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Malaria: Stopping a Global Killer

FROM *National Geographic*

IT BEGINS WITH A BITE, a painless bite. The mosquito comes in the night, alights on an exposed patch of flesh, and assumes the hunched, head-lowered posture of a sprinter in the starting blocks. Then she plunges her stiletto mouthparts into the skin.

The mosquito has long, filament-thin legs and dappled wings; she's of the genus *Anopheles*, the only insect capable of harboring the human malaria parasite. And she's definitely a she: male mosquitoes have no interest in blood, while females depend on protein-rich hemoglobin to nourish their eggs. A mosquito's proboscis appears spike-solid, but it's actually a sheath of separate tools — cutting blades and a feeding tube powered by two tiny pumps. She drills through the epidermis, then through a thin layer of fat, then into the network of blood-filled microcapillaries. She starts to drink.

To inhibit the blood from coagulating, the mosquito oils the bite area with a spray of saliva. This is when it happens. Carried in the mosquito's salivary glands — and entering the body with the lubricating squirt — are minute, wormlike creatures. These are the one-celled malaria parasites known as plasmodia. Fifty thousand of them could swim in a pool the size of the period at the end of this sentence. Typically, a couple of dozen slip into the bloodstream. But it takes just one. A single plasmodium is enough to kill a person.

The parasites remain in the bloodstream for only a few minutes.

They ride the flume of the circulatory system to the liver. There they stop. Each plasmodium burrows into a different liver cell. Almost certainly, the person who has been bitten hardly stirs from sleep. And for the next week or two, there's no overt sign that something in the body has just gone horribly wrong.

We live on a malarious planet. It may not seem that way from the vantage point of a wealthy country, where malaria is sometimes thought of, if it is thought of at all, as a problem that has mostly been solved, like smallpox or polio. In truth, malaria now affects more people than ever before. It's endemic to 106 nations, threatening half the world's population. In recent years, the parasite has become so entrenched and has developed resistance to so many drugs that the most potent strains can scarcely be controlled. This year malaria will strike up to half a billion people. At least a million will die, most of them under the age of five, the vast majority living in Africa. That's more than twice the annual toll a generation ago.

The outcry over this epidemic, until recently, has been muted. Malaria is a plague of the poor, easy to overlook. The most unfortunate fact about malaria, some researchers believe, is that prosperous nations got rid of it. In the meantime, several distinctly unprosperous regions have reached the brink of total malarial collapse, virtually ruled by swarms of buzzing, flying syringes.

Only in the past few years has malaria captured the full attention of aid agencies and donors. The World Health Organization (WHO) has made malaria reduction a chief priority. Bill Gates, who has called malaria "the worst thing on the planet," has donated hundreds of millions of dollars to the effort through the Bill and Melinda Gates Foundation. The Bush administration has pledged \$1.2 billion. Funds devoted to malaria have doubled since 2003. The idea is to disable the disease by combining virtually every known malaria-fighting technique, from the ancient (Chinese herbal medicines) to the old (bed nets) to the ultramodern (multidrug cocktails). At the same time, malaria researchers are pursuing a long-sought, elusive goal: a vaccine that would curb the disease for good.

Much of the aid is going to a few hard-hit countries scattered across sub-Saharan Africa. If these nations can beat back the disease, they'll serve as templates for the global antimalaria effort.

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And if they can't? Well, nobody in the malaria world likes to answer that question.

One of these spotlighted countries — perhaps the place most closely watched by malaria experts — is Zambia, a sprawling, landlocked nation carved out of the fertile bushland of southern Africa. It's difficult to comprehend how thoroughly Zambia has been devastated by malaria. In some provinces, at any given moment more than a third of all children under age five are sick with the disease.

Worse than the sheer numbers is the type of malaria found in Zambia. Four species of malaria parasites routinely infect humans; the most virulent, by far, is *Plasmodium falciparum*. About half of all malaria cases worldwide are caused by *falciparum*, and 95 percent of the deaths. It's the only form of malaria that can attack the brain. And it can do so with extreme speed — few infectious agents can overwhelm the body as swiftly as *falciparum*. An African youth can be happily playing soccer in the morning and be dead of *falciparum* malaria that night.

