NEWS

What Mosquitoes Want: Secrets of Host Attraction

Why do mosquitoes feast on some people and leave others alone? Researchers are trying to find out, hoping it will help them design the perfect mosquito trap

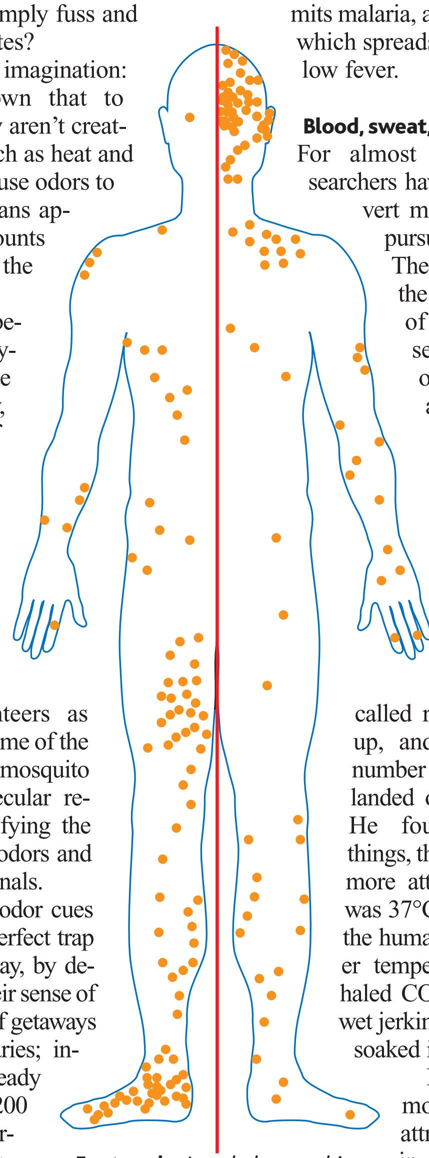
Life isn't fair. Whereas some people never seem to get bitten by mosquitoes—and often don't even seem to notice the critters—others spend their evenings frantically swatting them, usually to no avail. If you're in the latter category, you've probably wondered: Why me? Is it thin skin? My gorgeous body odor? Sumptuous blood vessels begging to be punctured? Or is it all between the ears, as some people say, and you simply fuss and fret more about mosquito bites?

Rest assured, it's not your imagination: Several studies have shown that to mosquitoes, all people really aren't created equal. Besides factors such as heat and carbon dioxide, mosquitoes use odors to find their victims, and humans appear to exude different amounts of the volatile compounds the insects love.

By studying mosquito behavior, entomologists are trying to tease out these favorite smells. It's a complex story, they say. Millions of years of evolution have resulted in sophisticated odor-based navigation systems that differ greatly from one mosquito species to the next, depending on where it lives and which host it prefers. Even so, chemical and behavioral studies—often using human volunteers as bait—have helped identify some of the smells that tempt several mosquito species. And recently, molecular researchers have begun identifying the receptors that pick up these odors and translate them into neural signals.

Researchers hope to use odor cues to lure mosquitoes into the perfect trap or otherwise outwit them—say, by designing repellents that foul their sense of smell. Garden parties and golf getaways might be the first beneficiaries; indeed, one U.S. company is already marketing the $500 to $1200 Mosquito Magnet, which purportedly attracts mosquitoes by emitting a compound called 1-octen-3-ol, as well as heat, CO_2, and water vapor.

But the ultimate goal is a far cry from such pricey gadgets, says Willem Takken of Wageningen Agricultural University in the Netherlands, a pioneer in the field. He'd like a simple, $1 or $2 trap that people in developing countries could affix to their doorposts to keep out the mosquitoes that spread deadly diseases. Key targets are *Anopheles gambiae*, the species that transmits malaria, and *Aedes aegypti*, which spreads dengue and yellow fever.



Footwork. *Anopheles gambiae* (*left*) bites mainly on the feet and ankles; *An. atroparvus* prefers the face.

SOURCE: MIRIAM COOPERBAND AND RING CARDÉ

Blood, sweat, and cheese

For almost a century, researchers have been trying to divert mosquitoes from their pursuit of human blood. The field blossomed in the 1950s, when dozens of entomologists in several countries set out to discover what attracts females—the only mosquitoes that bite—to their hosts. Anthony Brown of the University of Western Ontario in London, Canada, for instance, built human-shaped steel tanks, which he called robots, dressed them up, and then counted the number of mosquitoes that landed on them in a forest. He found, among other things, that the robots became more attractive if their skin was 37°C (the temperature of the human body) than at lower temperatures, if they exhaled CO_2, or if they wore a wet jerkin—or, better still, one soaked in human sweat.

