smallpox, modified to express the same malarial components as their DNA vaccine.

As science advances, the lingering pessimism in the field arises more from the financial constraints of developing a malaria vaccine. According to a recent NIH report, it takes more than a quarter of a billion dollars and a dozen years to take a vaccine from research through licensing in industry. Much of that money is spent on large-scale clinical trials, which are still a distant dream of malaria vaccine researchers.

"Within 5 years there will be a number of vaccines out there being tested for efficacy," predicts NIH's Miller. "Within 10 years, some will be ready for a company to try to get them licensed." The ultimate challenge, says Miller, may be convincing a company to take a chance on a vaccine for a market that is enormous but is also hopelessly impoverished.

–GARY TAUBES

MALARIA DRUGS

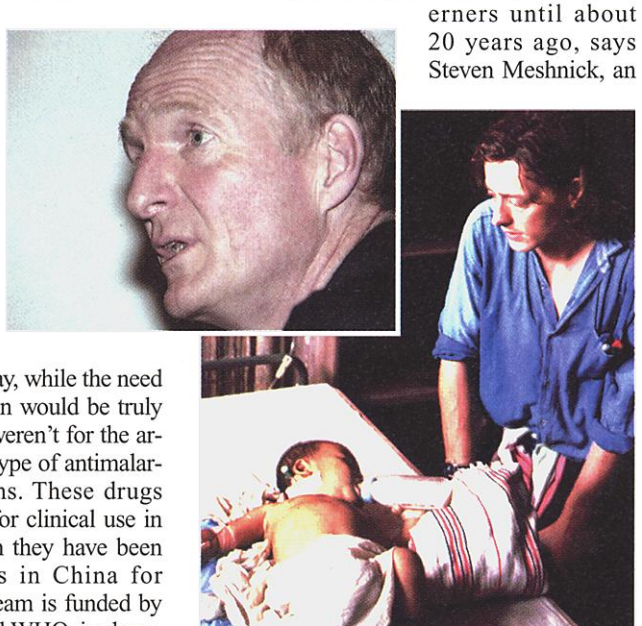
Reinventing an Ancient Cure for Malaria

As drug resistance renders cheap antimalarials ineffective, a promising candidate has emerged from an overlooked source

Nowhere on Earth is malaria more threatening than in northwestern Thailand. Here, the deadliest form of the parasite, *Plasmodium falciparum*, has been toughened by decades of exposure to antimalarial drugs—conditions that promote the survival of drug-resistant strains. In this caldron, says researcher Nicholas White of Bangkok's Mahidol University, a "nightmare scenario" is brewing: Local parasites are becoming resistant to every cheap drug that works. The old standby, chloroquine, "is gone, just about everywhere," agrees Pierro Olliaro of the World Health Organization (WHO), and resistance to newer drugs is emerging.

Flush with new funds and aiming at targets now being provided by genome sequencers, researchers are trying to concoct the next generation of antimalarials (see p. 439 and *Science*, 17 March, p. 1956). But those drugs are a decade away, while the need today is urgent. The situation would be truly desperate, White says, if it weren't for the arrival in the 1990s of a new type of antimalarial from Asia: artemisinins. These drugs haven't yet been approved for clinical use in Western countries, although they have been used as herbal remedies in China for 2000 years. White, whose team is funded by Britain's Wellcome Trust and WHO, is championing one member of this family, a water-soluble form called artesunate. He thinks it may be the most potent new weapon against malaria in decades. It could also be a lifesaver for children in remote villages.

Abundant clinical data show that artesunate knocks down the number of parasites in the blood faster than any other drug does, according to Steve Hoffman of the U.S. Naval Medical Research Center in Silver Spring, Maryland. If given early, it can stop an infection from progressing to a deadly coma. Yet it must be used with care, says White, partly because of concerns about neurotoxic effects but mainly to avoid promoting drug resistance. The past approach, using malaria drugs one at a time and replacing them as they toppled "like dominoes," only encouraged resistance. So White argues that artesunate must be deployed in combination with other drugs to hit the parasite with a complex challenge.



