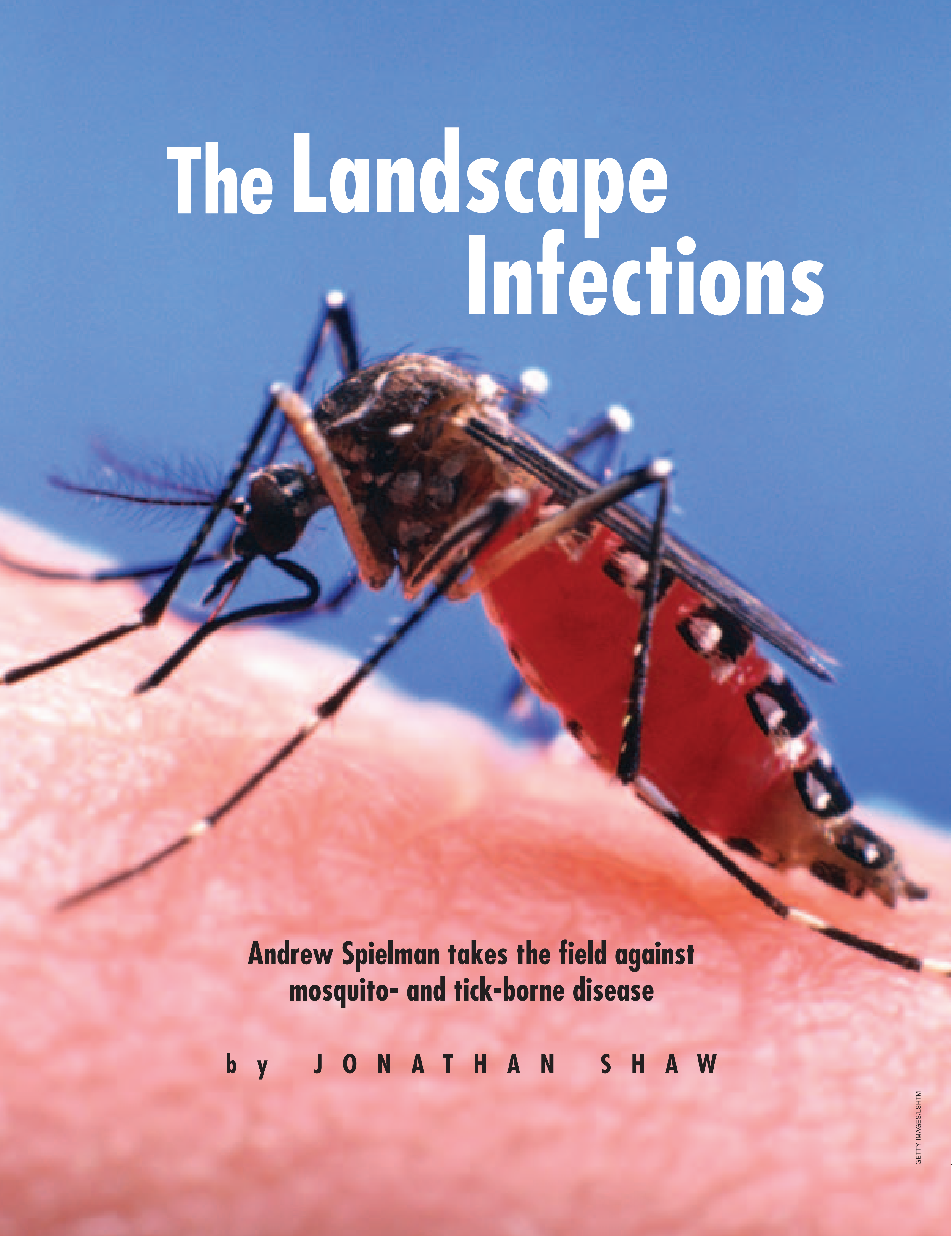

The Landscape Infections

Andrew Spielman takes the field against mosquito- and tick-borne disease

b y J O N A T H A N S H A W

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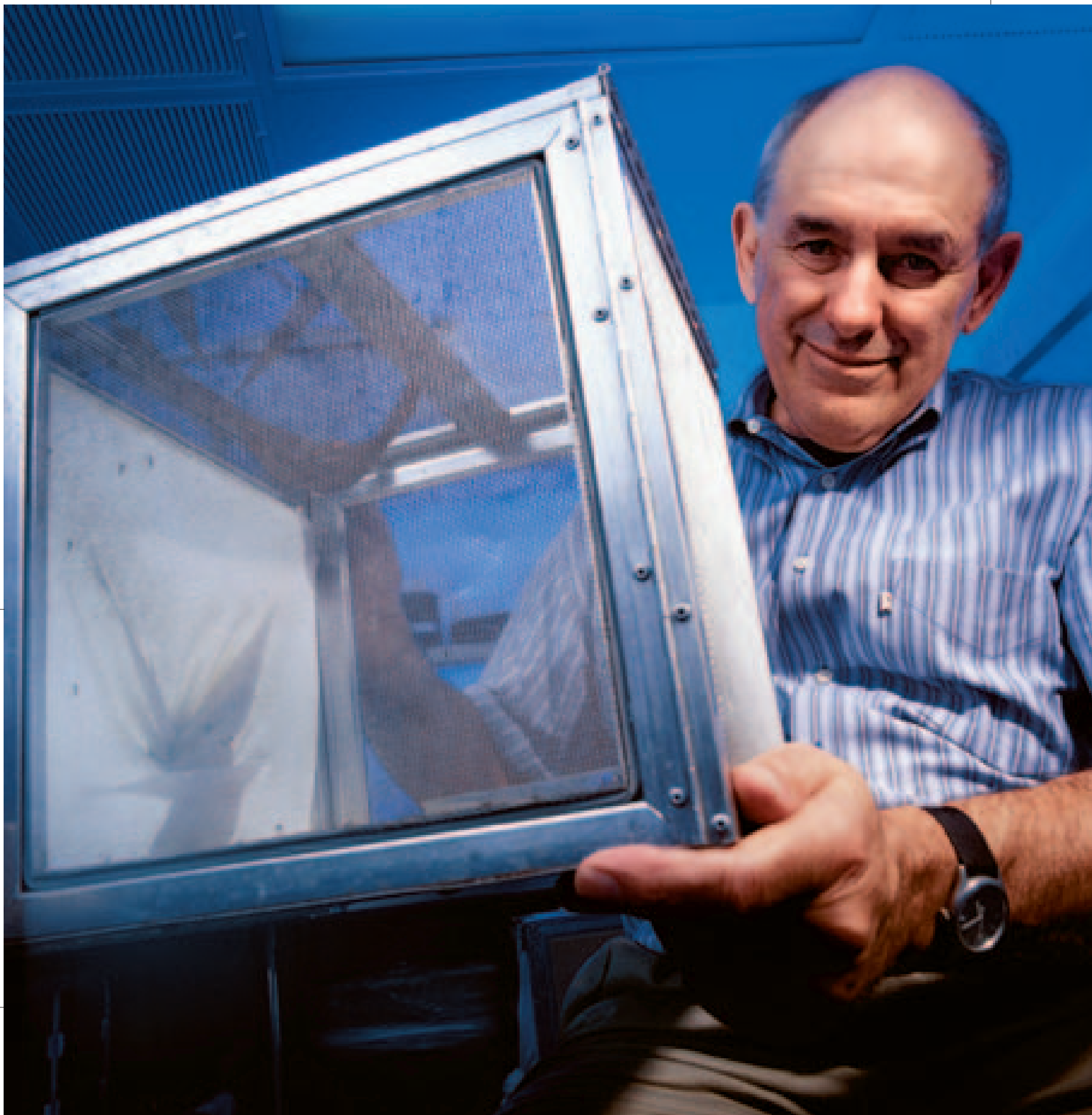
The assault begins on the note of high C, an annoying whine at your ear. Flying in low along the ground, then up your body in search of exposed flesh, a female mosquito has targeted you for her next blood meal. She will land without triggering nerves in your skin, and stab you with her daggerlike proboscis until she strikes blood. If she completes her feeding without detection, she will be able to fly only a few feet, heavy with her protein payload, to a wall or other nearby surface, where she will excrete the excess fluid in a pinkish stream over the next hour or so. Having stored sperm from an earlier mating, she now has everything she needs to lay eggs, and will in a few days seek to deposit them in a still pool of water.

