the other U.S. sponsors of basic malaria research also asked the Institute of Medicine to conduct a comprehensive review of the field and to submit recommendations in 1992 to guide future research. The chairman has not been named, but the staff study director has been selected. He is Stanley Oaks, formerly of the Department of Defense Medical Research and Development Command.

Several researchers are wondering whether all this turmoil means that AID's basic research program is about to end. Diggs, the current director, says there is no plan to retreat and that funding is expected to continue at around $8.5 million a year. But his boss, Bradshaw Langmaid, acting assistant administrator for science and technology at AID, concedes that everything depends on the will of Congress. Langmaid also explains that as a "service agency" AID always has a difficult time justifying a program of pure research if it is seen as requiring sacrifices in other, direct forms of assistance. But, he adds, "Malaria is a forgotten problem for much of the research establishment," and the agency intends to continue its support, if only because no one else seems ready to take on the job.

It would be fatuous to claim that the prospects for a "cure" are better in this decade than they were in the last. But researchers argue strongly for extending basic malaria studies on grounds that they are not only interesting biologically but because they remain the most cost-effective way to invest antimalaria funds. William Trager, a Rockefeller University scientist who with James Jensen discovered a method for raising *Plasmodium* in the laboratory, says that in spite of the setbacks in the 1980s, "very interesting progress has been made" in molecular studies of malaria, and "there are many reasons to be optimistic, even about the synthetic vaccines." Agabian, likewise, argues that scientists until now have used the tools of molecular biology in a superficial way, to apply old paradigms of immunology to the complex relationship between humans and *Plasmodium*. Real progress will come, she thinks, when researchers develop entirely new concepts in immunology arising from current work with *Plasmodium* and other protozoa.

Some agencies are finding it difficult to justify an open-ended commitment to basic research now that it is clear that genetic engineering will not deliver any quick or universal remedy for malaria. However, as Miller said recently, "Where there are no known solutions or only partial or expensive control measures, research, slow and unpredictable as it may be, is the only hope."

■ **ELIOT MARSHALL**

Malaria Vaccines: The Failed Promise

"1990—TROPICAL SCOURGE CONQUERED. The first human malaria vaccine reaches clinical use. Developed at New York University, the preventative is made from a gene-cloned protein from the cell surface of the malaria parasite. It is effective against all four species that infect human beings."

Or so the editors of *Omni* magazine predicted in 1985. Time's up. But a vaccine against malaria seems no nearer now than it did then. Why not?

The answer lies in the complex cycle that connects the parasite, called *Plasmodium*, the many species of anopheline mosquitoes in which it mates, and the humans who are bitten by those mosquitoes. The parasite has shown a surprising immunologic variability, and vaccine strategies that once seemed straightforward have proven frustratingly ineffective in recent years.

The life cycle of *Plasmodium* includes three main stages: the sporozoite, the merozoite and the gametocyte. When an infected mosquito bites, it injects thousands of sporozoites into the blood. Carried to the liver, they take up residence in liver cells. There they multiply, each forming hundreds of merozoites. Ultimately the packed liver cells burst, releasing merozoites into the blood stream.

Within seconds, each merozoite invades a red blood cell. Again, massive proliferation ensues, continuing until the red cells burst and release more merozoites. It is the simultaneous bursting of waves of infected red cells that leads—by mechanisms still not fully understood—to the chills and fever of malaria.

Sometimes after a merozoite infects a red blood cell, it develops not into more merozoites but into male and female gametocytes, which constitute the parasite's sexual stage. When a mosquito bites an infected person, it may suck up some gametocytes, which emerge from their red cells in the mosquito's stomach. There they find each other and mate, yielding an egg that eventually releases thousands of sporozoites to initiate the cycle again.

The presence of three tempting targets—sporozoite, merozoite, and gametocyte—once seemed to make the task of developing a malaria vaccine easier. And in 1985, when the savants at *Omni* were summing up the future, there was reason for optimism. The first *Plasmodium* gene had recently been cloned: the gene that codes for the circumsporozoite (CS) protein, which surrounds the infective sporozoite. It had been known since the 1940s that chickens could be protected by infecting them with sporozoites weakened by radiation; similar data were obtained for mice in the 1960s and humans soon after.