Ground zero. Nicholas White (*inset*) and François Nosten are conducting trials in Thailand.

Artemisinins were unknown to Westerners until about 20 years ago, says Steven Meshnick, an epidemiologist at the University of Michigan, Ann Arbor. But 2 millennia earlier, Chinese herbalists noted that fevers could be treated with a tea based on the flowering plant qinghao (*Artemisia annua*). An ether extract of qinghao, qinghao-su, gained scientific prestige in China during the 1960s, when a search for organic drugs revealed that it was effective against the mouse form of malaria. Chinese researchers developed new drugs and tested them on thousands of patients, publishing medical reports in English in the early 1980s.

One of the first Westerners to pounce was Dan Klayman, a U.S. Army malaria researcher, now deceased. Unable to obtain samples of qinghao from China, Klayman eventually found some *Artemisia annua*, a weed called sweet wormwood, growing near his lab in Washington, D.C., and cultivated it. (Klayman's review of the Chinese clinical work and his lab's work on qinghao's chemistry appeared in *Science*, 31 May 1985, p. 1049.) In the 1980s, both Army- and WHO-sponsored researchers began testing an oil-based version for intramuscular injection to treat severe malaria. It was a stable formula, but it was sometimes poorly absorbed, and in animal studies it injured the brainstem at high doses. White thinks it was a mistake not to move quickly to other formulations.

Meanwhile, Chinese research in the 1970s and 1980s suggested that the water-based artesunate formulation given by tablet or needle worked well. China now manufactures artesunate, and White estimates that more than 1 million people have used it safely in Asia. What's more, says White, recent trials in Thailand suggest that a combination of artesunate and mefloquine is rapidly absorbed and immediately bioavailable and is seemingly "a better drug."

But artesunate got trapped in a regulatory cul-de-sac. Although Chinese researchers had published safety and efficacy data, Western authorities looked askance at their research methods. WHO, for instance, declined to launch major clinical trials of artesunate in the 1980s, after some of its advisers expressed concerns about neurotoxic effects seen in animal studies. White suspects the biggest roadblock was that artesunate "came from the wrong place." It didn't have the right regulatory "credentials … which people seem to regard almost as religious edicts."

In 1994, as mefloquine resistance spread through Thailand, WHO decided to support trials of artesunate with mefloquine as the last line of defense. White and co-authors reported in the 22 July issue of *The Lancet* that this oral therapy yielded efficacy of "nearly 100%." Today, WHO, the Wellcome Trust,

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and others are backing advanced clinical trials in Africa as well, promoting a rectal suppository formulation, or "rectocap." The goal, says a WHO official, is to have a product that can be distributed to remote areas and administered in an emergency, giving a family time to get a child to the clinic before deep coma sets in. The advantage of this low-tech version, says WHO, is that it would be cheap, easy to store, not dependent on needles, and usable even in a child who is vomiting. Another advantage, says White, is that artesunate, especially in combination therapy, is less likely than older drugs to promote resistance, because it is rapidly eliminated from the body. "There is no sign of resistance to date," says White, "although you should never be complacent about malaria."

Given the promising data from Thailand, White and WHO officials are eager to deploy artesunate more widely. Because no drug company has taken the initiative, WHO plans to submit a drug application to the U.S. Food and Drug Administration (FDA) to obtain a license to develop the rectocap in collaboration with a European manufacturer. WHO doesn't need FDA's approval for research, but having it would make it easier to manufacture the drug later. An FDA official observes that artesunate looks "very, very promising," while cautioning that its potential toxicity must be studied further.

But White is impatient. "We need new combination drugs in the villages—yesterday," says White, who thinks they might have been able to halt the spread of mefloquine resistance that way: "It's a disaster that we didn't get them out 5 years ago."