Falciparum is a major reason that nearly 20 percent of all Zambian babies do not live to see their fifth birthday. Older children and adults, too, catch the disease — pregnant women are especially prone — but most have developed just enough immunity to fight the parasites to a stalemate, though untreated malaria can persist for years, the fevers fading in and out. There are times when it seems that everyone in Zambia is debilitated to some degree by malaria; many have had it a dozen or more times. No surprise that the nation remains one of the poorest in the world: a country's economic health has little chance of improving until its physical health is revitalized. Zambia's goal is to reduce malaria deaths by 75 percent over the next four years.

To witness the full force of malaria's stranglehold on Zambia, it's essential to leave the capital city, Lusaka. Drive north, across the verdant plains, past the banana plantations and the copper mines — copper is Zambia's primary export — and into the forested region tucked between the borders of Angola and the Democratic Republic of the Congo. This is North-Western Province. It is almost entirely rural; many villages can be reached only by thin footpaths worn into the beet-red soil. A nationwide health survey in 2005

concluded that for every 1,000 children under age five living in North-Western Province, there were 1,353 cases of malaria. An annual rate of more than 100 percent seems impossible, a typo. It is not. What it means is that many children are infected with malaria more than once a year.

In North-Western Province, competent medical help can be difficult to find. For families living in the remote northern part of the province, across more than 1,000 square miles of wild terrain, there is only one place that can ensure a reasonable chance of survival when severe malaria strikes a child: Kalene Mission Hospital. This modest health center, in a decaying brick building capped with a rusty tin roof, represents the front line in the conflict between malaria and man. Scientists at the world's high-tech labs ponder the secrets of the parasite; aid agencies solicit donations; pharmaceutical companies organize drug trials. But it is Kalene Hospital — which functions with precisely one microscope, two registered nurses, occasional electricity from a diesel generator, and sometimes a doctor, sometimes not (though always with a good stock of antimalarial medicines) — that copes with malaria's victims.

Every year for a century, since Christian missionaries founded the hospital in 1906, the coming of the rainy season has marked the start of a desperate pilgrimage. Clouds gather; downpours erupt; mosquitoes hatch; malaria surges. There's no time to lose. Parents bundle up their sick children and make their way to Kalene Hospital.

They come mostly on foot. Some walk for days. They follow trails across borders, into rivers, through brushwood. When they reach the hospital, each child's name is printed on a card and filed in a worn wooden box at the nurses' station. Florence, Elijah, Ashili. They come through the heat and the rain and the dead dark of the cloudy night. Purity, Watson, Miniva. Some unconscious, some screaming, some locked in seizure. Nelson, Japhious, Kukena. A few families with bicycles, Chinese-made one-speeds, the father at the pedals, the mother on the seat, the child propped between. Delifia, Fideli, Sylvester. They fill up every bed in the children's ward, and they fill up the floor, and they fill up the courtyard. Methyline, Milton, Christine. They pour out of the bush, exhausted and dirty and panicked. They come to the hospital. And the battle for survival begins.

From the mosquito's salivary glands to the host's liver cell: a

quiet trip. Everything seems fine. Even the liver itself, that reddish sack of blood-filtering cells, shows no sign of trouble. It's only in those few rooms whose locks have been picked by *falciparum* where all is pandemonium. Inside these cells, the malaria parasites eat and multiply. They do this nonstop for about a week, until the cell's original contents have been entirely digested and it is bulging with parasites like a soup can gone bad. Each *falciparum* that entered the body has now replicated itself 40,000 times.

The cells explode. A riot of parasites is set loose in the bloodstream. Within 30 seconds, though, the parasites have again entered the safe houses of cells — this time, each has drilled into a red blood cell flowing through the circulatory system. Over the next two days, the parasites continue to devour and proliferate stealthily. After they have consumed the invaded cells, they burst out again, and once more there is bedlam in the blood.

