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THE MALARIA FIGHTER

SCIENTIST **STEPHEN HOFFMAN** MAY BE CLOSE TO NEUTRALIZING ONE OF HISTORY'S MOST IMPLACABLE KILLERS—AND FORGING A NEW ENTREPRENEURIAL MODEL FOR ATTACKING GLOBAL DISEASES. **BY MICHAEL MYSER**

On a recent afternoon, in stifling 100-degree heat, eight fragile children lie in cribs covered with mosquito nets in the pediatric ward of a small hospital in Navrongo, a rural town in the West African country of Ghana. They all arrived today, burning up with malaria, a remorseless killer in this region. Their shell-shocked mothers look on as the kids shiver and moan. The nurses say business is slow; they normally admit 10 patients per day at this time of year. The kids in the ward, having survived a trek in from the bush that many malaria victims here don't, will get medicine and are likely to survive. But that does little to brighten the outlook of Patrick Atobrah, the hospital's sad-eyed medical superintendent. He and his few doctors are overwhelmed. "The results can be quite horrible," he says.

The area around Navrongo has one of the highest malaria rates in the world. During the rainy season, 82 percent of the area's children between the ages of 5 and 10 will be infected with the disease. Navrongo, in short, is a heavy contributor to malaria's brutal global toll: Roughly 2 million people die of the disease every year. Most are children. The death count is headed upward because the drugs and pesticides used to treat malaria are increasingly ineffective. "We need help," Atobrah says. More specifically, he needs "an

MARK TOMALTY/MASTERFILE

BUGGED
Anger at witnessing countless deaths from mosquito-borne malaria fuels Hoffman's crusade to create a vaccine against the disease.

PHOTOGRAPHS BY CHRIS MUELLER/REDUX

effective vaccine that protects children" from getting infected in the first place.

As it happens, the world may be close to having one. It's sitting in cryopreserved vials in a freezer at an industrial park in Rockville, Md.

Stephen Hoffman swings open a heavy steel door in a shabby brick building nestled between a rug outlet and a home appliance store in Rockville, a Washington suburb. Heat, thick and wet, wells up instantly; the room's climate is controlled to mimic the oppressive conditions of a West African rainy season—like, say, Navrongo's. Hoffman is the founder of a tiny startup called Sanaria. He is also one of the world's best-known tropical disease experts and a veteran malaria fighter.

Surrounded by vats of buzzing insects, Hoffman and his 25-member team are harvesting as many as 100,000 eggs a week from female mosquitoes, feeding the hatchlings human blood loaded with the mosquito-borne parasites that cause malaria and then zapping them with radiation. Once extracted, the radiation-weakened parasites will be whipped up into a vaccine that Hoffman believes will provide protection from malaria in 90 percent of the people who get injected—an unheard-of level of immunization that would transform the disease from an implacable scourge into just another public health nuisance.

No one, least of all Hoffman, underestimates how far he has to go to win approval for a vaccine, or to perfect his method. "It's not a hard process unless you try to do it," he deadpans. Under the best of circumstances, Sanaria's vaccine is years away. Still, some noted experts think Hoffman may be closer than anyone has ever been to a highly effective vaccine. Maurice Hilleman, who before his death last April had long been legendary for creating 40 different vaccines, said Sanaria's approach "might even be the only show in town" for truly taming malaria. Maxwell Appawu, a Ghanaian malaria expert who has visited Sanaria's facility, says Hoffman is "very close" to succeeding.

If he does, the consequences will be immense: Apart from the staggering death toll—malaria kills a child every 30 seconds—the disease exacts a brutal economic cost on the areas, mostly poor and deep in the Third World, where it thrives. Jeffrey Sachs, an economist at Columbia University's Earth Institute, estimates that the disease lowered incomes in impoverished African countries in the malarial hot zone by $130 billion between 1980 and 1995. Creating a vaccine that approaches the 90 percent effectiveness that Hoffman believes he can reach "would be a major, major event in the history of medicine," says Howard Markel, a noted medical historian at the University of Michigan. It would also be the stuff of Nobel Prizes.