By the mid-1960s, most research on host attraction had stopped, in part because DDT made mosquito extermination so easy. Lately, however, emerging resistance and second thoughts about insecticide use have sparked a renewed interest in alternative control methods.

Scouting for potentially attractive compounds, researchers are taking a closer look at the more than 300 chemicals present on human skin. Martin Geier of the University of Regensburg, Germany, for instance, takes skin rubbings and then chemically removes a certain group of compounds—say, the ketones or the fatty acids. If one group attracts mosquitoes, it can be further separated into its individual components, he says.

To test how compelling single compounds or mixtures are, researchers use a specialized instrument called an olfactometer, whose central part is a Y-shaped wind tunnel. Two different odors are blown into the short legs of the Y; when mosquitoes are set loose at the other end, they fly upwind and, like quiz show contestants choosing between two doors, decide whether to go left or right. Researchers can also fixate mosquitoes, apply miniature electrodes to their nerves, and test whether exposing them to a whiff of some compound elicits an electrical signal.

Recent studies have confirmed what Brown and others discovered half a century ago: that for most mosquito species, CO_2, heat, and moisture are key attractants. But these lead a mosquito to any warm-blooded animal—bird, cow, or human. That might be fine for species that aren't too picky, such as *Culex pipiens*, a West Nile vector in the United States. But those that dine almost exclusively on humans, such as *An. gambiae* and *Ae. aegypti*, need much more specific attractants.

Sexual predator
Deinocerites cancer (Crabhole mosquito)

credit: University of Florida/FMEL

The struggle for sex gets extreme. Adult males emerge first and grab female pupae with their forelegs while keeping other males at bay. Copulation, which lasts up to 30 minutes, takes place as the female emerges from her skin—a phenomenon dubbed "pupal rape."

Distribution: Coastal areas along the Gulf of Mexico, Caribbean, and Central America.
Breeding habitat: Has found a unique niche in the burrows of land crabs.
Feeding: Night feeder; host preferences unknown.
Diseases: None known.

Deinocerites cancer

Hunting for cues, Bart Knols, a researcher in Takken's group, noticed in 1995 that *An. gambiae* had a predilection for biting its victims on the feet and ankles—even when their entire bodies were exposed. (This clearly set it apart from related species, such as *An. atroparvus*, a mosquito from Holland that goes mainly for the face.) A native of the Dutch province of Limburg, Knols also realized that foot odor bears a remarkable resemblance to the pungent cheese from that region. And sure enough, *An. gambiae* turned out to be heavily attracted to the smell of Limburger cheese.

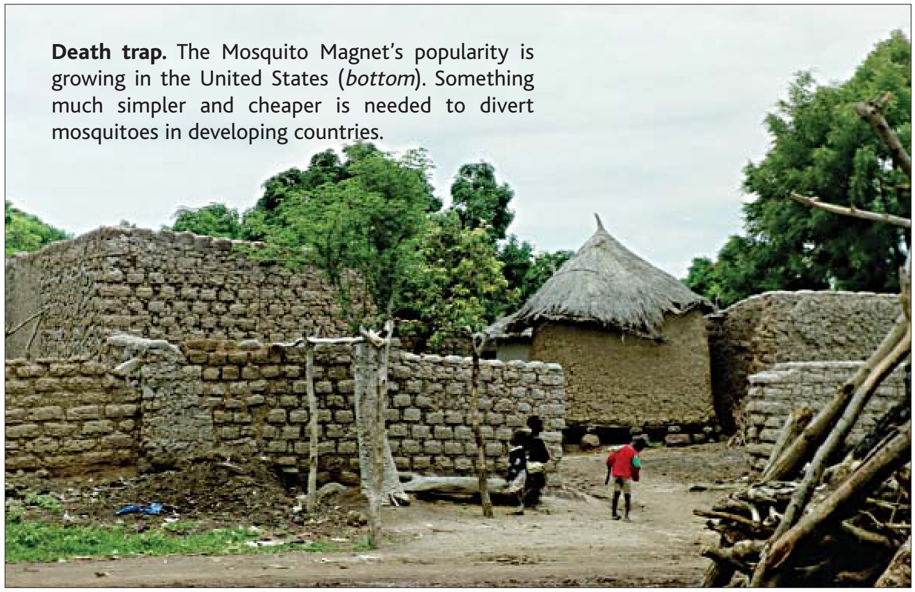
The finding, after making snickering headlines around the globe, led researchers to tempt different mosquitoes. "It became sort of a madhouse," Knols recalls. "People started taking Limburger cheese all over the world." But the stinky dairy product turned out to be an acquired taste, he says; just those few mosquitoes that feed primarily on humans were strongly attracted.