With those findings—and the CS gene in hand—it seemed a vaccine might be right around the corner. And prototype vaccines were right around the corner: the first trials took place just 3 years after the gene was cloned.

Unfortunately, vaccines based on a genetically engineered version of the CS protein were disappointing. In two trials of different vaccines only one of nine subjects was protected—and even that case is suspect. Andy Waters, a molecular biologist in the malaria section of the laboratory for parasitic diseases of the National Institute of Allergy and Infectious Diseases (NIAID), says the one lucky volunteer suffered an allergic reaction to the vaccine itself. The parasites were killed by the allergic reaction, Waters said; "it was nothing to do with immunization per se."

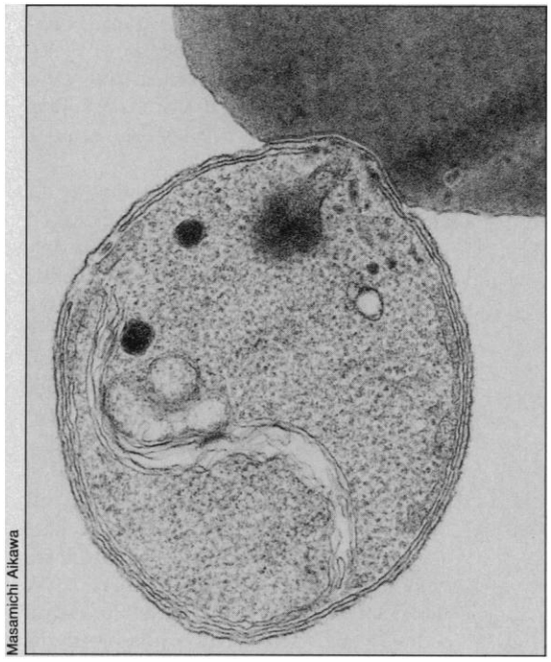
The reason for this failure may be that *Plasmodium* and the human immune system have been playing hide-and-seek for countless generations. In playing that evolutionary game, the sporozoite has acquired the capacity to change its CS protein coat in myriad ways, offering a bewildering variety of identities that enable at least a few sporozoites to evade immune surveillance. Hence a vaccine engineered against a particular CS protein is useless against the rest—and the infection takes hold. Even a "cocktail" of CS proteins is unlikely to be effective, because the parasite may quickly evolve new variants in its proteins.

Fortunately, researchers were also taking aim at the other targets. Target number two was the merozoite, the stage that multiplies asexually in the blood. The merozoite, however, is a fleeting target. At large in the blood for only a few seconds, it is—like the sporozoite—extremely variable immunologically. Therefore many malariologists were surprised in 1987 when Manuel Patarroyo and his colleagues at the National University of Colombia announced that they had suc-

cessfully protected Colombian soldiers against infection using synthetic peptides based on merozoite proteins.

That surprise turned to more substantial skepticism when others found it difficult to reproduce Patarroyo's results. Bill Collins, who works in the Malaria Branch of the Centers for Disease Control in Atlanta, performed a similar study last spring. "We did not get any protection at all in the trial we conducted," Collins told *Science*. While he concedes there were "slight differences" between CDC's procedure and Patarroyo's, Collins stresses that "in a similar trial, with similar antigens, we ended up with dissimilar results."

But Patarroyo hasn't given up. He has conducted a second trial on Colombian soldiers, and *Science* has learned that Patarroyo is now testing his anti-merozoite vaccine on some 1500 peasants in the eastern Venezuelan state of Bolivar. Arnoldo Gabaldón, dean of Venezuelan malariologists, was sufficiently impressed with Patarroyo's early results to join the Venezuelan government in inviting him to conduct a bigger trial in Venezuela. Chris Curtis of the London School of Hygiene and Tropical Medicine says there is "tremendous excitement" in Venezuela and Colombia about Patarroyo's merozoite vaccine.



Masamichi Aikawa

Give me fever. *A merozoite—the stage of the malaria parasite that causes the symptoms—invades a red blood cell.*

Few scientists outside those countries share wholeheartedly in that enthusiasm. Most are more enthusiastic about target number three: the gametocyte.