For the first time, the body realizes it has been ambushed. Headache and muscle pains are a sign that the immune system has been triggered. But if this is the victim's first bout of malaria, the immune response is mostly ineffective. The alarm has sounded, but the thieves are already under the bed: the parasites swiftly invade a new set of blood cells, and the sequence of reproduction and release continues.

Now the internal temperature begins to rise as the body attempts to cook away the invaders. Shivering sets in — muscle vibrations generate warmth. This is followed by severe fever, then drenching sweat. Cold, hot, wet; the symptoms are a hallmark of the disease. But the parasites' exponential growth continues, and after a few more cycles there are billions of them tumbling about the blood.

By this point, the fever has reached maximum intensity. The body is practically boiling itself to death — anything to halt the attack — but to no avail. The parasites can even commandeer blood cells to help aid their survival. In some cases of *falciparum*, infected cells sprout Velcro-like knobs on their surfaces, and as these cells pass through the capillaries of the brain, they latch on to the sides. The adhesion keeps them from washing into the spleen, which cleans the blood by shredding damaged cells. Somehow — no one is quite sure how — the adhesion also causes the brain to swell. The infection has turned into cerebral malaria, the most feared manifestation of the disease.

This is when the body starts to break down. The parasites have

destroyed so many oxygen-carrying red cells that too few are left to sustain vital functions. The lungs fight for breath, and the heart struggles to pump. The blood acidifies. Brain cells die. The child struggles and convulses and finally falls into a coma.

Malaria is a confounding disease — often, it seems, contradictory to logic. Curing almost all malaria cases can be worse than curing none. Destroying fragile wetlands, in the world of malaria, is a noble act. Rachel Carson, the environmental icon, is a villain; her three-letter devil, DDT, is a savior. Carrying a gene for an excruciating and often fatal blood disorder, sickle-cell anemia, is a blessing, for it confers partial resistance to *falciparum*. Leading researchers at a hundred medical centers are working on antimalarial medicines, but a medicinal plant described 1,700 years ago may be the best remedy available. “In its ability to adapt and survive,” says Robert Gwadz, who has studied malaria at the National Institutes of Health, near Washington, D.C., for almost thirty-five years, “the malaria parasite is a genius. It’s smarter than we are.”

The disease has been with humans since before we were human. Our hominin ancestors almost certainly suffered from malaria. The parasite and the mosquito are both ancient creatures — the dinosaurs might have had malaria — and this longevity has allowed the disease ample time to exploit the vulnerabilities of an immune system. And not just ours. Mice, birds, porcupines, lemurs, monkeys, and apes catch their own forms of malaria. Bats and snakes and flying squirrels have malaria.

Few civilizations, in all of history, have escaped the disease. Some Egyptian mummies have signs of malaria. Hippocrates documented the distinct stages of the illness; Alexander the Great likely died of it, leading to the unraveling of the Greek Empire. Malaria may have stopped the armies of both Attila the Hun and Genghis Khan.

The disease’s name comes from the Italian *mal’aria*, meaning “bad air”; in Rome, where malaria raged for centuries, it was commonly believed that swamp fumes produced the illness. At least four popes died of it. It may have killed Dante, the Italian poet. George Washington suffered from malaria, as did Abraham Lincoln and Ulysses S. Grant. In the late 1800s, malaria was so bad in Washington, D.C., that one prominent physician lobbied — unsuccessfully — to erect a gigantic wire screen around the city. A million Union Army casualties in the U.S. Civil War are attributed to

malaria, and in the Pacific theater of World War II casualties from the disease exceeded those from combat. Some scientists believe that one of every two people who have ever lived have died of malaria.

