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**San Francisco Chronicle****EPIDEMIC****On the Front Line****Malaria kills one child every 30 seconds worldwide, and Kyle Webster aims to stop it**

- Janet Wells  
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Kyle Webster, a research scientist and U.S. Army officer, wakes up one night, feverish, his sheets soaked with sweat. The next morning he is so exhausted he can hardly stand upright. He drags himself out of bed and goes straight to his lab, where a technician pricks his finger and smears a drop of his blood on a glass slide. The technician looks into the microscope and waves Webster over.

Adjusting the magnification, Webster zeroes in on a cluster of his red blood cells. There, inside, faint but unmistakable, is a constellation of tiny dots signifying a growing infestation of *Plasmodium falciparum*, the deadly malaria parasite.

Webster isn't surprised at the diagnosis. After all, he infected himself.

A week before, as part of a malaria vaccine development program at the Army's tropical infectious disease research lab in Thailand, Webster had "challenged" his immune system by upending a small glass jar on his forearm and inviting five malaria-toting mosquitoes inside to have a feast. So Webster was expecting -- more accurately, hoping -- that he would soon begin to develop the hallmark signs of malaria.

What Webster doesn't anticipate, however, is how tough it will be to get rid of the parasites multiplying by the thousands in his blood. As chief of the Army's Department of Immunology and Parasitology at the Armed Forces Research Institute of Medical Sciences in Bangkok, Webster had helped develop two of the most powerful drugs in the world for treating malaria, which are sitting ready on the shelf. For the other four scientists who volunteered as test subjects, a dose of mefloquine does the trick. But the wily bugs inside Webster mutate, and the cycle of fever, chills and sweating returns. Then the second drug, halofantrine, fails. If Webster doesn't find a successful treatment within a few days, he -- like so many others each year -- could die.

Webster's bout with malaria was more than 15 years ago, and he was fortunate: An experimental drug cured him, and he went on to play a key role in the efforts to treat and

prevent the world's deadliest disease. Now, at age 64, Webster leads a unique malaria drug development project for San Francisco's Institute for OneWorld Health, the nation's first nonprofit pharmaceutical company.

Barrel-chested, with a broad face, Webster is both casual and no-nonsense. He wears jeans and an untucked black T-shirt and pads around his house Asia style -- barefoot, shoes left at the front door. Colorful masks, ikat weavings, ceramics and teak furniture adorn his airy Santa Cruz Mountains home, evidence of the years he spent in Thailand with his wife and their two children. Webster's postcard view of the forest sweeping down to Monterey Bay is a far cry from the steamy malarious jungles of Asia, but he has no trouble conjuring up the enemy.

"Malaria is cool, clever, deadly," he said. "A mosquito bites you and injects an infective form of the parasite, the sporozoite. Even one can infect you. Its whole purpose is to establish itself, multiply and produce daughter cells. It does this on a grand scale."

Two billion people -- one-third of the world's population -- live at risk for malaria, and some 1 billion people carry the parasite in them at any one time, providing a nearly bottomless reservoir of infection. Clinical malaria hits 300 million to 500 million people each year, killing 2 million to 3 million -- most of them children. In the decades since Webster and his colleagues slapped that mosquito-filled jar on their arms, the disease -- spurred by poverty, drug resistance and politics -- has only become more widespread and entrenched.

Malaria kills one child every 30 seconds worldwide and is the leading cause of death among children younger than 5 in Africa. In areas of intense infection, 40 percent of toddlers may die. While mostly eradicated in the United States, malarial mosquitoes are still alive and well here, and some scientists predict a re-emergence of the disease in North America and Europe.

In 1998, the World Health Organization launched its high-profile Roll Back Malaria campaign to halve the number of malaria deaths by 2010, but the effort is nowhere near its goal, even with financial support from around the world. The Seattle-based Bill & Melinda Gates Foundation alone has given nearly \$400 million in malaria research grants and aid.

Despite global economic development and enormous strides in health technology, despite global mosquito eradication efforts and considerably more than \$1 billion spent worldwide on the treatment and prevention of malaria -- although it is a curable disease -- more people die from malaria now than 40 years ago.