Though we tend to think of mosquitoes as merely a nuisance, mosquito-borne pathogens claim millions of lives each year. In the undeveloped world, the mosquito's distinctive whine is too often a siren claiming another victim of yellow fever, malaria, or dengue. Afflictions such as these isolate populations, paralyze trade, and curb development, says entomologist Andrew Spielman, a professor at Harvard's School of Public Health. Worldwide, the social and economic impact of this tiny, efficient vector is enormous—malaria alone, he says, affects 10 percent of the world's population.

Since the 1999 outbreak of West Nile virus that killed seven people in the New York metropolitan area, the soft-spoken Spielman has become something of a celebrity. West Nile, a flu-like African import that can lead to death in the elderly or immune-compromised, is expected to spread nationwide. The outbreak elevated the mosquito vector from its lowly status as backyard barbecue pest to a new position in the American consciousness: serious health threat. After the publication this past spring of his *Mosquito: A Natural History of Our Most Persistent and Deadly Foe* (written with reporter Michael D'Antonio), Spielman appeared frequently on the radio and in print to discuss the mosquito and the importance of understanding its behavior.

There are more than 2,500 species of mosquitoes, and most must feed on blood in order to reproduce. They suck protein from birds, reptiles, and mammals, and seem to serve no higher purpose—



Female mosquitoes can transmit disease during blood meals. Beautiful but deadly *Aedes aegypti* (left) breeds in small containers near human habitations, feeding principally at dusk and dawn. It has a stronger preference for human blood than the similar *Aedes albopictus,* making it a more efficient vector of yellow fever and dengue. Andrew Spielman (right) studies mosquitoes in his lab at the Harvard School of Public Health to learn more about their habits and life cycles.

JIM HARRISON

they are not an important food for any other creature, nor do they do useful things like pollinate flowers. We don't know why mosquitoes need blood to reproduce, but once they have it, they land on water and lay hundreds of eggs in a raft-shaped mass smaller than a grain of rice. Larvae hatch two days later, swimming and feeding in water, breathing through a tube at the surface. Larvae give rise to the pupal stage in 12 days. Two days more and a young mosquito emerges—there are billions of such births every day. They may grow in water-filled tree-holes, the cup of a bromeliad, or a poorly drained gutter. And they can thrive almost anywhere, from the heat of arid wastes to the frigid Arctic. Spielman describes eggs in deserts that survive decades between rainfalls, and swarms on the tundra so thick that they can drain the blood from the carcass of a caribou. A few species can develop even in salty water. Mosquitoes can see, smell, hear, and sense heat. Most are nocturnal, and can navigate by the stars. Few species bite humans, but humans provide wonderful habitat for mosquitoes in all stages of their life cycle. Dig a hole, dam a river—anything that fills with rainwater is a potential breeding site, while homes provide mosquitoes with perfect shelter from the sun's scorching rays during the day. Spielman describes huts in Africa where the inner walls are so thick with them that they appear to move like a living carpet. Sometimes, human interactions with mosquitoes have been history-making: if not for mosquitoes, Rome might have been permanently taken by Visigoths; western Europe might have been overrun by Genghis Khan's hordes; and the French might have built the Panama Canal. Even in modern times, armed with knowledge of how diseases like malaria and yellow fever are transmitted, people can't always agree on a remedy.

Spielman recounts a slew of misguided attempts to control mosquito-borne diseases, each the result of failure to understand the vector—a formidable foe, as he makes clear. When a particularly efficient malaria vector, *Anopheles gambiae,* arrived in Brazil from Africa in 1930, one local official opposed a relatively simple control method—the flooding with salt water of a former marsh that had recently been turned into a hay field—a decision that within eight years contributed to the largest malaria outbreak ever in the Western Hemisphere. One hundred thousand people became ill, and as many as 20,000 died. This catastrophe led to a massive, heroic effort to eliminate the vector mosquito itself. Remarkably, with the use of military-style tactics, including searches of vehicles leaving malarious regions and the use of a potent new weapon—the insecticide DDT—the effort was successful.