Knols says the common denominator between feet and cheese is obvious: a bacterium used in cheese production, called *Brevibacterium linens*, which is a close relative of *Brevibacterium epidermis*, a bug known to reside in the warm, humid clefts between human toes. Both turn glycerides into a specific set of breakdown products, such as fatty acids. Takken's group is now trying to find out exactly which products provide the draw.

Over the years, researchers have found that individual species have their own idiosyncratic tastes for various attractants. *Ae. aegypti* find lactic acid—which humans produce on their skin but other mammals don't—sublime; to *An. gambiae*, it's only so-so. With ammonia, it's the other way around. And even in *Aedes*, Geier explains, lactic acid alone isn't all that attractive; rather, it boosts the appeal of several other compounds.

Complicating matters, explains Ring Cardé of the University of California, Riverside, an effective trap depends not just on the right attractants but also on the physical properties of the odor plume. Cardé has spent most of his career studying how male moths home in on females by navigating pheromone plumes—which, from the insect's viewpoint, consist of a series of small odor filaments swirling through the air. More recent work in mosquitoes, carried out by Cardé's colleague Teunis Dekker, suggests that they, too, use the fine structure of an odor plume to navigate, and Cardé believes that the shape and structure of a plume will determine any trap's efficacy.

Takken and others hope that molecular researchers, who joined the field just 2 years ago, will help make sense of it all. They are making some headway: In a study published on page 176, a team led by Laurence Zwiebel at Vanderbilt University in Nashville, Tennessee, has scoured the newly sequenced *An. gambiae* genome for so-called G protein–coupled receptors, which include odor receptors.



Death trap. The Mosquito Magnet's popularity is growing in the United States (*bottom*). Something much simpler and cheaper is needed to divert mosquitoes in developing countries.

CREDITS: (TOP TO BOTTOM) G. VOGEL/*SCIENCE*; AMERICAN BIOPHYSICS CORP.

The team, working with researchers at the University of Notre Dame in Indiana, the University of Illinois, Urbana-Champaign, and Celera Genomics in Rockville, Maryland, found 79 odor-receptor candidates, only five of which had been known before. Of these, 64 were expressed solely in the mosquitoes' olfactory tissues—evidence that they're probably involved in odor recognition. And at least one of the candidate receptors is produced only in mature females—an important clue that it might be involved in host seeking. So far, the group hasn't been able to link any of the odors known to attract *An. gambiae* to any of the receptors. Still, the study is a "nice breakthrough," says Takken, that might speed the discovery of other, more powerful attractants.

Building the perfect trap

Whether chemical lures can be fashioned into an irresistible mosquito trap, much less one that would be cheap and effective in developing countries, isn't clear. But there is a precedent. In many East African countries, simple traps have helped virtually eradicate tsetse flies, the carriers of sleeping sickness and a livestock disease called nagana. (One trap consists of a simple black-and-blue cloth, baited with acetone and octenol—or, alternatively, buffalo urine—and sprayed with insecticide.)

Mosquitoes, however, could pose a more daunting challenge. One tsetse fly produces only a handful of offspring over her lifetime, making the population vulnerable to even a slight increase in mortality. By contrast, mosquito mothers can produce hundreds of young. It might also be "very difficult," says Geier, to produce a trap that can compete with the real thing: living, breathing humans who emit not just smell but also heat and moisture. (A trap could do that too, of course, but it would quickly get too complicated and costly.) But even if they only reduced the number of mosquitoes, "traps could have a fantastic impact," says Takken. "We all agree that no single measure will ever solve the malaria problem completely."

Short of that ambitious goal, traps might also be effective in monitoring the risk of epidemics and focusing control efforts. Some countries already use a relatively unsophisticated trap developed by the U.S. Centers for Disease Control and Prevention (CDC) to keep track of pathogens. But this trap, which relies on just CO_2, light, or a combination, catches a motley array of insects—often not those most relevant to human health. To catch *An. gambiae*, says Takken, a human needs to be nearby, and because the attractiveness of people varies, so does the nightly catch. Spiking such a trap with a specific odor blend could lead to a much better and more reproducible haul, he says.

Other mosquito-thwarting strategies on the drawing board are clever new repellents. If, for instance, researchers could find compounds that overstimulate crucial odor receptors, they might be able to disorient the insects, dooming them to a life of aimless buzzing, Zwiebel says. It might even be possible, he says, to tinker with the receptors that help mosquitoes find nectar or places to lay their eggs.