Webster allows that he may have had a nervous flutter when the second drug failed against his malaria in Thailand, but he took the health risks of his profession in stride. (In fact, he can't remember whether he infected himself in 1988 or 1989: "Irrelevant," he says.) Even now, Webster downplays his flesh-and-blood offering. It was noteworthy, he implies, only because of what he learned about the disease.

The silver-haired, soft-spoken grandfather doesn't seek the limelight for his accomplishments, and his unassuming mien belies his intensity about "the bugs." But search the medical journals and Webster's name crops up as an author of more than 170 malaria-related articles.

In Thailand, Webster organized the first malaria vaccine field trial conducted by the U.S. military. He had a hand in numerous drug efficacy and safety trials, and established evidence of the *P. falciparum* parasite's increasing multidrug resistance in Asia. He helped bring the world's new malaria wonder drug, artemisinin, to the West. He also helped train a generation of young Thai scientists and contributed to the science infrastructure that would serve Thailand in its fight against aggressive malaria, HIV/AIDS and other infectious diseases.

"To make a contribution to both drug and vaccines is a very large accomplishment," said Lt. Col. Douglas Walsh, a physician who is chief of the department of clinical investigation at Eisenhower Medical Center in Fort Gordon, Ga. Walsh worked for Webster at the Army research institute in Thailand, and eventually followed in his footsteps as chief. "Most scientists go down one road or another, not both," he said. "To be able to cross over underscores the breadth of his skills."

Victoria Hale, chief executive officer of the Institute for OneWorld Health, put it another way: "Kyle is very, very passionate about malaria."

Malaria is ancient -- older than man, most likely -- and has killed more of the human race than any other single entity. The deaths of Alexander the Great and Genghis Khan? Probably malaria. Oliver Cromwell and Caravaggio? Malaria. Modern luminaries who had malaria and recovered: Sir Arthur Conan Doyle, Ernest Hemingway, Ho Chi Minh and John F. Kennedy.

Scientists have been thwarted at every turn by malaria's complexities, and breakthroughs come in the tiniest of increments. There are no effective vaccines against any parasite, and malaria's bug is remarkably crafty, going through multiple phases as it invades the human body. While there have been several drugs to treat malaria, the parasites -- in particular *P. falciparum*, Webster's strain -- have a history of developing stalwart resistance.

The malaria vector -- the anopheline mosquito -- is astoundingly efficient, with the insects siphoning blood from one person, then moving on to bite multiple others, injecting parasites each time. While a single case of smallpox has the potential to spread to four or five other people, one case of malaria can infect 100, according to Robert Desowitz, author of "The Malaria Capers: Tales of Parasites and People."

Only AIDS rivals malaria as a leading cause of infectious-disease fatalities each year. But much of malaria's devastation comes from its insidious persistence, rather than its deadly aim. The *P. falciparum* parasite is the cause of nearly all malaria deaths and a large proportion of the morbidity. But it, along with the other three malaria parasites that

invade humans -- *P. vivax*, *P. malariae* and *P. ovale* -- can be readily cured. But most countries can't afford the best drugs, nor do they have the resources to keep malaria from recurring. Anopheline mosquitoes come around every evening, and malaria returns, causing widespread anemia, learning disabilities and brain damage in children.

In countries where malaria is most intense -- sub-Saharan Africa, Southeast Asia, India and Central and South America -- the disease wreaks economic havoc by incapacitating the labor force and discouraging tourism and business investment. Malaria costs an estimated \$12 billion annually in lost gross domestic product in Africa alone, where it consumes 40 percent of the continent's public health budgets, according to the World Health Organization.

Malaria was once a scourge in the United States, as well. One of the first military expenditures of the Continental Congress was \$300 to buy quinine to protect George Washington's troops, according to "The Malaria Capers." (Smart move: In 1781, British Gen. Charles Cornwallis surrendered to Washington at Yorktown in part because a good number of his soldiers were deathly ill with malaria.) During the Civil War, malaria accounted for 20 percent of all hospitalizations, and some four-fifths of the black soldiers of the Union Army got malaria annually. In 1914, there were 600,000 cases of malaria in the United States. By the 1940s, water management and improved public health and socioeconomic conditions had vastly reduced malaria locally. But the anopheline mosquitoes are still here, present in every state except Hawaii. And malarial mosquitoes are likely hitchhiking into the country, as well: The World Health Organization has documented dozens of "airport malaria" cases in Europe, with jet-setting mosquitoes disembarking from international flights and infecting people who never left their country.

