disrupting ecosystems may also lead to mosquito-driven spillover events, via zoophilic mosquito species acquiring a taste for human blood. Granted, at the time of this writing there is no shortage of bad tidings to keep one awake at night: a runaway pandemic with no end in sight, growing civil unrest in the United States and uncertainties regarding the prospect of a peaceful transfer of power, looming economic troubles within the European Union, a middle east in perpetual turmoil, all while the Siberian permafrost thaws. Nevertheless, the threat from mosquito-borne diseases is still here and will only grow. Determining what drives mosquitoes to switch to human-biting is therefore not only an intriguing academic topic, but imperative for the development of efficient control strategies, as well as to predict future disease outbreaks.

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Evolution: Shape-Shifting Social Parasites

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Ants exploit differences in body surface chemistry to distinguish nestmates from colony intruders. Socially parasitic ants in Madagascar have convergently evolved morphological similarities to host worker anatomy, implying that body shape may also be surveilled. Studies of tactile behaviors in ant societies are now needed.

Since their emergence during the early Cretaceous, ants have diversified into ecologically dominant insects that impact the biosphere in ways unmatched by most animal groups [1]. Ant colonies police landscapes, regulate nutrient flows and control the abundance of other life forms. Key to this ecological hegemony is social cohesion, manifested in a division of labor among workers, and between workers and reproductives [2]. As in all eusocial insects, the emergent behaviors of ant colonies depend on chemical cues that enable reliable nestmate recognition [3]. The integral compounds are cuticular hydrocarbons (CHCs): long chain alkanes and alkanes, which are secreted onto the ant body surface in complex blends [4,5]. When encountering another insect, ant workers will sense the insect’s CHCs and compare them to their own, colony-specific profile. If there is a mismatch, the insect is recognized as foreign, and the ants will respond aggressively to extinguish the threat. This CHC-based model of nestmate recognition is broadly accepted and has spawned a consensus view that olfaction is the predominant sensory modality underlying colony cohesion [4,5]. Indeed, ants provide an archetypal model for how chemosensory information controls social behavior that is now being examined at the neurobiological level [6]. However, a new study by Georg Fischer, Evan Economo and colleagues in this issue of Current Biology [7] challenges the absolute explanatory power of this chemocentric view. Their findings indicate that tactile sensing of external anatomy may represent a parallel information channel for nestmate recognition.

To reach this controversial conclusion, Fischer and colleagues [7] report evidence from a newly discovered group of ‘socially parasitic’ ants. Social parasites are animals that make a living inside ant colonies. Bountiful, climatically controlled ant nests are targeted by a veritable zoo of such intruders, including thousands of species of ‘myrmecophiles’ — non-ant arthropods such as beetles, flies, crickets and butterfly caterpillars that are specialized for colony infiltration [8,9]. In addition, there are more than 400 socially parasitic ant species that are obligately dependent on the social environment provided by host colonies of other ant species [10]. Social parasites employ diverse strategies to evade detection inside nests. Many species are able to assimilate into the ant society by mimicking how their hosts recognize and interact with each other, a phenomenon termed ‘Wasmannian mimicry’, after Erich Wasmann, the Austrian entomologist who pioneered the study of myrmecophile biology [8]. Social parasites that are integrated in this way provide valuable windows into how ants communicate: their Wasmannian adaptations reveal fundamental phenotypic traits that are necessary to be treated as a nestmate.

Studies of both ant and non-ant social parasites indicate that chemical deception is paramount, with many social parasites capable of mimicking their hosts’ CHC profiles [11].

The new study of Fischer and colleagues [7] suggests that all may not be so straightforward. The authors inferred the phylogenetic relationships of 80 Malagasy species of the large ant genus Pheidole. Within the Malagasy Pheidole radiation, they recovered a single origin of social parasitism with 13 descendent species. Crucially, each species within this clade has evolved to target another, distantly related free-living species within the Malagasy Pheidole clade (Figure 1). These replicate instances of social parasitism on phylogenetically distinct hosts provide an opportunity to ask a simple question: what happens to a social parasite’s body plan as it adapts to a novel host? To answer this question, the authors used micro-CT scans to build 3D anatomical reconstructions of workers of ten social parasite–host pairs (parasite and host queens were also examined in this way if specimens were available). They then quantified anatomical similarities between host and parasite, employing both linear measurements of body structures and geometric morphometrics to estimate multivariate shape parameters. Plotting measurements of host versus parasite across species, striking correlations emerged: social parasite workers show