Hoffman's hunt for a malaria vaccine is a tale of scientific derring-do, marked by a lot of prowling in the jungle and the occasional brush with death. But it also contains a dose of shrewd entrepreneurial maneuvering. Hoffman has come up with a clever way to cope with one of the biggest obstacles faced by all vaccine hunters: the fact that research funding has been minuscule for decades. Governments and pharmaceutical giants have seen malaria thwart many promising—and costly—efforts to control it in the past; moreover, the places where it runs riot haven't promised the profits that lead to heavy research spending. Only recently, through initiatives largely led by Microsoft chairman Bill Gates, has malaria begun to attract serious philanthropic funds.

So Hoffman is drawing on public funds to get Sanaria through Food and Drug Administration trials. If his vaccine works, some experts believe, Sanaria could transform the malaria vaccine industry into a $3 billion business and provide a financial road map for attacking other scourges. For Hoffman, that payoff would be secondary. "I haven't spent 25 years working on diseases of the most disadvantaged and neglected people in the world," he says, "to start a company that's just here to make money."

DOLLARS AND SENSE

Malaria kills up to 3 million people each year and has cost Third World nations hundreds of billions of dollars. Yet despite the enormous potential for good (and profit), funding for vaccine research has been relatively limited.

FUNDING RECEIVED BY SANARIA
$10 million

AMOUNT NEEDED TO COMMERCIALIZE A VACCINE
$500 million

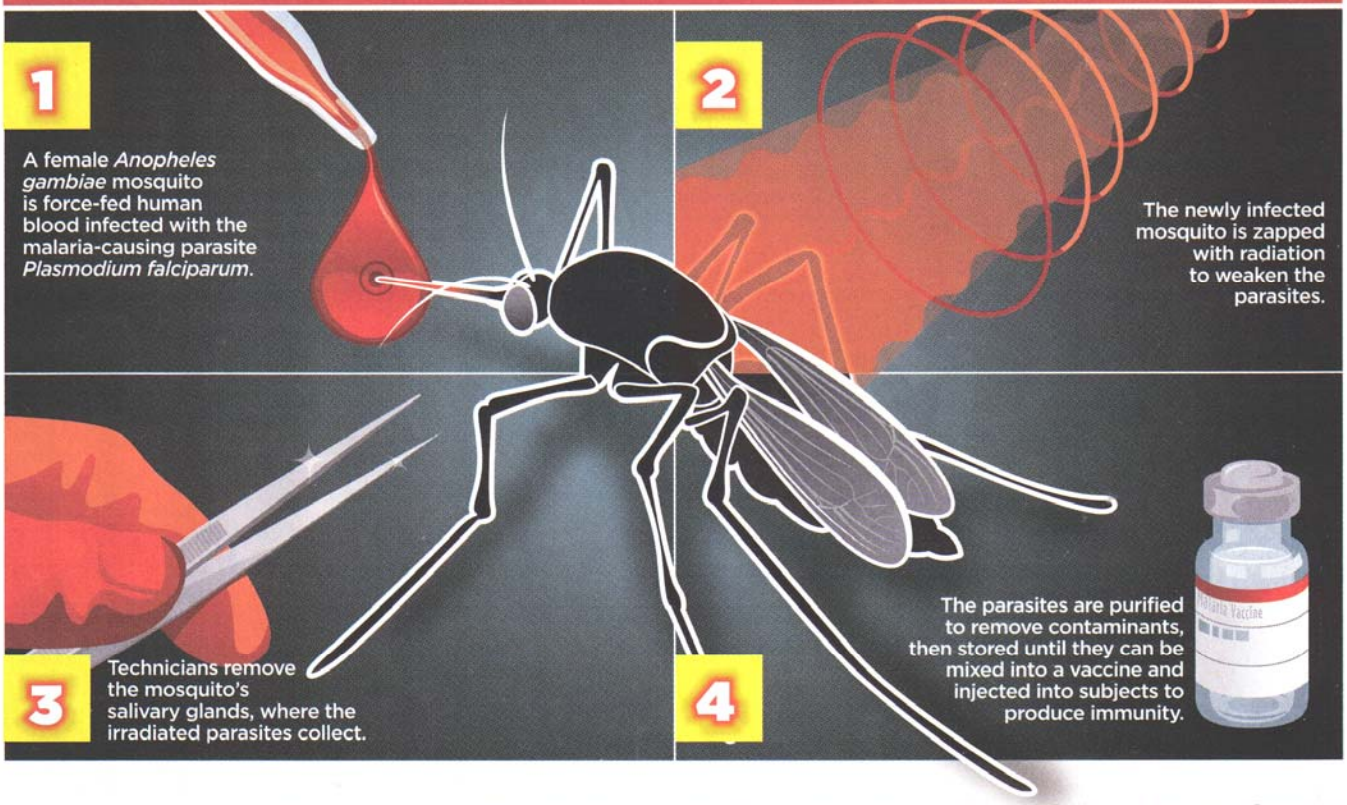
POTENTIAL SIZE OF MALARIA VACCINE MARKET
$3 billion/year