The first widely known remedy was discovered in present-day Peru and Ecuador. It was the bark of the cinchona tree, a close cousin of coffee. Local people called the remedy *quina quina* (bark of barks), and it was later distributed worldwide as quinine. Word of the medicine, spread by Jesuit missionaries, reached a malaria-ravaged Italy in 1632, and demand became overwhelming. Harvested by indigenous laborers and carried to the Pacific coast for shipment to Europe, the bark sold for a fortune.

Several expeditions were dispatched to bring seeds and saplings back to Europe. After arriving in South America, the quinine hunters endured a brutal trek through the snow-choked passes of the Andes and down into the cloud forests where the elusive tree grew. Many perished in the effort. And even if the quinine hunters didn't die, the plants almost always did. For two hundred years, until the cinchona tree was finally established on plantations in India, Sri Lanka, and Java, the only way to acquire the cure was directly from South America.

Quinine, which disrupts the malaria parasites' reproduction, has saved countless lives, but it has drawbacks. It is short-acting, and if taken too frequently can cause serious side effects, including hearing loss. In the 1940s, however, came the first of two extraordinary breakthroughs: a synthetic malaria medicine was introduced. The compound was named chloroquine, it was inexpensive and safe, and it afforded complete, long-lasting protection against all forms of malaria. In other words, it was a miracle.

The second innovation was equally miraculous. The Swiss chemist Paul Müller discovered the insecticidal power of a compound called dichlorodiphenyltrichloroethane, better known as DDT. Müller was awarded the 1948 Nobel Prize in medicine for his discovery, for nothing in the history of insect control had ever worked like DDT. Microscopic amounts could kill mosquitoes for months, long enough to disrupt the cycle of malaria transmission. It lasted twice as long as the next best insecticide and cost one-fourth as much.

Armed with the twin weapons of chloroquine and DDT, the

World Health Organization in 1955 launched the Global Malaria Eradication Programme. The goal was to eliminate the disease within ten years. More than a billion dollars was spent. Tens of thousands of tons of DDT were applied each year to control mosquitoes. India, where malaria had long been a plague, hired 150,000 workers, full-time, to spray homes. Chloroquine was widely distributed. It was probably the most elaborate international health initiative ever undertaken.

The campaign was inspired by early successes in Brazil and the United States. The United States had recorded millions of malaria cases during the 1930s, mostly in southern states. Then an intensive antimalaria program was launched. More than 3 million acres (1.2 million hectares) of wetlands were drained, DDT was sprayed in hundreds of thousands of homes, and in 1946 the Centers for Disease Control was founded in Atlanta specifically to combat malaria.

America's affluence was a major asset. Almost everyone could get to a doctor; windows could be screened; resources were available to bulldoze mosquito-breeding swamps. There's also the lucky fact that the country's two most common species of *Anopheles* mosquitoes prefer to feed on cattle rather than humans. By 1950 transmission of malaria was halted in the United States.

The global eradication effort did achieve some notable successes. Malaria was virtually wiped out in much of the Caribbean and South Pacific and in the Balkans and Taiwan. In Sri Lanka, there were 2.8 million cases of malaria in 1946 and a total of 17 in 1963. In India, malaria deaths plummeted from 800,000 a year to scarcely any.

But it was also clear that the campaign was far too ambitious. In much of the deep tropics malaria persisted stubbornly. Financing for the effort eventually withered, and the eradication program was abandoned in 1969. In many nations, this coincided with a decrease in foreign aid, with political instability and burgeoning poverty, and with overburdened public health services.

In several places where malaria had been on the brink of extinction, including both Sri Lanka and India, the disease came roaring back. And in much of sub-Saharan Africa, malaria eradication never really got started. The WHO program largely bypassed the continent, and smaller-scale efforts made little headway.

