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

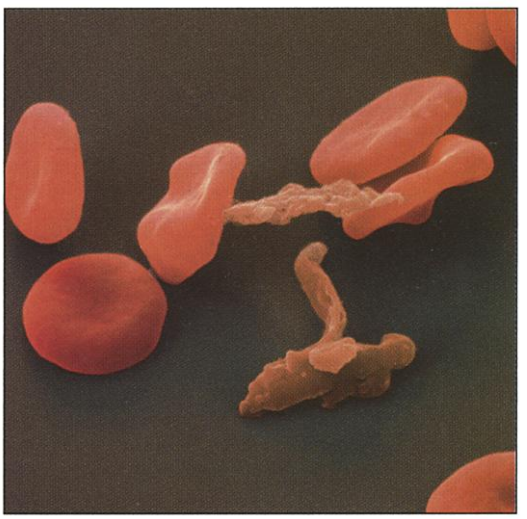
Closing In on a Deadly Parasite's Genome

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.

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