Sources: Center for Global Development; Malaria Foundation; Sanaria

Malaria has been a prolific killer for thousands of years: Some scientists theorize that a widespread malaria upsurge contributed to the fall of the Roman Empire. The nastiest form of the disease takes hold when a female *Anopheles gambiae* mosquito infected with *Plasmodium falciparum* parasites feeds on the blood of a human. Parasites released into the bloodstream multiply by the thousands in liver cells, ultimately bursting those cells and invading and multiplying again in red blood cells. While the parasites run wild, initial flulike symptoms give way to

FROM CARRIER TO CURE

How Sanaria turns the insects that transmit malaria into incubators for its vaccine.



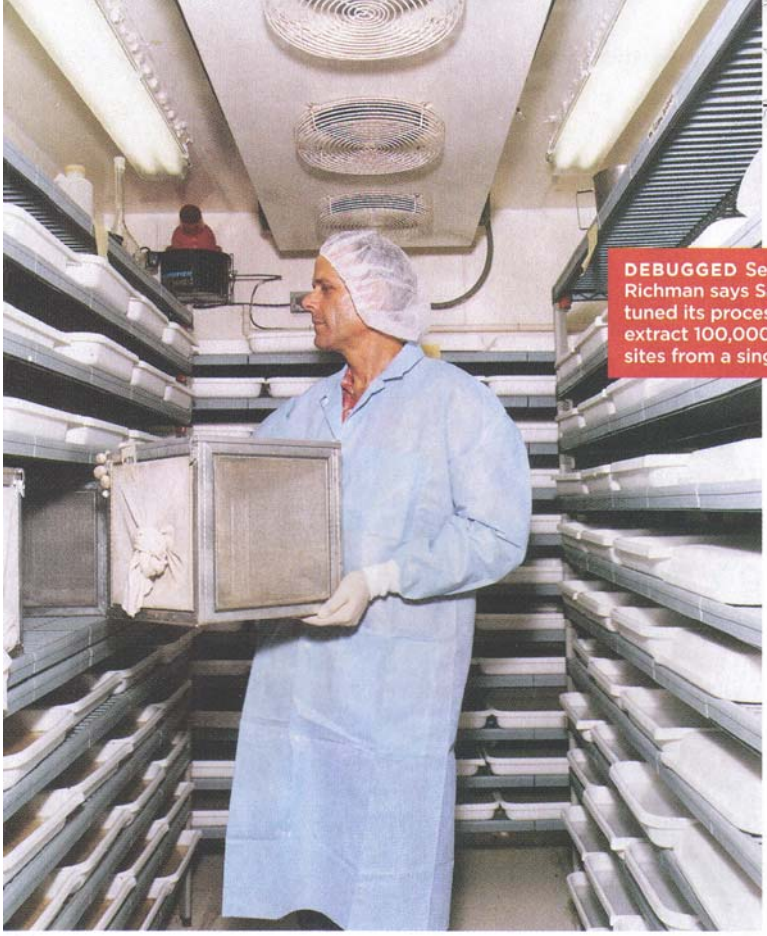
raging fever and devastating headaches. Left untreated, the disease can cause severe anemia or develop into cerebral malaria, which attacks the brain and kills as many as half of its victims. Though malaria was eradicated in much of the world more than half a century ago, the disease now kills more people than it did 40 years ago, and the parasite has developed at least partial immunity to almost all of the drugs used to treat it.