In time, scientists would learn that DDT was not the magic bullet it first appeared to be. As we now know, it lingers in the environment and can have numerous detrimental effects, particularly on birds. But the successful elimination of *Anopheles gambiae* was such a triumph, Spielman writes, that it led to overreliance on the insecticide and fostered the notion that malaria could be eliminated. Inconsistently applied methods of control and a growing mosquito resistance to insecticides ultimately doomed the effort to rid the world of malaria.

Left: Day-old *Culex* larvae emerging from an egg raft. *Culex* species are the principal vectors of West Nile virus in this country. Above: Mosquito larvae float head down and direct food to their mouths with tiny body hairs.

Spielman nevertheless believes that mosquitoes and the diseases they carry can be controlled. That is reassuring in an age when rapid intercontinental transport virtually guarantees that other mosquito-borne pathogens, some much more virulent than West Nile virus, will cross oceans.

Mosquitoes easily slip aboard as stowaways on ships or airplanes. When in 1983 Paul Reiter (see "Fighting West Nile," page 46) of the Centers for Disease Control (CDC) found the first Asian tiger mosquito (*Aedes albopictus*) ever seen in the United States—in a Memphis graveyard—he couldn't imagine how the mosquito got there. It is an aggressive biter and a significant "bridge vector," so called because it attacks humans, birds, and other targets indiscriminately, thereby facilitating interspecies transfers of disease. Reports of voracious mosquitoes in the Houston area two years later identified a large infestation of the tiger, and detective work by Reiter implicated the huge intercontinental used-tire trade. (Houston is a major center for retreading old tires.) Because tires fill with water and aren't easily drained, they are perfect breeding grounds for many species of mosquito, which can easily survive ocean crossings in container ships. We export, as well as import, mosquitoes: an American native called *Aedes altropalpus* recently turned up in northern Italy. Neither *Aedes* carried a disease, but that, too, will come, says Spielman. It is just a matter of time.

The host of a radio program recently introduced Spielman as "a man who has devoted his life's work to the study of mosquitoes." That's not quite true, Spielman says mildly. "I also study ticks." In fact, Spielman's work with ticks, which transmit disease in much the same way as mosquitoes, directly informs his mosquito research. He has written more than 150 papers on each of these blood-sucking carriers of disease.

"In 1969," he recalls, "a woman on Nantucket Island in her upper sixties, who had been very healthy, developed what appeared to be malaria. They treated her with chloroquine, which had no effect on the course of the infection. The diagnosis then was drug-resistant malaria, indigenous, which was very startling." But it was not malaria. The CDC in Atlanta eventually identified the agent of infection as a parasite called *Babesia microti*, which had been discovered at Harvard in 1937 by Ernest F. Tizzer, then head of the department where Spielman now works. The woman had contracted the first human case ever of babesiosis.

In 1969, Spielman was not involved in the investigation. "But then in 1973," he continues, "a neighbor of the index case acquired the same infection, and there we had the key epidemiological requirement of cases associated in place and time. That took the case out of the realm of the improbable and made it really worth taking a look at, to see whether we could understand what was going on." His earlier work with what is now called Lyme disease led him to start the search for *Babesia microti* with the assumption that there would be a tick vector and a mouse reservoir for the disease. Spielman, his lab technician, and the man's girlfriend boarded the ferry for Nantucket. "I anteed up a few bucks for the fare, and we loaded our bicycles with all kinds of animal traps and equipment," Spielman remembers. The initial visit led to a long-term interest there. Spielman defined the life cycle of *Babesia microti,* and ultimately developed a similarly definitive body of information on the agents of Lyme disease, human granulocytic erhlichiosis (HGE), and deer tick virus (the latter two developed with department lecturer Sam Telford and graduate student Greg Ebel, M.T.P. '97, respectively). He also identified the deer tick as the vector for all three diseases and babesiosis; they are frequently transmitted together.