A gametocyte vaccine would be something of an altruistic oddity, protecting not the person who receives it but those to whom mosquitoes carry the disease. The reason is that the gametocyte stage is involved only in the transfer of the parasite to a mosquito and not in causing the symptoms. Hence a vaccine against gametocytes would not protect the person to whom it is administered but would prevent him from transmitting the disease to others.

But the victim himself would not be forgotten. Robert Sinden, professor of parasite cell biology at Imperial College in London, says such a vaccine might be offered in conjunction with chemotherapy or another vaccine, so that transmission and infection could be dealt with at the same time.

One reason malariologists favor a gametocyte vaccine is that the sexual stage of the parasite is likely to be far less immunologically variable than the others. Many of the sexual stage proteins currently being engineered are expressed only when the parasite enters the mosquito—they are not present when the parasite is in the blood. Since they are not seen by the human immune system, they are less likely to vary.

Given that the gametocyte antigens are not present in the blood, one might ask what good it would do to to raise antibodies against them with a vaccine. Yet an anti-gametocyte vaccine could still be effective. The reason is that antibodies to gametocyte antigens would be carried into the mosquito along with the blood, and as soon as the gametocyte emerges from the red cell in the mosquito's stomach, the antibodies would be there to do their job. This is more than a speculative possibility: Sinden has used it in a mouse model and blocked transmission for 39 weeks.

A gametocyte vaccine isn't without problems, however. Lindsay Martinez, secretary of the Immunology of Malaria Steering Committee at WHO's Special Programme for Research and Training in Tropical Diseases (TDR), suggests that a few antibody molecules in the mosquito's blood meal might actually bring male and female gametocytes together, increasing the chances of a successful mating and hence making the disease more infectious. Sinden concedes the point, but argues that it applies only at antibody levels so low they are seldom reached in a natural population subject to reinfection; in his mouse work, he says, there was no sign of increased infectivity.

Quite apart from the difficulties of devising a vaccine, there is reason to think that immunization might not be the panacea for malaria. Indeed, in some circumstances a vaccine could make things worse. Natural protection against the disease depends on continuous exposure to keep the immune system up to the mark. African students who come to Europe or America to study often suffer dreadful malaria attacks when they return home, because the lack of re-infection has made them susceptible once again. By reducing rates of transmission and exposure, a vaccine could actually make things worse when people do get infected.

Why then are so many pursuing a vaccine with such vigor? One reason is the difficulties that have been encountered with effective forms of therapy (see main story). Furthermore, as Martinez of the WHO points out: "Vaccination is the most cost-effective and efficient method of prevention of [certain] infectious diseases." A vaccine probably could not completely prevent transmission—the mathematics of malaria show that it would have to reach more than 99% of the population in order to do that—but if a single inoculation could prevent disease, then the single greatest tropical scourge would have been conquered.

Yet some might argue that a vaccine isn't, after all, necessary. Most of those infected with malaria recover and go on to acquire immunity. There may, however, be hidden damage even among those who survive. A malariologist who prefers anonymity because he fears people will think he is casting aspersions on people who live in countries where the disease is endemic notes that the majority of children who have malaria pass through several crises, involving convulsions, perhaps even coma, which may lead to blockage of blood vessels in the brain.

Such damage might impair intellectual performance later in life, he notes. "Is the damage measurable? I don't know. Are you doing something to that individual when he's an adult? I don't know... does it influence populations? I don't know. Would they be better off if they never had a severe attack of malaria? I think they would."

A vaccine remains the likeliest way of preventing entire populations from having a severe attack of malaria. When might such a boon arrive? After the frustrated hopes of the mid-1980s, no one is willing to hazard a guess. "I don't think it's this year," is all Bill Collins of the CDC will say.

And Lindsay Martinez, who ought to be a professional optimist by virtue of her position, is guarded. "It's always been dangling 5 years ahead, and it always is 5 years ahead. I doubt if there's going to be anything on the market before 5 years from now. I hope it's not going to be much longer than that."

■ JEREMY CHERFAS