Worse, the bug has proven even more adept at thwarting vaccines that would prevent the disease from ever taking hold. The parasite is genetically complex and produces some 5,300 antigens, substances the body can potentially recognize and attack to fend off disease. HIV, by contrast, has just 11. "I think the fundamental issue is we don't know which part of the parasite a vaccine needs to interact with to prevent infection," says Carlos "Kent" Campbell, former head of the malaria program at the Centers for Disease Control and Prevention and current director of malaria control at the nonprofit Program for Appropriate Technology in Health (PATH).

Hoffman has a long and close acquaintance with the disease. After receiving his MD from Cornell University, he joined the Navy and shipped out to study tropical diseases in Jakarta, Indonesia, in 1980. For the next 18 months, he and his colleagues set about finding a new way to treat severe typhoid, a disease Hoffman had contracted in Ecuador while in med school. (He didn't tell his parents that he lay near death in a rural Ecuadoran clinic, rattling with fever.) In 1984 the team published a study in the *New England Journal of Medicine* that has become the standard for treating typhoid. "The best thing I ever did in my career was the first thing I ever did," he says. "Matching that is very difficult." Hoffman saw malaria as a potential second act. He started focusing on it in the mid-1980s, beginning in New Guinea with an attempt to treat cerebral malaria. It didn't go well. "I'd see children I thought I had saved die three hours later," he says.

In 1984 he returned to the United States bent on preventing the disease from spreading. For the next 16 years, Hoffman directed the malaria program at the Naval Medical Research Center, spending years in tropical jungles, seeing numerous vaccine candidates fail, and witnessing countless deaths. The work wasn't just dispiriting; it was dangerous. Once, in the late '80s, a small plane ferrying Hoffman to a research site in Kenya crash-landed; he managed to walk away. In 1987 he flew from Washington to San Diego for a conference and awoke the next morning feeling terrible. "I think I have the flu," he told his wife, Kim Lee Sim, a biologist who runs her own biotech startup. "Are you crazy? You have malaria," she replied. She was right: He had contracted it while volunteering in a trial of a potential vaccine.

Two years later Hoffman had a sudden flash of insight that opened the way to Sanaria, when his mind alighted on some intriguing research that had long lain dormant. In part to better



DEBUGGED Senior entomologist Richman says Sanaria has fine-tuned its process and can now extract 100,000 irradiated parasites from a single mosquito.

understand how the body reacts to malaria, scientists in 1973 had begun successfully vaccinating volunteers by administering about 1,000 bites from mosquitoes that were infected with the parasite but weakened by radiation.

Hoffman compiled data from other largely forgotten tests of the same technique and concluded that the approach was extraordinarily effective, protecting 90 percent of volunteers for more than 10 months. The distribution mechanism—mosquitoes—was so impractical, though, that no one pursued the findings as the basis for a vaccine. To fashion a practical vaccine based on irradiated mosquitoes required figuring out a way to extract the nuked parasites and distill them into a concentrated soup that could deliver the wallop of 1,000 mosquito bites in a single hypodermic injection.

