POISED FOR THE STING

Facing the re-emerging enemy, the scientists in the Department of Tropical Medicine at the Tulane University School of Public Health and Tropical Medicine continue to battle this ancient foe in an effort to counter the global threat of mosquito-borne diseases.

By Susan Sarver Illustrations by Mark Andresen

THE mosquito is barely perceptible as it lands on its prey, furtively piercing the flesh beneath it. Through a wound scarcely the size of a pinprick, it feeds on blood, leaving behind a trace of any pathogen it bears. Its cargo is well known—the parasites of malaria and viruses that cause dengue and some forms of encephalitis—diseases that in many parts of the world have made the mosquito public health enemy number one.

In the Department of Tropical Medicine at the Tulane University School of Public Health and Tropical Medicine (SPHTM), scientists continue to battle this ancient foe in an effort to counter the global threat of mosquito-borne diseases. While many think of such illnesses as belonging to the past, mosquitoes continue to transmit a number of debilitating and fatal diseases at an alarming level, especially in developing countries in tropical regions of the world. According to the World Health Organization (WHO) malaria infects about 400 million people annually, killing about two million people a year in Africa alone. Here in the U.S., at least a half-dozen different types of mosquitoes are known transmitters of encephalitis, West Nile virus has appeared for the first time, and dengue, mainly considered a disease of the tropics, is now a domestic threat.

"The public is just not prepared to confront the idea that there might actually be flying mosquitoes that could make them sick," says Donald Krogstad, MD, director of the Tulane Center for Infectious Diseases. That idea occupies the minds of many in the Department of Tropical Medicine, casting Tulane in a role as something of a public health superpower within the global community. As Tulane takes the lead in developing strategies to control and conquer mosquito-borne diseases, it must meet the challenges posed by drug and insecticide resistance, environmental and demographic changes, and the existing public health problems unique to developing countries.

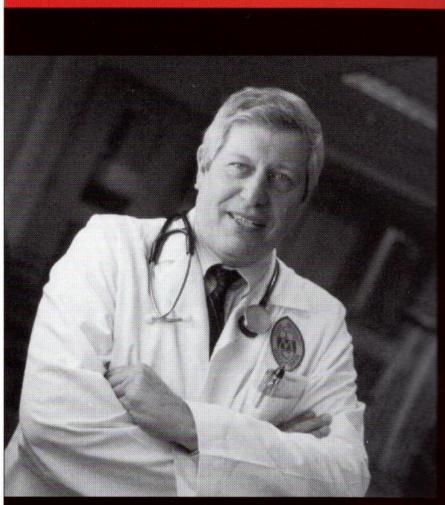
Looking Closer

"A surprising fraction of people in the U.S. actually think that malaria has been eradicated," says Krogstad. Given that only the anopheles mosquito carries malarial parasites and only the females undertake the blood feedings necessary for transmission, the enemy is well defined. However, in the 1950s, when the WHO and the World Bank made a significant effort to rid the world of malaria, they quickly encountered two major problems—DDT resistance and the deviant behavior of some mosquitoes that cause them to dodge the deadly chemical.

Another resistance problem sprung from the widespread use of chloroquin, the drug used to treat and prevent malaria. "The original idea," explains Krogstad, "was to use enough chloroquin that you would essentially treat everyone in the community and at the end of the treatment, there wouldn't be anymore infected humans to re-infect the mosquitoes." In Southeast Asia and South America, chloroquin was actually ground up and put in table salt so as to deliver a preventive dose of the drug whenever salt was added to a meal.

With such extensive use, chloroquin has become less effective in many parts of the world. "The worldwide resurgence of malaria...has been driven by drug resistance which is now prevalent in Asia, South America, and Africa," says Krogstad. Other drugs have shown a similar resistance pattern and still others remain unaffordable for people in the developing world. Krogstad believes that pharmaceutical companies under pressure to turn profits for their stock holders simply aren't interested in developing new and affordable anti-malarials.

Prior to his arrival at Tulane, Krogstad's laboratory actually discovered the mechanism behind chloroquin resistance. Taking this research forward at Tulane, Krogstad worked with Dibyendu De, PhD, research assistant professor of tropical medicine, and Larry D. Byers, PhD, professor of chemistry, to determine the parts of the chloroquin molecule that were responsible for specific biological activities.



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During that effort, Krogstad's wife, Frances Marsh Krogstad, MA, a medical research specialist in the Department of Tropical Medicine, discovered between 30 and 40 compounds that were effective against resistant parasites. Krogstad was dubious and asked her to repeat the test two more times. "When we saw it the third time, we said, 'this has to be real.'" Three of the most promising compounds were tested and remained active in monkey models of human malaria. One was finally selected for further development.

