INFECTIOUS DISEASES

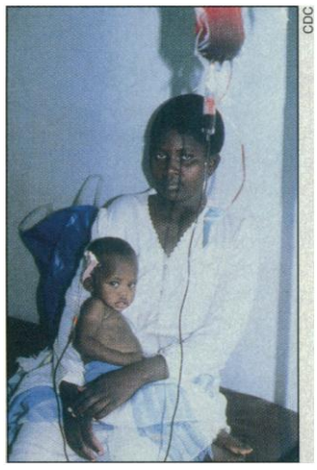
# Malaria Fighters Gather At Site of Early Victory


**HYDERABAD, INDIA**—One hundred years ago, Britain's Sir Ronald Ross (inset) discovered that the malaria parasite is transmitted by the *Anopheles* mosquito. To honor that historic work, done in a lab outside this city, and to assess the state of the war against the disease, some 700 scientists from 30 countries gathered here on 18 to 22 August for the Second Global Meeting on Parasitic Diseases.

## Malaria and AIDS

In addition to its staggering political and economic problems, sub-Saharan Africa is also home to two of the world's most dreaded infectious diseases, AIDS and malaria. Now researchers are gathering evidence in both field and lab studies suggesting that those two killers may be stalking the continent in tandem.

In vitro studies conducted at the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta show that malaria infection, by stimulating the white blood cells that are targeted by HIV, can speed up replication of the virus. Recent epidemiological studies in Africa also hint that malaria may be a deadly cofactor for HIV, hastening the death of those who carry both infections. But more field data are needed to draw a complete picture of the interaction. "In vitro evidence suggests a link between malaria and HIV, and now we need to find evidence for it in vivo," says Bernard Nahleen, a medical epidemiologist and director of the CDC's station in Kenya.


CDC

**Fatal gift.** Infants of mothers with HIV and malaria face higher mortality rates.

The laboratory evidence comes from studies by Altaf Lal, chief of CDC's molecular vaccine section. He found that when malaria antigens activate CD4 T lymphocytes—the white blood cells HIV infects—and stimulate the production of the immune system messengers called cytokines, HIV replication increases sharply. The result was a 30- to 100-fold increase in HIV load in activated CD4 cells, he reported at the meeting.

That kind of synergy, if it takes place in infected people, could have deadly effects in Africa. Recent estimates from the World Health Organization, for example, note that about 60% of all cases of HIV—some 13.3 million—occur in sub-Saharan Africa, which is also home to almost 90% of the nearly half-billion cases of malaria reported globally each year. In addition, epidemiological data suggest that the HIV-malaria connection may be real.

Studies in Malawi and Kenya, for example, show that infants born to HIV-positive and malaria-positive mothers have four times the mortality rate of those whose mothers suffer from a single infection. That's because the maternal antigens that protect them against malaria in the first year also serve as cofactors for the HIV. "From a clinical point of view, HIV-infected individuals deteriorate faster with every bout of malaria," says Subhash Hira, a professor of infectious diseases in the Health Sciences Center at the University of Texas, Houston. What's more, HIV infection in sub-Saharan Africa progresses to full-blown AIDS in roughly 5 years—about half the time it takes in the West. "This sudden acceleration of the disease could be due to the rampant presence of malaria in the region," speculates Lal, who hopes to do longitudinal studies on humans at the CDC's Kenya station.

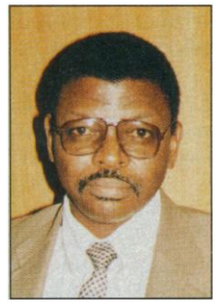
"The implications of the HIV-malaria connection are very serious," says John LaMontagne of the U.S. National Institute of Allergy and Infectious Diseases, in Bethesda, Maryland. In an ironic side effect, a demonstrated link may also boost the willingness of organizations to raise their investment in malaria research, says Louis Molineaux, former chief of operational research for the WHO's tropical disease control division. "AIDS scares the rich and malaria does not," says Molineaux. "So if there is a connection, more money could come in for research on malaria."