Soon after the program collapsed, mosquito control lost access to its crucial tool, DDT. The problem was overuse — not by malaria fighters but by farmers, especially cotton growers, trying to protect their crops. The spray was so cheap that doses many times stronger than necessary were sometimes applied. The insecticide accumulated in the soil and tainted watercourses. Though nontoxic to humans, DDT harmed peregrine falcons, sea lions, and salmon. In 1962 Rachel Carson published *Silent Spring*, documenting this abuse and painting so damning a picture that the chemical was eventually outlawed by most of the world for agricultural use. Exceptions were made for malaria control, but DDT became nearly impossible to procure. “The ban on DDT,” says Gwadz of the National Institutes of Health, “may have killed 20 million children.”

Then came the biggest crisis of all: widespread drug resistance. Malaria parasites reproduce so quickly that they evolve on fast-forward, constantly spinning out new mutations. Some mutations protected the parasites from chloroquine. The trait was swiftly passed to the next generation of parasites, and with each new exposure to chloroquine the drug-resistant parasites multiplied. Soon they were unleashing large-scale malaria epidemics for which treatment could be exceedingly difficult. By the 1990s, malaria afflicted a greater number of people, and was harder to cure, than ever.

The story of malaria is ~~currently being written~~ — by hand, in ballpoint pen — by the staff of Zambia’s Kalene Mission Hospital. Every morning, soon after dawn, a nurse’s aide who has just finished the night shift records a brief update on each child in the intensive care ward. The report is written on lined notebook paper and clipped into a weathered three-ring binder. The day workers add frequent notations on the small patient cards, kept at the nurses’ station. Together, the night report and the cards form a compelling, immediate account of a deadly disease.

Many entries are simply terse, staccato jottings. “Mary: Has malaria. Unconscious.” “Belinda: Malaria. Seizures.” But others are far longer, enumerating clinical details about medicines and dosages and checkup times, as well as offering vivid glimpses into the struggle for survival in one of the world’s most malarious places. Leaf through the pages, flip through the cards — there are thousands upon thousands of entries — and the stories emerge.

Here's Methyline Kumafumbo, a skinny three-year-old who was taken to Kalene Hospital by her grandmother. They journeyed ten miles from their home village, and by the time they arrived, malaria parasites had already latched on to Methyline's brain. "Admitted yesterday," the night report reads. "Fever and seizures. Malaria." The right side of Methyline's head was shaved, and an IV line inserted. Quinine, which remains Kalene Hospital's frontline drug for severe cases, was administered, dose after dose, each treatment dutifully recorded.

For almost a week, Methyline languished in a coma. A malarial coma can be a horrible thing to observe: arched back, rigid arms, twisted hands, pointed toes. A still life of agony. The reports continue their unblinking assessment. "Unconscious. Continues on IV quinine." "Still unconscious though not seizing." "Still unconscious."

Then the seizures started again. There are times when the night report reads almost like a personal diary. "I was worried," the aide wrote about Methyline. "So I informed Sister" — the honorific bestowed on the hospital's two nurses — "who came and ordered Valium, which was given with relief."

Finally, the entries turn hopeful. "She's opening up her eyes but she still looks cerebral." "Drinking and eating porridge." And then: "Is conscious and talking!!" Three days later, Methyline was released from the hospital. "Looking bright," says the report. "But still not walking well."

One insidious thing about malaria is that many who don't die end up scarred for life. "Her walking issues point to larger problems," Robert Gwadz says after reviewing the progression of Methyline's sickness. "She may have permanent neurological damage." This legacy of malaria has sobering repercussions for people and nations. "It's possible," says Gwadz, "that due to malaria, almost every child in Africa is in some way neurologically scarred."

And Methyline has to be considered one of the fortunate ones. The Kalene Hospital night report is filled with heartbreak. Christabel: "The patient is in bad condition. Grunting and weary. Irregular breathing. Sister was informed. Midnight she collapsed and died. The body was taken home. May her soul Rest in Peace." There's an entry like this on nearly every page. Ronaldo: "Semi-conscious. IV for quinine. Seizure. Valium. Pain suppository. Fever.

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More pain suppository. At 0500 hrs, child had gasping respiration. Finally, child suddenly collapsed and died. His body was taken home."