Following the elaborate process of transforming a promising compound into a usable drug, AQ13 is being tested on humans in the Clinical Research Center (CRC) at Charity Hospital. Krogstad points out that the development of AQ13 is a good illustration of the way in which Tulane resources pull together to advance a project. Researchers drew upon the Department of Chemistry to synthesize compounds, relied on the Lindy Boggs instrumentation facility to validate structures, and worked with Simon J. Hocart, PhD, research professor of medicine in the Peptide Research Laboratory in the School of Medicine to perform molecular modeling. With Frank Cogswell, PhD, Pete Didier, DVM, PhD, James Blanchard, DVM, PhD and Peter J. Gerone, ScD, at the Tulane Regional Primate Research Center, candidate compounds were tested in two monkey models of human malaria. If the studies currently underway in the CRC prove successful, AQ13 may find new clinical testing grounds at the NIH-funded Mali-Tulane Tropical Medicine Research Center (TMRC) in Mali, West Africa.

Tulane's presence in Mali has supported training programs for African investigators while taking the understanding of malaria to a new level through molecular biology. By studying the disease on a molecular level, Ousmane Koita, PharmD, a Malian graduate student in Krogstad's laboratory, has discovered hybrid parasites that appear to have a 16 times greater chance of causing cerebral malaria—the most life-threatening complication. This is an important discovery for young children who tend to acquire more severe forms of the disease, particularly in sub-Saharan Africa, where it is estimated that one child under age five dies from malaria every 20 seconds. Molecular studies have also revealed that some of the antigen genes within the parasite are constantly changing, making them moving targets—a finding that has important implications for vaccine development, which, thus far, has been unsuccessful.

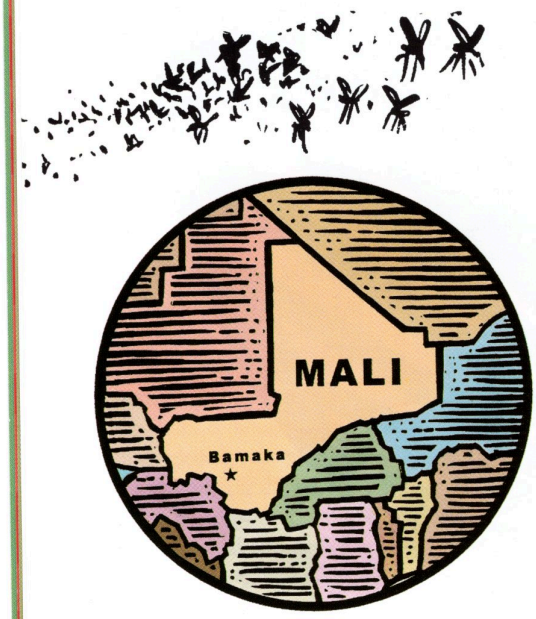
Battling Afar

At the TMRC, foreign and Tulane scientists work side-by-side not only to gain a greater understanding of the transmission process, but to understand how parasites survive across a range of environmental conditions, says John C. Beier, ScD, professor of tropical medicine. An entomologist, Beier has been involved in research in Mali for about five to six years while helping Malian scientists develop their own research programs.

According to Beier, "The most important part of malaria prevention is reducing the intensity of the transmission through proper vector control. Drugs alone are not going to control malaria for people living in endemic areas like Africa." To develop improved control methods, researchers are trying to better understand the vector populations, their biology, distributions and timing of transmissions.

One vector control strategy that has been used throughout Africa is insecticide-treated bed nets. "Proper use of treated nets can reduce transmission dramatically—in some cases, more than 90 to 95 percent," says Beier. "But you still have enough mosquitoes coming through to maintain the cycle of transmission so their overall effects on malaria prevalence are negligible. People are still becoming infected. They're dying at the same rates as without any bed nets."

The need to develop new strategies to control transmission led to an internationally coordinated program in Kenya that Beier directs. With the help of NIH funding, the International Center for Infectious Disease Research (ICIDR) program is undertaking research on African malaria vectors while providing a training ground for African medical entomologists. The research team is also setting the stage to determine if there are genes in the mosquito that are refractory, making them incapable of becoming infected with malaria. The program operates primarily through the International Center of Insect Physiology and Ecology (ICIPE) in Nairobi, Kenya—the largest organization in Africa that deals with sciences related to "dudus," the Swahili word for insects.



"We now have a team of 30 people...we also have an international network of collaborators," says Beier. Amid this international effort, Beier notes that the community has taken a strong interest in the team's fieldwork. Researchers bearing screened cartons filled with flying mosquitoes can quickly become the talk of the villages. People often track the scientists down and invite them to come and sample the mosquitoes in their own homes. According to Beier, this leads to good communication on all sides. Such communication not only fosters better understanding, it also can have an impact on community health. Beier recalls one education program that preceded the research team's arrival in Mali, which involved teaching mothers to take children with malaria symptoms to the clinics in a timely manner. As a result, "there were impressive drops in the incidence of severe disease," Beier says.