## Itching for a Solution to Drug Resistance

A one-time magic bullet against malaria may be ready to make a comeback, if some suggestive results in Africa hold up. Field trials by researchers at the University of Ibadan in Nigeria suggest that the combination of chloroquine and various anti-itching drugs could make the former wonder treatment work again.

Chloroquine is the preferred drug for treating malaria because of its low cost and easy availability. But parasites resistant to the drug have spread across Africa in recent years and reduced its effectiveness as both a treatment and a prophylactic, forcing doctors to rely on more expensive compounds.

A widely reported side effect of chloroquine in Africa, however, yielded a hint about how to restore its potency. Many patients complained of intense itching; to control it, health workers routinely prescribed various antihistamines. A few years ago, Ayodae M. J. Oduola, a physician at the University of Ibadan, found that chloroquine seemed to be working in areas where it should have failed when it was prescribed with chlorpheniramine, a cheap, easily available antihistamine.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**Double dose.** Oduola's work suggests value of twin-drug therapy against malaria.

Since then, Oduola and A. Sowunmi of Ibadan's Malaria Research Group have done four trials involving 400 patients with acute uncomplicated malaria; half were treated with the combination drugs. In an area with 45% chloroquine resistance, the WHO-defined success rate for the combination treatment was 81% for those with chloroquine-resistant malaria and 96% for those with acute, uncomplicated infections, said co-investigator Colonel Wil Milhous, director of experimental therapeutics at the Walter Reed Army Institute of Research in Washington, D.C. In an earlier study with *Aotus* monkeys, Oduola found similar results with a combination of chloroquine and promethazine, another antihistamine that appears to help reverse resistance. A larger study is under way to explore the mechanism of action, said Milhous, who presented highlights of the in-press findings.

Milhous cautions that "this may only be a stopgap arrangement, as the half-lives of these antihistamines are very short and you need to have large dosages of them in the body." Moreover, not everybody is convinced that the two-drug approach will actu-

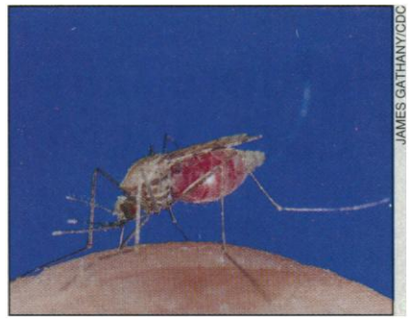
ally make a dent in the toll from malaria. "The people who need treatment for malaria are so poor that they can't even buy one drug," says Win L. Kilama, director-general of the National Institute for Medical Research in Dar es Salaam, Tanzania. "Why would you now expect them to buy two drugs?"

Although most scientists deferred comment until the results are published, several pointed to the potential payoff from the dual-drug approach. "Chloroquine was such a marvelous drug, and everyone was desperate when it was lost," says Wallace Peters, head of malaria chemotherapy at the International Institute of Parasitology in Herts, United Kingdom. "If this combination drug is safe and it works, it would have greatly restored the value of chloroquine."

### Malaria-Free *Anopheles* Mosquitoes

Even better than an effective treatment for malaria, or even a vaccine, would be eliminating the vector itself. But because eradicating mosquitoes is a Sisyphean challenge, the next best thing may be to genetically engineer the *Anopheles* mosquito so that it can't carry the malarial parasite. Scientists have now taken the first step toward that goal, by successfully transferring foreign genes into a mosquito.

These particular genes don't affect the mosquito's ability to transmit disease, and the work was done in *Aedes aegypti*, a mosquito that transmits yellow fever and other diseases but not malaria. Still, says Vinod Prakash Sharma, director of the Malaria Research Center in New Delhi, "this is an important milestone in our understanding of the basic research behind inserting alien genes into mosquitoes."



JAMES GATHANY/CDC

**Free lunch.** Blocking the parasite would make *Anopheles* just another pest.

Medical entomologist Frank H. Collins of the University of Notre Dame in Indiana and Anthony James, a vector biologist at the University of California, Irvine, used genetically modified transposable elements—stretches of DNA that readily move around in the genome—to introduce foreign eye-color genes into mosquito embryos. The result: eight stably transformed lines of mosquitoes sporting altered eye colors. "Until now people always thought this could be done, but we have provided the proof to the principle," says James, who presented the work at the conference.