In 2001, there were nearly 1,400 malaria cases in the United States, resulting in 11 deaths, according to the Centers for Disease Control and Prevention in Atlanta. The vast majority stemmed from exposure outside the country. But local mosquitoes have also been the culprits.

"We've had mini-outbreaks in Palm Beach, Michigan, California," said author Desowitz, professor emeritus of tropical medicine and microbiology at the University of Hawaii.

While it is unlikely that the disease will reach epidemic proportions here again, "The Malaria Capers" posits that global warming "may make our own temperate zone malarious once again."

Webster's fascination with microscopic bugs started when he was just old enough to peer through a microscope.

"Even in his early school years, he was studying paramecium," said his wife, Marian, who met her husband-to-be while they were undergraduates at the University of Florida. "I think he was born a science person."

Webster received his doctorate at Georgetown University, and after five years with the Office of the Army Surgeon General, he joined the malaria team at Walter Reed Army Institute of Research in Washington.

Because new drugs and vaccines cost hundreds of millions of dollars to develop and bring to market, and there is little profit to be made from what is primarily a disease in developing countries, malaria is virtually ignored by our pharmaceutical industry. But malaria is the No. 1 tropical disease faced by the U.S. military, and the Army has done seminal work in the field, spending hundreds of millions to develop drugs and research vaccines.

Webster realized that if he wanted to be a malariologist, he needed to follow the disease, and in 1981 transferred to the Army's research lab in Thailand. Not long after arriving, Webster, along with scientists from the British biomedical research foundation, the Wellcome Trust, traveled to China to check out reports of an ancient herbal remedy that appeared to have anti-malarial properties. There they met Professors Li Guo Qiao and Jing Bo Jang, who showed them a compound extracted from the quinghao plant, *Artemisia annua*. Known in the West as sweet wormwood, the dried leaves, infused in hot water, had been used as a fever remedy for 2,000 years.

When the scientists left China, according to a Wellcome Trust report, they were handed the ultimate farewell present -- a bottle of the powdered compound, now known as artemisinin. While intrigued, Webster had no inkling the role it would eventually play in his life, personally and professionally.

"There was no reason to think that this drug was any more promising than any of the others we were looking at," Webster recalled. His lab tinkered some with the new compound, and he introduced it to his Army colleagues in Washington, but continued to focus on mefloquine and halofantrine.

Within a few years, however, problems with the Army's drugs surfaced. Halofantrine exhibited cardiovascular side effects, and mefloquine showed adverse neurological effects. In addition, Webster and his colleagues had discovered that the Army's new anti-malarials were going the way of chloroquine, antifolates, pyrimethamine and DDT -- succumbing to the parasite's adaptability.

"People weren't happy with me, because I was saying [mefloquine] had resistance before it was even fully in use. I felt it might not last more than three to five years, which turned out to be true, unfortunately," Webster said.

As his three-year appointment in Thailand stretched to 11, Webster spearheaded the U.S. military's first malaria vaccine field trial with the Thai army, on the Cambodian border. In the early 1990s, shortly before returning to the United States, Webster directed vaccine development along Thailand's border with Burma (also known as Myanmar), where he witnessed malaria's deleterious effects up close.

"When you go into a village, malaria isn't just a disease, it's a way of life," Webster said. "They live with it and suffer."

Since 1988, an ongoing civil war and military dictatorship have driven 400,000 Burmese -- many of them ethnic minorities -- to flee through the malaria-ridden jungle to Thailand. Another half-million have been uprooted from their homes and pushed into makeshift villages in eastern Burma, where the conflict still simmers.

While malaria still plagues Thailand's border provinces and consumes considerable resources, it is well controlled. Next door, however, malaria is the leading cause of disease and death.