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Spielman's studies of tick-borne diseases continue. Several years ago, his lab discovered how the new Lyme disease vaccine works. "It has a unique mode of action," he says. "Its venue of activity is in the mid-gut of the tick. Usually when you are vaccinated against disease, the action is inside you—the fact that this vaccine works in the tick has all kinds of important implications," says Spielman. "For one thing, there is no boosting of the immune system." Vaccines usually work by establishing an immune system "memory" of a certain antigen (disease agent or toxin), so that when the antigen shows up again, the immune reaction instantly boosts the number of antibodies in the bloodstream. "In the case of the Lyme disease vaccine, there is no boosting," says Spielman, "so everything hangs on its concentration in your blood when you're infected. That imposes a peculiar requirement for revaccination."

Spielman knows as much about the history of Lyme disease as he does about recent efforts to combat it. "Lyme disease was here at least 130 years ago," he says. Mice collected on Cape Cod around 1870, now stored at Harvard's Museum of Comparative Zoology (MCZ), carry both Lyme disease and human babesiosis. "But there were no human cases at that time because the vector, the mouse tick, doesn't bite humans." The mouse tick is still present well up the coast of Maine, but elsewhere the deer tick, which *will* bite humans, has displaced the mouse tick, and become the "bridge vector" that carries these diseases between humans and other mammals.

"Another form of tick-borne babesiosis, Texas cattle fever, is the thing that set off the range wars," says Spielman. In 1893, a scientist named Theobald Smith—Spielman calls him "amazing"—published a paper that established the cause of the disease and demonstrated not only how it was transmitted but also that there was a tick vector. Furthermore, he outlined the strategy for eliminating it from the United States, and his tactic worked. Smith discovered that the tick vector would survive less than a year if it had no cattle to feed on. He set up a system of field rotation so that no cattle would be kept in the same field two years in a row. "Simple and effective," is how Spielman characterizes the approach, "but requiring deep understanding and all kinds of discovery." It was the first demonstration that a blood-sucking arthropod, an insect, could acquire infection in a blood meal and transmit it to another animal in a subsequent feeding. "For this reason," says Spielman, "Theobald Smith should be regarded as the father of public-health entomology." Smith came to Harvard in 1895 and set up the department of comparative zoology at the Medical School, now established in the School of Public Health as the department of immunology and infectious disease. "I trace my science to Theobald Smith, right here," says Spielman. Smith's insight into the role of blood-sucking arthropods was groundbreaking because it led to the understanding that malaria is transmitted in a similar way by another vector: mosquitoes. And it demonstrated the importance of understanding the life cycle of the vector in fashioning a response.

Malaria is the most important of the more than 100 arthropod-borne diseases—or arboviruses—that affect humans. Nowhere does it have a greater impact than in Africa. Like tick-borne diseases, "malaria is a landscape infection," says Spielman, "anchored in the environment." As long as the relationship between the inhabitants of a malarious village and malaria is stable, the effect on life in the village is a low-level drain on resources. Children under five typically suffer six bouts of malaria a year, and affected families clear only 40 percent as much cropland as do healthy families. All adults are immune (though women in their first pregnancy are at risk).

The infection of each village is different, but some generalizations are possible, says Spielman, who also directs the malaria project at Harvard's Center for International Development (CID). "In an infected village, the force of transmission is very high. There are many villages in West Africa where the average person is exposed to more than 100 infectious bites per year." In some places, there may be several infectious bites per person per night. There, "the force of transmission is *huge.* Anyone who comes to the village will acquire the infection if they stay there for more than a few nights and are not adequately protected," he says. That has the effect of isolating the inhabitants from the outside world, because people know that it is dangerous to live there or even to visit. "People from less affected areas will avoid the village," Spielman says, "and tradespeople will hesitate to go there."

It is equally dangerous for the villagers to leave for any extended period, because immunity begins to wane within a year. "The indigenous people will hesitate to send their children away to school because they cannot return after several years and still expect to be in good health," he explains. The effect is to further isolate the village.

CID director Jeffrey Sachs, an economist who is Stone professor of international trade, completed a macroeconomic survey of malaria's impact on Africa several years ago that Spielman says "demonstrated conclusively that if you don't do anything about malaria, you can forget everything else." The total economic damage that malaria can inflict far exceeds what can be explained by the various microeconomic factors. "If you ask how much a death costs, how much a life is worth—if you measure everything," says Spielman, "it comes nowhere near the measurable economic impact. In fact, it is off by something like an order of magnitude" due to the isolation effect. In his role at the CID, Spielman has begun to study, from an economic perspective, the problem of developing sustainable interventions.