The more Hoffman noodled on it, though, the more he came to believe that he could cook up an injectable vaccine from the weakened bugs. A lot of his colleagues thought he was nuts, but he founded Sanaria in 2002 to pursue the approach, and the company has already overcome many of the technical hurdles that discouraged others for three decades. For instance, most researchers can get only a limited number of parasites (up to 30,000) into a single mosquito. But Sanaria has developed a method that crams larger quantities of them into blood cultures; it has also developed more effective ways of getting that blood into mosquitoes. Sanaria senior entomologist Adam Richman says the biological challenge of combining these two live organisms is extremely difficult, but by carefully honing the process, Sanaria can now milk as many as 100,000 irradiated parasites—believed to be the number required to create immunity—from one mosquito. That potentially huge breakthrough means that Sanaria, at least in the lab, can create a concentrated form of irradiated parasites that theoretically could be administered with a few shots, even just one.

There are other tricky issues. One is ensuring that the vaccine is pure, with no bacteria or other contaminants slipping in during the process. To demonstrate how his team approaches that challenge, Hoffman dons a lab coat and, somewhat gingerly, enters a sealed room resembling a bank vault at Sanaria headquarters. "This is the leading cause of death in children in the world, so you need high security," he says. Behind two password-protected doors, a researcher is at work under a biohood, infecting human blood with *Plasmodium falciparum*. That blood will be fed to mosquitoes raised in incubators, and one incubator sits in a corner, full of mosquitoes bloated with parasites.

A nearby irradiator nukes the infected mosquitoes, after which technicians dissect them and remove the salivary glands, where the parasites collect. The next step is to isolate the parasites by removing mosquito saliva and other contaminants. Here, too, the team has made critical advances; Sim's company has developed a process to cleanse the parasites, as well as a test to ensure that they're free of impurities. Then the parasites are packed in vials and frozen until the day the vaccine can be administered to test subjects.

Hoffman doesn't know when that day will be— it's at least a year away. In the meantime, even as he grapples with the technical challenges, he has to keep Sanaria solvent. For vaccine-seeking malaria fighters, getting money has proven almost as frustrating as battling the parasites. Hoffman has done better than most, but it hasn't been easy.

After founding Sanaria, Hoffman initially looked toward Big Pharma and deep-pocketed investors for funding. His pitch drew multimillion-dollar offers, but each required that Hoffman cede control of the company. That was a deal breaker. But while mounting his road show, Hoffman had also joined the long line of researchers applying for grants. He was able to sign the Navy on as a research partner, which gave him added credibility, as did the fact that Sanaria's board featured luminaries like Sachs and vaccine legend Hilleman. Hoffman lined up about $1.5 million from the Institute of OneWorld Health, a nonprofit whose malaria vaccine program is funded by the Bill & Melinda Gates Foundation. Last May, Sanaria received a $4.1 million grant from the Army, and it has expanded its grants from the National Institutes of Health to $4.8 million, bringing the company's total to just over $10 million.

Commercializing a single malaria vaccine is estimated to cost $500 million or more, so Hoffman will obviously need a lot more money in the future. And he is by no means the only malaria fighter grasping at the relatively small pie of money. While Hoffman has yet to begin FDA testing, a handful of other vaccines are well into the process.

One, called RTS,S, is being developed by GlaxoSmithKline,

though it has largely been funded in recent years by PATH's Malaria Vaccine Initiative, which received $150 million from the Gates Foundation. A trial in Africa with more than 2,000 children between the ages of 1 and 4 found that the vaccine reduced infection risk by 37 percent for six months and the incidence of severe malaria by 58 percent. Licensing of a vaccine is expected by 2010.

Some experts, however, question the value of a vaccine that lowers infection risk by just 37 percent. "Other vaccines, one shot and you're taken care of for life," says Kwadwo Koram, a malaria expert in Accra, Ghana's capital. "We don't want people to take the vaccine, quit other treatments, and then start dying."