The next step is to identify and sequence the major genes that make certain mosquitoes resistant to carrying malaria. Once that is done, a similar technique could be used to breed a mutant of the *Anopheles* mosquito that would not transmit the parasite.

To be an effective deterrent, of course, the modified mosquitoes must also be able to establish themselves in the general population. Then there are the environmental safety issues that would surround what would be the first release of a transgenic animal species into the wild. "It's a one-way street," says Louis Miller, chief of the Laboratory of Parasitic Diseases at the U.S. National Institute of Allergy and Infectious Diseases, in Bethesda, Maryland. "You may not be able to pull the genes back once they have been pushed into the wild."

Even so, Miller and others see genetically altered mosquitoes as a promising approach in their age-old battle against the disease. "It gives you a quantum leap in technology and, at a very low cost, the hope of eliminating malaria," says Miller.

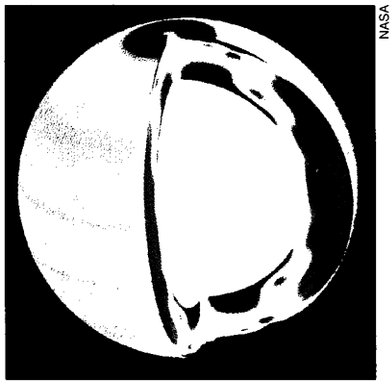
**–Pallava Bagla**

*Pallava Bagla is a science writer in New Delhi.*

SOLAR PHYSICS

# SOHO Traces the Sun's Hot Currents

The mostly ionized gases of the sun's outer layers, at temperatures of hundreds of thousands of degrees, have little in common with Earth's chilly upper atmosphere. But last week researchers announced that data from the Solar and Heliospheric Observatory (SOHO) spacecraft, which watches the sun continuously from a vantage point 1.5 million kilometers sunward of Earth, have revealed rivers of solar material flowing beneath the surface of the sun near its north and south poles. The rivers look somewhat like the jet streams—narrow, high-speed air flows that encircle Earth high in the atmosphere.



NASA

**Weather map.** On this image of the sun, red and yellow represent faster rotation. Red ovals near the poles are "jet streams."

Reported last week at a NASA press conference, the solar jet streams are just one of several glimpses of large-scale circulation in the sun described by the SOHO team. The findings, says Douglas Gough, a Cambridge University astrophysicist, "herald what I believe will be a new era of solar meteorology." SOHO also detected other slower bands of gas flow encircling the sun, which Gough and other researchers—extending the meteorological metaphor—compared to Earth's trade winds. These complex circulation patterns, the solar researchers hope, may prove key to unraveling the mystery of the sun's 11-year cycle of magnetic activity.

The results come from SOHO's Michelson Doppler Imager (MDI), one of 12 instruments on board the European Space Agency craft. The MDI makes sensitive measurements of the undulations on the sun's surface at about 700,000 points at once. These undulations show where acoustic waves traveling through the sun reach the surface, and their frequencies and patterns hold clues to conditions in the subsurface regions probed by the waves. Although Earth-based instruments can also study these oscillations, "we would never have seen [the rivers]" from Earth, says Gough, because of the high sensitivity required to detect them.

These rivers are about 30,000 kilometers across, flowing 40,000 kilometers beneath the sun's visible surface at 140 kilometers an hour, 10% faster than the surrounding gases. The trade-wind-like bands circulate more slowly, at 30 km/hour, at depths ranging from at least 18,000 km all the way to the surface. Astronomer John Harvey of the National Solar Observatory in Tucson, Arizona, says the bands had been glimpsed from Earth as patterns on the sun's visible surface, but the SOHO data confirm "that the surface effect actually does go deeper into the sun; it's not some skin effect."

The SOHO results also confirm that the bands coincide with collections of sunspots, which are a manifestation of the sun's magnetic activity. That raises researchers' hopes that the newly discovered circulation patterns will prove key to understanding the sun's magnetic cycle. Says Gough, "We're getting these fantastic measurements, and if things go the way they went with terrestrial meteorology, this is going to enable us to have a much deeper understanding of the dynamics of the sun."

**–David Ehrenstein**