All of Zambia, it seems — from the army to the Boy Scouts to local theater troupes — has been mobilized to stop malaria. In 1985 the nation's malaria-control budget was \$30,000. Now, supported with international grant money, it's more than \$40 million. Posters have been hung throughout the country, informing people of malaria's causes and symptoms and stressing the importance of medical intervention. (The vast majority of the nation's malaria cases are never treated by professionals.) There are even Boy Scout merit badges for knowledge about malaria. Zambia's plan is to educate the public, then beat the disease through a three-pronged assault: drugs, sprays, and mosquito nets.

The country has dedicated itself to dispensing the newest malaria cure, which also happens to be based on one of the oldest: an herbal medicine derived from a weed related to sagebrush called sweet wormwood, or artemisia. This treatment was first described in a Chinese medical text written in the fourth century A.D. but seems to have been overlooked by the rest of the world until now. The new version, artemisinin, is as powerful as quinine with few of the side effects. It's the last remaining sure-fire malaria cure. Other drugs can still play a role in treatment, but the parasites have developed resistance to all of them, including quinine itself. To help reduce the odds that a mutation will also disarm artemisinin, derivatives of the drug are mixed with other compounds in an antimalarial barrage known as artemisinin-based combination therapy, or ACT.

Zambia is also purchasing enough insecticide to spray every house in several of the most malarious areas every year just before the rainy season. It has already returned to DDT — though just for indoor use, in controlled quantities. In the face of the growing malaria toll, access to DDT is gradually becoming easier, and even the Sierra Club does not oppose limited spraying for malaria control. Finally, the Zambian government is distributing insecticide-treated bed nets to ward off mosquitoes during the night, when the malaria-carrying *Anopheles* almost always bite.

The plan sounds straightforward, but progress against malaria

never comes easily. Many Zambians living far from hospitals depend on roadside stalls for medicines. There ACT can cost more than a dollar a dose — virtually unaffordable in a country where more than 70 percent of the population survives on less than a dollar a day. So people buy other drugs for as little as 15 cents. They provide temporary relief, reducing the malarial fever, but may do little to halt the parasites.

Then there are widespread traditional beliefs. One of the posters plastered across Zambia reads: "Malaria is not transmitted by witchcraft, drinking dirty water, getting soaked in rain, or chewing immature sugar cane." When children suffer from seizures — a symptom of advanced cerebral malaria — some parents interpret it as a hex and head straight to a traditional healer. By the time they make it to the hospital, it's too late.

Even the gift of a bed net can backfire. There's no question that the nets can save lives, especially the latest types, which are impregnated with insecticide. But first they need to reach the people most in need, and then they must be properly used. "Distributing nets to remote villages is a nightmare," says Malama Muleba, executive director of the nonprofit Zambia Malaria Foundation. "It's one thing for me to convince Bill and Melinda Gates to donate money; it's quite another to actually get the nets out."

The Zambian army has been employed to help, but even after delivery, people can be reluctant to sleep beneath nets, which make a hot and stuffy part of the world feel hotter and stuffier. If a leg pops out at night or the fabric is torn, mosquitoes can still reach the skin. And the nets are sometimes misused as fishing gear. Theater troupes are spreading out into the Zambian countryside, emphasizing the proper use of bed nets through stage productions in settlements large and small.

Despite the difficulties, Zambia's campaign has started to produce results. In 2000 a study showed that fewer than 2 percent of children under the age of five slept under an insecticide-treated bed net. Six years later, the number had risen to 23 percent. The government of Zambia says an ACT known as Coartem is now available cost-free to the entire population. In a country that was steadily losing 50,000 children a year to malaria, early indications are that the death rate has already been reduced by more than a third.

But what if donor money dries up? What if Zambia's economy collapses? What about political instability? Both Angola and the Democratic Republic of the Congo, which flank Zambia, have a history of war. In the 1970s, during a civil war in Angola, six bombs landed near Kalene Mission Hospital; in the Congo war years, some of the nearby roads were mined.