In the meantime, attraction studies with human volunteers suggest another, more down-to-earth approach to keeping mosquitoes at bay. Among his human subjects, chemist Ulrich Bernier of the U.S. Department of Agriculture in Gainesville, Florida, has found some people who are almost never bitten. His team has isolated compounds from their skin—he declines to discuss which ones—that he believes might be a clue to the protection. Someday, he speculates, they could serve as a natural, less toxic alternative to DEET.

Splashing yourself or your house with somebody else's body odor might not sound all that enticing. But at the levels needed to keep bugs away, Bernier assures, humans won't smell a thing. –MARTIN ENSERINK

NEWS

Lab v. Field: The Case for Studying Real-Life Bugs

Molecular entomology is all well and good, some researchers say—but what about studying insects where they live and breed: in the field?

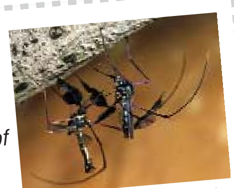
These querulous observers don't want to sound like curmudgeons. Nor do they want to take away anyone's scientific glory. But some tropical disease researchers say they just can't get very excited about the sequence of the *Anopheles gambiae* genome, published in this issue of *Science*. To be sure, the sequence promises to reveal the inner workings of the mosquito in unprecedented detail, shedding light on everything from its metabolism to insect evolution. But skeptics aren't convinced it will actually help control malaria—or, as Chris Curtis of the London School of Hygiene and Tropical Medicine puts it, "pass the so-what test."

For more than a decade now, Curtis and other vector ecologists have argued that the field of insect-borne diseases—whether malaria, dengue, West Nile virus, or Lyme disease—is betting too many of its scarce research dollars on high-tech work like DNA sequencing and too few on studies of insect behavior and ecology, the type of fieldwork that gets your back sweaty and your hands dirty. To figure out how these diseases behave, they say, you have to don your boots rather than start your sequencer (see p. 87).

The riposte from molecular researchers is that ecological studies are important, but given the lack of progress in the fight against insect-borne diseases, new strategies are needed. "If ecology had all the answers, there wouldn't be molecular biology," says Anthony James, a molecular entomologist at the University of California, Irvine. In the past few years, the sparring has gotten especially intense over molecular biologists' boldest plan: to control malaria by releasing transgenic mosquitoes (see Morel Viewpoint on p. 79). Some ecologists have dismissed the scheme as a grandiose folly—a Star Wars of infectious disease—that is diverting money from more "down to earth" research. James chalks up part of the bickering to the "impoverished mentality" that afflicts all of tropical disease research. When funding is tight, he explains, "people start fighting over whose work is more important."

Handsome devil

Sabethes cyaneus



credit: W. A. Foster

Males of this mosquito species, one of the most beautiful on Earth, display an elaborate courtship dance in which they wave one of their legs and swing their bodies back and forth. They sometimes court other males, too.

Distribution: New World tropics, from Belize to northern Argentina.

Breeding habitat: Deep rot holes in trees, where the low evaporation rate allows breeding throughout the dry season.

Feeding: Most likely a daytime biter; hosts unknown (monkeys?).

Diseases: Not incriminated as a vector, although a close relative transmits yellow fever to monkeys.

Sabethes cyaneus

Sexier science

Field studies of mosquitoes, which peaked during the vector biology heyday of the 1940s and 1950s, were dealt their first heavy blow when DDT and other insecticides promised to end insect-borne disease. By the time insecticide resistance and growing opposition to chemical use shattered that dream, the molecular biology revolution was well under way, and chasing mosquitoes in the field seemed old-fashioned and obsolete. "People just find molecular biology sexier," concedes Duane Gubler, chief of the division of insect-borne infectious diseases at the U.S. Centers for Disease Control and Prevention (CDC) in Fort Collins, Colorado. "It's seen as the future."

Indeed, for the last 15 years or so, molecular scientists have dominated mosquito research grants and high-profile publications. Of more than 130 mosquito studies currently funded by the U.S. National Institute of Allergy and Infectious Diseases (NIAID), only about one in five includes fieldwork, while DNA work booms. The World Health Organization (WHO) has also made the transgenic mosquito one of its top priorities in fighting malaria.

The funding shift, some say, created a self-perpetuating cycle: Universities hired molecular researchers because they could pull in grants, and vector biology departments took on a decidedly molecular bent. "The molecular people are multiplying like flies," laments Yale medical entomologist Durland Fish. Even if they would like to do field studies, he says, young scientists are forced to follow the money and end up in molecular research.

As a result, studies that could make a dent in disease transmission are lacking, ecologists say. Dengue fever, a debilitating and sometimes fatal disease transmitted by a mosquito species called *Aedes aegypti*, is a case in point, says CDC entomologist Paul