In eastern Burma, the repressive government provides little or no health care and strictly prohibits access by foreigners. Among internally displaced refugees, malaria constitutes one-quarter of the caseload and leads to 44 percent of the deaths, according to data compiled by the Los Angeles-based Global Health Access Program (GHAP), one of the few organizations currently funding a malaria control program inside Burma's conflict zones.

With resources and training from GHAP, refugee health workers distributed insecticide-treated bed nets to 3,500 displaced villagers in eastern Burma in 2003, tested the villagers for malaria, and gave drug therapy to those with a positive test, whether or not they were sick. The health workers returned at six-month intervals to test and treat again. The idea was for the drugs to attack malaria lurking in the human reservoir, and for the bed nets to keep the mosquitoes at bay, preventing the reservoir from filling up again. In two years, the program resulted in a 90 percent decrease in malaria in the five pilot villages.

In one of the pilot villages in 2004, a villager broke into a betel-nut-stained grin when asked about her health by a visiting reporter. "I used to have malaria very often, three, four times a year," said the 20-year-old woman, in Karen, a hill-tribe language translated by a medic. The woman's young children sat next to her on the bamboo slats of their rickety open-air hut. "After the net, zero malaria. The children, too. I thought I was going crazy. I didn't think a net could stop malaria."

One of the village elders added with a laugh, "This is like malaria-free zone."

The drug that GHAP used with such resounding success? Artemisinin. By the late 1990s, the drug was being heralded as the malaria miracle. While Western pharmaceutical companies ignored artemisinin, the Chinese quietly pioneered the development of derivatives like artesunate and artemether.

Artemisinin-class drugs have not been approved by the U.S. Food and Drug Administration, and a lack of long-term clinical safety data concerns some scientists. However, based on studies done in Asia and Africa showing minimal adverse effects, the World Health Organization adopted artemisinin therapy as its recommended malaria treatment worldwide. The derivatives have saved countless lives, and so far, the malaria

parasite has exhibited negligible resistance. (To keep it that way, artemisinin derivatives are combined with older malaria drugs, giving the parasite a one-two punch.)

But artemisinin drugs have a downside: They cost as much as \$2.40 per adult dose (compared to 10 cents for chloroquine) -- out of reach of most developing countries and cash-strapped humanitarian organizations. In addition, because of increased demand, the price of China's sweet wormwood tripled this year, making supplies scarcer, and rampant counterfeits have flooded the world market.

This year, GHAP expanded its malaria control program to 11 more villages, covering 10,000 refugees in eastern Burma. The group could do even more if it had cheap, ready access to drugs, test kits and nets.

"Could we expand the program to cover the majority of [internally displaced persons]? Sure, if the resources were there," said Dr. Adam Richards, GHAP's malaria program manager. "We have the most drug-resistant malaria in the world. We need artemisinin combination therapy because nothing else works."

That's where Webster and OneWorld Health come in. With a \$42.6 million grant from the Gates Foundation, OneWorld Health, partnered with UC Berkeley and Amyris Biotechnologies, is working to perfect a microbial factory for making artemisinin and to develop the process for large-scale production. The goal: in five to seven years, a readily available, FDA-approved genetically engineered drug as potent and curative as plant artemisinin derivatives, selling for under \$1 per dose.

Webster took on the project in January, lured from the lucrative private sector, where he worked for the medical technology company Becton Dickinson after retiring from the Army in 1993. It wasn't hard for nonprofit OneWorld Health to reel in Webster. He was delighted to be back on the front lines of malaria, reclaiming the sense of purpose he had with the Army.

For Webster, the value of artemisinin isn't just academic. In Thailand, after two drugs failed him, he was on the verge of undergoing intravenous quinine therapy, which can lead to cardiac arrest. Instead, he thought about the vial he had carried back from China years before. While the Army had none of the then-experimental drug, Webster went across the street to a Thai colleague, Sornchai Looareesuwan, whose lab was getting ready to put the drug into clinical trials. Kyle Webster was probably the first Westerner to take an artemisinin derivative for malaria. By the next day, he was back at work. Within a week, the parasites were gone from his bloodstream.

"It was," he said simply, "dramatic."

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