"This is a critical moment," says Kent Campbell, program director of the Malaria Control and Evaluation Partnership in Africa. "There are no national models of success with malaria control in Africa. None. All we've seen is pessimism and failure. If Zambia is a success, it will have a domino effect. If it's a failure, donors will be discouraged and move on, and the problem will continue to get worse."

No matter how much time, money, and energy are expended on the effort, there still remains the most implacable of foes — biology itself. ACTs are potent, but malaria experts fear that resistance may eventually develop, depriving doctors of their best tool. Before the ban on DDT, there were already scattered reports of *Anopheles* mosquitoes resistant to the insecticide; with its return, there are sure to be more. Meanwhile, global warming may be allowing the insects to colonize higher altitudes and farther latitudes.

Drugs, sprays, and nets, it appears, will never be more than part of the solution. What's required is an even more decisive weapon. "When I look at the whole malaria situation," says Louis Miller, cochief of the malaria unit at the National Institute of Allergy and Infectious Diseases, "it all seems to come down to one basic idea: we sure need a vaccine."

It's easy to list every vaccine that can prevent a parasitic disease in humans. There are none. Vaccines exist for bacteria and viruses, but these are comparatively simple organisms. The polio virus, for example, consists of exactly 11 genes. *Plasmodium falciparum* has more than 5,000. It's this complexity, combined with the malaria parasite's constant motion — dodging like a fugitive from the mosquito to the human bloodstream to the liver to the red blood cells — that makes a vaccine fiendishly difficult to design.

Ideally, a malaria vaccine would provide lifelong protection. A lull in malaria transmission could cause many people to lose any

immunity they have built up against the disease — even adults could, immunologically speaking, revert to infant status — rendering it more devastating if it returned. This is why a partial victory over malaria could be worse than total failure. *Falci-parum* also has countless substrains (each river valley seems to have its own type), and a vaccine has to block them all. And of course the vaccine can leave no opening for the parasite to develop resistance. Creating a malaria vaccine is one of the most ambitious medical quests of all time.

Recent malaria history is fraught with grand pronouncements that turned out to be baseless. MALARIA VACCINE IS NEAR, announced a *New York Times* headline in 1984. “This is the last major hurdle,” said one U.S. scientist quoted in the article. “There is no question now that we will have a vaccine. The rest is fine-tuning.” Seven years of fine-tuning later, another *Times* headline summarized the result: EFFORT TO FIGHT MALARIA APPEARS TO HAVE FAILED. In the late 1990s, the Colombian immunologist Manuel Patarroyo claimed, with much media fanfare, that he had found the answer to malaria with his vaccine, SPf-66. Early results were tantalizing, but follow-up studies in Thailand showed it worked no better than a placebo.

At least ninety teams around the world are now working on some aspect of a vaccine; the British government, by way of incentive, has pledged to help purchase hundreds of millions of doses of any successful vaccine for donation to countries in need. The one closest to public release, developed by the pharmaceutical company GlaxoSmithKline Biologicals in collaboration with the U.S. Army, is called RTS,S. In a recent trial in Mozambique, it protected about half the inoculated children from severe malaria for more than a year.

Fifty percent isn't bad — RTS,S might save hundreds of thousands of lives — but it's not the magic bullet that would neutralize the disease once and for all. Many researchers suspect an all-encompassing cure isn't possible. Malaria has always afflicted us, they say, and always will. There is one man, however, who not only believes malaria can be defeated, he thinks he knows the key.

Stephen Hoffman is the founder and CEO of the only company in the world dedicated solely to finding a malaria vaccine. The com-

pany's name is Sanaria — that is, “healthy air,” the opposite of malaria. Hoffman is fifty-eight, lean, and green-eyed, with a demeanor of single-minded intensity. “He’s impassioned and impatient and intolerant of negativity,” is how one colleague describes him.

