that the parasite is resistant to this as well. It is only a matter of time before the resistance spreads, Campbell says, and "there aren't a lot of alternatives sitting around."

Although the chemical assault seems nearly spent now, it worked well in the beginning—deceptively so. As the WHO set itself the goal of eradicating malaria with the massive use of DDT in the late 1950s, many countries scaled back traditional mosquito control efforts, just at a time when resistance to pesticides and drugs began to appear. The reversal was striking. In Sri Lanka, for example, where only 17 cases of malaria were reported in 1963, an epidemic affecting millions erupted in 1968.

Today the mosquitoes and the four disease-causing strains of *Plasmodium* threaten to regain the ground they lost during the years of heavy pesticide use in the 1950s and 1960s. In fact, the situation may be as bad as it was two decades ago.

Carlos Campbell of the CDC says the big new issue is urban malaria. Disease-bearing mosquitoes are now appearing in cities such as Dar es Salaam and Kinshasa. In addition, environmental change seems to be stimulating the spread of malaria in Brazil, Indonesia, and Madagascar, to a "disastrous" extent, Campbell says. As jungles are cleared and forests burned, the local temperature may rise. Infected mosquitoes are moving into higher elevations while people with no natural immunity are moving into areas where the infected mosquitoes live. At present, for example, 90% of the malaria cases in the Western Hemisphere are reported in Brazil, where forest clearing proceeds on a vast scale.

Nor is the problem limited to the Third World. A "few dozen" local cases of malaria have appeared in a county near San Diego for 4 years in succession, says Campbell; the focus of infection seems to be migrants from Mexico or further south who first contracted the disease outside the United States.

In view of the need for immediate action, some public health officials are calling for modest, practical goals, such as educating

USAID

Not under control. *Spraying to kill anopheles mosquitoes in Haiti. In most parts of the world control measures have not succeeded.*

High-Tech and Low-Tech: Control Strategies Today

In 1957 the World Health Organization declared war on malaria. Armed with DDT to kill the mosquitoes and chloroquine, a cheap and effective drug, to cure the disease, armies of health workers around the world set to the task. At first all went well, but by the mid-1970s the disease had reappeared with a vengeance, largely because the disease-causing parasites had developed resistance to chloroquine (see story on page 399).

According to David Davidson, Jr., secretary of WHO's tropical disease program Scientific Steering Committee on Chemotherapy of Malaria, "there are very, very few areas where chloroquine is fully effective, as it was 25 years ago." For similar reasons insecticides are also less useful than they were a decade or two ago. Which leaves only the vaccine (see story on page 402).

Or does it? In the face of failure to come up with a workable, effective vaccine, many malariologists are again looking to other control strategies, some very high-tech indeed, others resurrecting the simplest of methods.

John Playfair, professor of immunology at University College and Middlesex School of Medicine in London, is attacking the symptoms of malaria rather than the parasite itself. Although it is still not understood how the flood of merozoites produces the symptoms of malaria, Playfair points to a correlation between substances called cytokines (which include such things as tumor necrosis factor) and acute illness in malaria patients. In mice, at least, Playfair has shown that the release of cytokines does underlie development of severe symptoms.

Playfair's group and others have established that the burst of merozoites is accompanied by the release of antigens; those antigens are capable of stimulating cells in culture to release tumor necrosis factor. Playfair has made antibodies to the stimulator molecules, and he envisions—in the far-off future—a vaccine that does nothing to prevent transmission of malaria but protects young children from its deadly pathology.

"The best analogy," Playfair says, "is to antitetanus or diphtheria vaccines, which neutralize the toxins but have no effect on the bacteria that produce them, which are essentially harmless."

A different—but equally high-tech—tack is being taken by Robert Gwadz at the U.S. National Institutes of Health. Gwadz is attempting to genetically engineer mosquitoes that do not transmit malaria and use those strains to displace the ones that do.

Some strains of mosquito, we know, do not spread malaria in the wild. At every link in the chain that makes up the parasite's complex life cycle, Gwadz sees opportunities to "build better mosquitoes" by breaking those links, using suitable genetic engineering methods. His group has already inserted a foreign gene into mosquitoes, where it has so far remained stable for more than 50 generations.

The next step is to find the right weapons—perhaps some of the immune compounds newly discovered in other insects—and splice the genes for them into mosquitoes. Gwadz would then like to link expression of those genes to the expression of the genes that manufacture yolk for nourishing the female's eggs. The yolk genes are switched on after the female takes her blood meal; a killer compound switched on at the same time could destroy the parasites within the mosquito.

The way Gwadz tells it, swarms of the engineered nontransmitting mosquitoes would be released at opportune moments—occupying all available habitats and keeping out ordinary mosquitoes that are capable of spreading malaria. But Chris Dye, a researcher at the London School of Hygiene and Tropical Medicine who studies mosquito behavior, is skeptical. "This kind of optimism was around in the sixties and seventies, when people . . . were merely selecting refractory strains of mosquitoes. The results

Third World officials on how to use existing technology more effectively. This is the aim of a relatively new joint endeavor of the Rockefeller Foundation and WHO.