These *Culex pipiens*, or common house mosquitoes, were collected from Boston's Forest Hills Cemetery and used to establish a colony in Spielman's laboratory. The females of the species prefer to bite animals, but will deign to feed on human blood under certain circumstances. *Culex pipiens* males, like the one at right, are easily identified by their long shaggy antennae and palps. Males are shorter-lived than females, and eat nectar and other sugars.

The challenge he says, is to set in motion a cycle of health and wealth. Wealthier people are healthier, and vice versa. Because of the isolating effects of malaria, simply saving lives may not be enough. "We need to devise sustainable antimalaria strategies that will improve lives—that is, improve the general well-being of the public, but *also* contribute to real economic growth," Spielman says. Of the macroeconomic approach to public health, he says, "This is new territory."

The key is reducing the force of malaria transmission in villages. But the danger in undertaking any intervention is that it might fail. "An unsuccessful, or temporarily effective, intervention can be a terrible thing," Spielman says, "because it results in reduced herd immunity on the site. If the intervention used either insecticides or drugs, then the mosquito vector and the malaria parasite are likely to have acquired tolerance to chemicals. People will have an unrealistic expectation of health, and donors will become fatigued. Instability, or temporary good work, is bad."

But there are a number of strategies that are effective. One, sure to provoke controversy, is to use DDT, which was nearly banned globally last year. Spielman thinks that would have been a colossal mistake. He studied with Rachel Carson, and is certainly not blind to the dangers of DDT, but the insecticide is very cheap and, when used indoors where people sleep, highly effective at controlling malaria. "The power of DDT really comes as a function of a simple behavioral characteristic of the vector," he says. When a mosquito feeds, it may triple or quadruple its weight, which makes flight very difficult. Because 99 percent of the malaria vectors are nocturnal, indoor biters, they fly to a nearby wall after a meal, and rest there, excreting excess fluid for about an hour. DDT is soluble in a mosquito's waxy body coating, and when applied to an indoor wall kills almost all the potentially infectious mosquitoes, powerfully reducing the force of transmission. "If we can reduce the probability of survival for mosquitoes that are potentially infectious," notes Spielman, "then we have done something far more important than reducing the absolute number of mosquitoes out there."

That raises the possibility of developing other methods of control. A peculiar characteristic of malaria is that it takes about 10 or 12 days for a mosquito to become infectious—yet most mosquitoes live only a week. "It is only the Methuselah mosquito that is dangerous," says Spielman. Young mosquitoes are vastly more numerous than old ones, so if we can find a way to reduce the tail end of the mosquito lifespan, we can control malaria.

Understanding the vector's life cycle also provides an understanding of how environments that humans create can provide rich mosquito habitat. In one village in Africa, for example, residents build their huts with mud dug from holes, often right next to their homes. These fill with water when it rains, providing ideal mosquito breeding habitat. Even worse, pollen from the corn that the villagers plant beside their huts drifts into the water-filled pits, providing food for larval mosquitoes. Spielman found that pollen-fed larvae produce many more adult mosquitoes. Now, in Ethiopia and Namibia, he is studying the relationship between house quality and malaria, and the way garden corn can facilitate the expansion of mosquito vector populations. Perhaps better housing *is* the solution. Spielman imagines creating "clean cities," malaria-free, that could act as centers of investment and tourism.

Even in the United States, human behaviors are expected to have an impact on the virulence of West Nile virus. Investigators don't expect to see many deaths in Texas, for example, because almost everyone there lives in screened, air-conditioned homes. In New York City, on the other hand, a number of the documented cases struck people who had chosen to sleep outside overnight because of the summer heat. Simple lifestyle changes, Spielman reminds us, can alter the impact of vector-borne disease.

Managing editor Jonathan Shaw '89 lives in southeastern Massachusetts, a center of mosquito-borne eastern equine encephalitis, the most virulent of this country's current landscape infections.