Hoffman is intimately familiar with the pitfalls of the vaccine hunt. During his fourteen-year tenure as director of the malaria program at the Naval Medical Research Center, he was part of the team working on the vaccine promised in the 1984 *New York Times* article. He was so confident of the vaccine that he tested it on himself. He exposed himself to infected mosquitoes, then flew to a medical conference in California to deliver what he thought would be a triumphant presentation. The morning after he landed, he was already shaking and feverish — and, soon enough, suffering from full-blown malaria.

Now, more than two decades later, Hoffman is ready to return to prominence. He couldn't have found a more uninspiring launch pad: Sanaria is headquartered in a dismal mini-mall in suburban Maryland, near a picture-framing shop and a discount office-supply store. From the outside, there's no mention of the company's mission. A window badly in need of washing bears the company name in tiny adhesive letters. Hoffman realizes it's probably best if the office-supply customers aren't fully aware of what's going on a few doors away.

Inside, generating a hubbub of activity, are some thirty scientists from across the globe. The lab's centerpiece is a room where Hoffman raises mosquitoes infected with the *falciparum* parasite — yes, in a quiet mini-mall. Hoffman claims it's the world's most secure insectary. To enter, a visitor must pass through multiple antechambers sealed between sets of doors, like a lock system in a canal. Everyone has to wear white cotton overlays, masks, shoe covers, and gloves. White makes it easier to see a stray mosquito. The air is recirculated, and the insectary is checked daily for leaks. Signs abound: WARNING! WARNING! INFECTIOUS AGENT IN USE. And hanging on a wall is a time-honored last line of defense: a fly swatter.

The mosquitoes are housed in a few dozen cylindrical containers, about the size of beach buckets, covered with mesh lids. They're fed *falciparum*-infected blood, then stored for two weeks while the parasites propagate in the insects' guts and migrate to the

salivary glands, creating what are known as "loaded" mosquitoes. The loaded insects are transferred carefully to a kilnlike irradiator to be zapped with a quick dose of radiation. Then, in a special dissecting lab, the salivary glands of the mosquitoes are removed. Each mosquito's glands contain more than 100,000 parasites. Essentially, the vaccine consists of these irradiated parasites packed into a hypodermic needle. The idea is based on research done in the late 1960s at New York University by Ruth Nussenzweig, who demonstrated that parasites weakened by radiation can prompt an immune response in mice without causing malaria. Hoffman's vaccine will deliver the wallop of a thousand mosquito bites and, he says, produce a complete protective response. Thereafter, any time the vaccinated person is bitten by a malaria-carrying mosquito, the body, already in a state of alert, will not allow the disease to take hold.

Hoffman's lofty goal is to eventually immunize all 25 million infants born in sub-Saharan Africa every year. He believes that at least 90 percent of them will be protected completely from malaria. If so, they'll be the first generation of Africans, in all of human history, not to suffer from the disease.

But which generation will it be? Although Sanaria's vaccine may undergo initial field-testing next year, a federally approved version won't be available for at least five years — and maybe never. Given the track record of malaria vaccines, that's a distinct possibility. After so many million years on Earth and so many victories over humanity, the disease, it is certain, will not surrender easily.

When it comes to malaria, only one thing is guaranteed: every evening in the rainy season across much of the world, *Anopheles* mosquitoes will take wing, alert to the odors and warmth of living bodies. A female *Anopheles* needs to drink blood every three days. In a single feeding, which lasts as long as ten minutes, she can ingest about two and a half times her pre-meal weight — in human terms, the equivalent of downing a bathtub-size milk shake.

If she happens to feed on a person infected with malaria, parasites will accompany the blood. Two weeks later, when the mosquito flies through the open window of a mud hut, seeking her next meal, she'll be loaded.

Inside the hut, a child is sleeping with her sister and parents on a

blanket spread over the floor. The family is aware of the malaria threat; they know of the rainy season's dangers. They've hung a bed net from the ceiling. But it's a steamy night, and the child has tossed and turned a few times before dropping back to sleep. Her foot is sticking out of the net. The mosquito senses it and dips down for a silent landing.