—ELIOT MARSHALL

MALARIA
GENOME SEQUENCING

Closing In on a Deadly Parasite's Genome

Extremely difficult to decipher, the *Plasmodium* genome is already providing targets for new drugs. Next project: the mosquito genome

There's no better way to locate the soft underbelly of a pathogen than through its genome. The genome provides a view of all the key proteins involved in infection and in the pathogen's life cycle. And those proteins make good drug targets. Sequencers are now barreling through the genome of the most virulent malaria parasite, *Plasmodium falciparum*, and they hope soon to turn their sequencing machines loose on the genome of the *Anopheles* mosquito that transmits it. Combined with the emerging data on the human genetic code, "the three [genomes] will go a long way in helping us understand this disease," says Michael Gottlieb, a parasitologist at the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland.

Unexpectedly, the smallest genome of the trio may be the toughest to sequence. Although relatively puny (fewer than 30 million bases compared to, say, the 100-million-base genome of the nematode *Caenorhabditis elegans*), the parasite's genome has put up quite a fight. In 1996, work on the genome began on both sides of the Atlantic. The sequencing groups, each with its own source of support, have coordinated their effort, dividing up the genome and talking often about their progress—or lack thereof.

Almost as soon as they started, the teams ran into trouble. Compared to the genomes of other organisms tackled to date, *P. falciparum* is chock full of adenines and thymines, two of the four nucleotide bases that are the building blocks of DNA. The proportion of A's and T's averages 82% and soars to 97% in spots, says molecular biologist Sharen Bowman of the Sanger Centre near Cambridge, U.K. This not only makes copying the DNA a challenge but also bogs down the sequencing and analysis. *P. falciparum* "has been much more difficult" than "every other organism we've experienced," says Bowman. Indeed, "most of the malaria community said we'd never be able to do it," recalls Malcolm Gardner of The Institute for Genomic Research (TIGR) in Rockville, Maryland.

Sneak attack. Genetic data may reveal how *Plasmodium* destroys red blood cells and causes disease.

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Nevertheless, the first two of *P. falciparum*'s 14 chromosomes were completed fairly quickly, in 1998 and 1999, proving that it could be done (*Science*, 6 November 1998, p. 1126; *Nature*, 5 August 1999). And even before these chromosomes were finished, there was a groundswell of support for tackling the entire genome. NIAID; the Military Infectious Diseases Program of the U.S. Department of Defense; the Burroughs Wellcome Fund, based in Morrisville, North Carolina; and Britain's Wellcome Trust have kicked in a total of about $23 million for various sequencing efforts over the past 3 years. Stanford sequenced chromosome 12; TIGR and the U.S. Naval Research Center did 14, 10, 11, and 2; and Sanger tackled the rest.

The Sanger group may have landed the toughest task: deciphering the "Blob"—three chromosomes that have to be treated as one. To work on any chromosome, each lab separates the DNA by allowing the entire genome to migrate through a gel. Because lighter chromosomes travel farther, each can be identified and be cut out of the gel for sequencing. But chromosomes 6, 7, and 8 are so close in size that they cannot be separated.

Sequencing of all the chromosomes—including the Blob—is virtually complete, but the groups are now struggling to assemble the thousands of pieces of sequence for each chromosome in the right order. "It's a long, hard slog," says Gardner, who, with Leda Cummings, has led TIGR's effort. The problem is that lots of pieces don't seem to fit anywhere because of long, difficult-to-sequence stretches of the same base. Nevertheless, Bowman expects that within 9 months most of the genome will be finished and annotated, with the Blob coming a year or so later. In the interim, all the labs are releasing their raw data daily, and malaria researchers have already identified new drug targets from those data. If the *Anopheles* genome project, being spearheaded by Frank Collins of the University of Notre Dame in Indiana and colleagues in Crete, Germany, and France, gets off the ground, drug designers may soon be able to find still more chinks in malaria's armor.

—ELIZABETH PENNISI