Fighting on the Home Front

The home front battle against mosquito-borne diseases centers primarily on viruses, specifically those that cause Eastern Equine Encephalitis (EEE), St. Louis Encephalitis (SLE), West Nile virus, and dengue. "Human cases of encephalitis caused by mosquito-transmitted viruses have increased dramatically in Louisiana in the past six years, equaling 43 percent of all cases in the past 36 years," says Dawn Wesson, PhD, associate professor of tropical medicine at the SPHTM. "This represents an increase of 285 percent when comparing the last six years to the previous 30." With funding from the Centers for Disease Control and support from the Office of Public Health, Wesson is working to strengthen the surveillance system for arboviruses (mosquito-borne viruses) in Louisiana. Studying these viruses also involves looking at migratory birds, as there is a natural mosquito-to-bird transmission segment that is part of the cycle. Last summer, not only were there high numbers of EEE cases in horses, there were two human cases in the state as well. "It tends to be quite a severe virus with potentially 40 to 50 percent mortality," says Wesson. "In March of 2000, there was already a fatal horse case of

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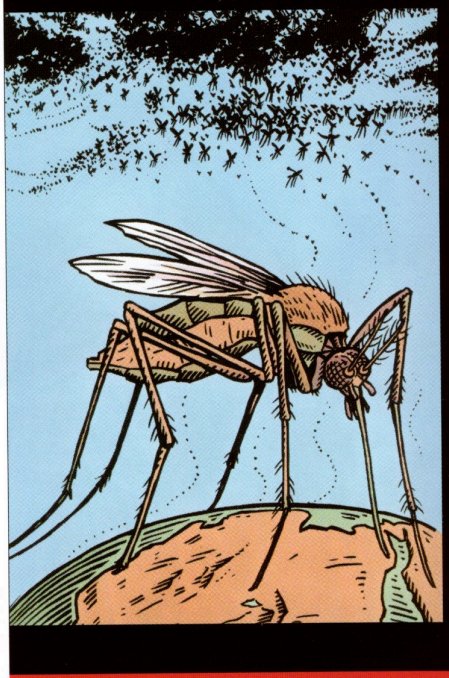

mosquito-borne encephalitis, although those cases usually do not occur until June or July. This suggests that warm winter temperatures have supported continued virus transmission. Usually, transmission is interrupted because cold winter weather kills off mosquito populations, but the past two winters have been too warm for that to occur."

In the field, Wesson's efforts help to define the environmental characteristics associated with higher transmission levels and determine the risk for transmission in various parts of the state. She also works with officials in both Mississippi and Alabama—states with very limited surveillance systems. The ultimate goal of these efforts is to translate findings into public health activities to prevent disease. Such activities often revolve around integrated pest management initiatives that combine chemical and mechanical methods of controlling vector populations. This approach involves using chemical insecticides carefully to reduce the risk of resistance development in combination with natural predators such as fish and turtles to reduce mosquito populations. It also relies on public education to protect against exposure through the use of chemical repellants and screens, and to reduce breeding sites.

While EEE and SLE remain a concern in Louisiana, it was the appearance of the West Nile virus that caused 61 cases of severe disease and seven deaths in the New York City area last summer that captured the nation's interest. According to Wesson, this was the first time the virus had been seen in this country or even in this hemisphere. There is a concern that the virus could move down the Eastern Seaboard via migratory birds and into South America and beyond.

Dengue poses another threat in this country that is relatively new. Also known as break bone fever, dengue causes a spectrum of clinical illness ranging from a viral syndrome to fatal hemorrhagic disease. Worldwide, it is the most common mosquito-borne virus and is prevalent in Puerto Rico, parts of Mexico and areas of Central and South America. It surprised researchers by establishing itself in southern Texas this past summer. According to Wesson, given the New Orleans climate, the tourist industry, and the fact that the city hosts both species of mosquitoes that transmit the dengue virus, there is a genuine concern that the disease could establish itself in Louisiana and other parts of the South. "We're going to be hearing more and more about these diseases," says Wesson.

Malaria, EEE, SLE, West-Nile virus, dengue—mosquito-borne diseases continue to create significant socioeconomic and health burdens for individuals, communities and even entire countries. It will take an ongoing collaborative effort on an international scale to remain positioned to take down the mosquito and transform it from an ancient enemy into a mere pest. Undoubtedly, Tulane will continue to lead this important public health battle as the world anxiously awaits the sting.