Likewise, says Jose Najera, director of WHO's division of tropical disease control, his agency long ago abandoned its more grandiose plans and now concentrates on training health-care workers to mitigate malaria's worst effects. At present, he says, "there are more countries where the situation is deteriorating than countries where it is improving." In what resembles a triage strategy, WHO recognizes that there are many places where broad control efforts cannot be sustained—perhaps because of local wars or strip-and-burn development. It focuses "in a selective manner" on building expertise in areas of high incidence, such as West Africa. One important goal, Najera says, is to dispel the notion that this is an outdated profession and to draw young people back into the field of mosquito and parasite control, which is now seriously short of expertise.

However, it would be a mistake to emphasize fieldwork at the expense of basic science, says Nina Agabian, a parasitologist with a joint appointment at the University of California at Berkeley and San Francisco. She also sits on AID's malaria peer-review panel. "There's a huge interest in the developing world in technology transfer," she says, "but you've got to have something in the pipeline" to deliver. Like many biologists, she is enthusiastic about extending the basic discoveries of the 1980s as a source of new technology for the future. This approach, she argues, will eventually yield the largest reward—perhaps a breakthrough in understanding the parasite's interactions with the human immune system.

The United States now spends about $26 million on malaria research—a "dismal" effort, considering the size of the problem, says Denis Prager, director of health programs at the John D. and Catherine T. MacArthur Foundation. This is one of the few private organizations that support tropical disease research, having spent $30 million over the past 5 years for studies on basic parasitology. Although MacArthur considered dropping out last year, it has made a pledge to continue, for now.

Several other international foundations make a significant contribution, as do the governments of Australia, Britain, France, and the Netherlands. But the global sum is still a tiny fraction of the amount the United States spends on, say, AIDS research alone.

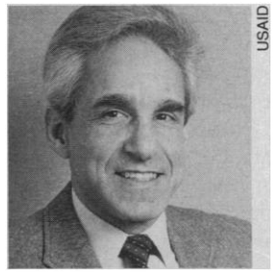
The steadiest international commitment has come from WHO, which spends roughly $5 million a year for fundamental research, according to Tore Godal, director of WHO's Tropical Disease Research program. The agency tries to support ideas that are not well funded by governments or industry, Godal says. These include an attempt to develop a "transmission blocking" vaccine that could knock down rates of incidence but would not directly benefit recipients. WHO also has drafted some academic centers to serve in a role normally played by drug companies—testing new ideas for chemotherapeutic agents and developing them into practical medicines. Because industry is not interested, Godal says, "we find that we increasingly have to focus on a few areas" of high-risk research.

Indeed, it was academic science in Europe and America that offered the best chance of progress during the 1980s as the situation worsened in the Third World. Molecular biologists reasoned that they could use their new tools—monoclonal antibodies and gene splicing—to create a vaccine based on the structure of the surface coat of the sporozoite, which is the form of the parasite injected by mosquitos into the blood.

Funding agencies poured millions of dollars into a high-profile crusade to do precisely this. Researchers and pharmaceutical companies joined the excitement, signing agreements, issuing press releases, and injecting test sporozoite vaccines into primates and humans.

When the new ideas were tried in clinics, however, the parasite-host interaction proved more complex than expected, and the strong immunological response that appeared in animals did not show up in humans. Today, research on this technology continues as before, making steady scientific progress, but it has not yet come near the goal of providing a vaccine. The experience has been disappointing, although many parasitologists say it was not the researchers who created the impression that success was just around the corner, but agency directors seeking to justify budgets.

"The reason the vaccine work on malaria has been a disappointment is that we got our expectations too high," says Prager. "And the reason we got our expectations too high, in my view, was that AID [the biggest backer of vaccine research] tried to promise too much too quickly and they tried to get publicity for the early research before it was appropriate." He adds that it is slightly reminiscent of "the cold fusion business: if you hold press conferences and draw attention to very early preliminary results, the likelihood in this field is that you're going to be disappointed, because this is an unbelievably complex area."



"Dismal": *Denis Prager on U.S. funding of basic research in malaria.*

For those who made promises, however, like AID, the disappointment hit hard. Not only did the vaccine program fail to produce a clear success, but top management at AID succumbed to internecine personal battles, prompting Congress to order an investigation by the General Accounting Office.

The report, issued in October 1989, urged AID to overhaul the program and introduce a more rigorous system of peer review, among other things. Since then, AID has gone through several programmatic upheavals, canceled a few longstanding grants, appointed new reviewers, and provided evidence for indictments against a leading malaria researcher, Wasim Siddiqui, and the program's former chief technical officer, James Erickson, alleging that they misappropriated funds. AID and

were always failures. . . ."

If high-tech solutions fail, then, as Bill Collins of CDC in Atlanta says, it's "back to the turn of the century and bed nets."

But bed nets, like malaria itself, are staging a comeback—with a new wrinkle. Several groups are experimenting with bed nets impregnated with insecticides. The big advantage of the treated nets is that because they kill the mosquitoes rather than just keeping them out, they work even when they have some holes or when an arm or a leg touches the net.

In China, 2 million impregnated nets have proved "extremely effective," according to Chris Curtis of the London School of Hygiene and Tropical Medicine. A trial in The Gambia that had been planned to run 2 years was halted after 1 year because the impregnated bed nets were so effective "it was unethical to continue," says Curtis. And his own research in Tanzania indicates villagers are happy to reimpregnate their own nets every 6 months.

These three control strategies are but a few of those that researchers are currently considering. Since a malaria vaccine has taken on something of the character of a mirage—vanishing as it is approached—control strategies can be expected to assume even greater significance in the next few years. ■ **J.C.**