Hoffman believes that his vaccine's effectiveness would allow it to leapfrog over RTS,S—and cure a host of problems plaguing malaria researchers. For instance, most experts still see the primary markets for a vaccine as the poor countries where the disease is rampant and question whether those countries can help offset the hundreds of millions of dollars required to bring a vaccine to market. Hoffman thinks a vaccine that's 90 percent effective would open other markets, including the armed forces of developed countries. He points out that malaria killed more U.S. soldiers in the 20th century than bullets did. It's questionable whether travelers from developed countries would find much use for a 37 percent likelihood of protection, but Hoffman and several other experts believe that Sanaria's vaccine would be a huge hit among travelers to China and Southeast Asia. Hoffman thinks these potentially huge global markets clear up issues about how he'd fund the long march toward commercialization.

Which brings us back to the only real question for Hoffman: Will his stuff work? A number of highly regarded malaria experts have their doubts. They question whether Sanaria is really on track to produce enough irradiated parasites, adequately pure, to make a workable vaccine or win FDA approval. "Can it be made on a large scale? Probably not," says Col. Donald Heppner, chief physician of the malaria vaccine program at the Walter Reed Army Institute of Research. "There are significant regulatory and technological barriers."

Others are more optimistic. Hilleman thought Hoffman might well be capable of producing commercial-scale quantities by 2007. PATH's Campbell calls Hoffman's work "groundbreaking." "He's working on a vaccine based on the only highly effective approach, and up to this point people didn't believe you could do it," he says. "He's proving that you can."

The answer will come only with human trials. Hoffman says he expects to begin first-stage trials within a year; the FDA won't comment. Even though field testing may be years away, Hoffman long ago developed a detailed protocol.

He plans to conduct the tests in Navrongo. He knows the area well: Its cruel distinction as a premium malaria hot zone has made Navrongo an attractive center for tropical disease researchers for nearly 20 years, with good equipment, decent communications, expert local researchers, detailed epidemiological data—and, of course, abundant malaria parasites. So many, in fact, that Hoffman says he and his team of Sanaria, Navy, and local researchers expect to have a "statistically valid" picture of whether his vaccine provides protection from the disease within two months of injecting his first human subjects. "The team is already in place," he says, "and it's ready to roll."

Atobrah, the director of Navrongo's hospital, seems ready for action too. The physician won't venture an opinion on Hoffman's approach, but he thinks a vaccine is the only real solution to the area's merciless malaria problem. "Our patient numbers," he says, "would come crashing down." Outside his sweltering office early on a Sunday, a line of women carrying listless children has already formed. Just by looking, the doctor can tell why they're here. The kids have malaria. ■

Michael Myser is a freelance writer in New Jersey.

BATTLE LINES

Sanaria's vaccine is but one of many efforts to defeat malaria. Here are some of the most promising.

Using irradiated mosquitoes as the basis for a malaria vaccine is certainly a promising approach—but it's hardly the only one. Nearly 60 vaccine programs are currently in the works; most are trying to use the parasite's genetic material as the source for compounds to stimulate the human immune system. Oxford scientist Adrian Hill has created a vaccine using fragments of parasite proteins. The compound has shown promise in small-scale trials, though it is several years from formal tests.

Meanwhile, Hoffman's approach has inspired others to follow similar veins. Stefan Kappe of the Seattle Biomedical Research Institute weakens parasites by deleting a single gene. A vaccine using the modified bugs has conferred close to 100 percent immunity in lab mice.

There is also new hope for treating the disease after it takes hold. Novartis has created a drug called Coartem based on the sweet wormwood plant, an age-old folk remedy used in China that contains an extract, called artemisinin, that kills parasites. A cocktail of Coartem and the typical quinine-based medicines has in some cases proven more effective than quinine-based compounds alone. Novartis sold $6.4 million worth of Coartem over the past year. Wormwood, however, is relatively rare; thus, Novartis and others are looking to synthetic compounds that could produce more powerful ways to attack malaria. — MEREDITH SADIN