Malaria

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The contents of this course are taken from the U.S. Department of Health & Human Services, National Institute of Allergy and Infectious Diseases. Learning objectives and post test have been prepared by Dr. Ratnakar P. Kini

Objectives:

Upon completion of this course, the learner will be able to:

1. Define what is malaria
2. Explain the life cycle of malarial parasite
3. Discuss the symptoms of malaria
4. Explain how to diagnose and treat malaria
5. Discuss how to prevent malaria
6. Explain how malaria affects pregnancy
7. Discuss the research done in malaria

QUICK FACTS

INCIDENCE:

Worldwide: Up to 2.7 million people die each year from malaria, most of them African children. Between 400 million and 900 million cases of acute malaria occur annually in African children alone.

United States: According to the U.S. Centers for Disease Control and Prevention, more than 1,000 new cases are reported annually in travelers returning from malaria-endemic areas.

CAUSE:

One-celled parasite, genus *Plasmodium*
Four species infect humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale*

TRANSMISSION:

Most commonly, from an infected *Anopheles* mosquito bite.

SYMPTOMS:

Flu-like, including chills, fever, and sweating accompanied by headache, nausea, and vomiting; attacks can recur. Life-threatening illnesses, such as severe anemia or cerebral malaria, may occur in some infected individuals.

DIAGNOSIS:

Based on symptoms and travel history; confirmed by blood smears that identify the parasite.

TREATMENT:

Chloroquine, where parasite is not resistant to it; combination of antimalarial drugs where chloroquine is ineffective; treatment of symptoms as required.

PREVENTION:

Chloroquine or other antimalarial drugs taken before and during travel to a malarious area and continued for several weeks after returning; mosquito repellants and sleeping under bed nets; no approved vaccine is currently available.

CONTENTS

WHAT *is Malaria?*

Malaria is a disease caused by a **parasite*** that lives part of its life in humans and part in mosquitoes. It remains one of the major killers of humans worldwide, threatening the lives of more than one-third of the world's population. Malaria thrives in the tropical areas of Asia, Africa, and South and Central America, where it strikes millions of people. Sadly, as many as 2.7 million of its victims, mostly infants and children, die yearly.

Although malaria has been virtually eradicated in the United States and other regions with temperate climates, it continues to affect hundreds of people in this country every year. In 2000, health care workers reported 1,400 cases of malaria to the U.S. Centers for Disease Control and Prevention (CDC). Malaria in the United States is typically acquired during trips to malaria-endemic areas of the world and therefore is often called travelers' malaria.

During the past 10 years, CDC has documented local cases of malaria in states as varied as California, Florida, Texas, Michigan, New Jersey, and New York. In the summer of 1999, one highly publicized case occurred at a Boy Scout camp on Long Island, New York, where two boys were infected by mosquitoes.

HISTORY *of Malaria*

Malaria has been around since ancient times. The early Egyptians wrote about it on papyrus, and the famous Greek physician Hippocrates described it in detail. It devastated the invaders of the Roman Empire. In ancient Rome, as in other temperate climates, malaria lurked in marshes and swamps. People blamed the unhealthiness in these areas on rot and decay that wafted out on the foul air, or, as the Italians were to say, "mal aria" or bad air. In 1880, scientists discovered the real cause of malaria, the one-celled ***Plasmodium*** parasite, and 18 years later, they attributed the transmission of malaria to the ***Anopheles*** mosquito.

Historically, the United States is no stranger to the tragedy of malaria. The toll that this disease, commonly known as "fever and ague," took on early settlers is vividly depicted in the popular children's book "Little House on the Prairie" by Laura Ingalls Wilder. Historians believe that the incidence of malaria in this country peaked around 1875, but they estimate that by 1914 more than 600,000

*****Note: Words in bold are defined in the glossary at the end of this booklet.*

new cases still occurred every year. Malaria has been a significant factor in virtually all of the military campaigns involving the United States. In both World War II and the Vietnam War, more personnel time was lost due to malaria than to bullets.

The malaria parasite typically is transmitted to humans by mosquitoes belonging to the **genus** *Anopheles*. In rare cases, a person may contract malaria through contaminated blood, or a fetus may become infected by its mother during pregnancy. The **larval** stage of the *Anopheles* mosquito thrives in still waters, such as swamps. The discovery by scientists that mosquitoes carried the disease unleashed a flurry of ambitious public health measures designed to stamp out malaria. These measures were targeted at both the larval and adult stages of the insect. In some areas, such as the southern United States, draining swamps and changing the way land was used was somewhat successful in eliminating mosquitoes.

The pace of the battle accelerated rapidly when the insecticide DDT and the drug **chloroquine** were introduced during World War II. DDT was remarkably effective and could be sprayed on the walls of houses where adult *Anopheles* mosquitoes rested after feeding. Chloroquine has been a highly effective medicine for preventing and treating malaria.

In the mid-1950s, the World Health Organization (WHO) launched a massive worldwide campaign to eliminate malaria. At the beginning, the WHO program, which combined insecticide spraying and drug treatment, had many successes, some spectacular. In some cases, malaria was conquered completely, benefiting more than 600 million people, and it was sharply curbed in the homelands of 300 million others.

Difficulties soon developed, however. Some stumbling blocks were administrative, others financial. Even worse, nature had begun to intervene. More and more **strains** of *Anopheles* mosquitoes were developing **resistance** to DDT and other insecticides. Meanwhile, the *Plasmodium* parasite was becoming resistant to chloroquine, the mainstay of antimalarial drug treatment in humans.

Researchers estimate that infection rates increased by 40 percent between 1970 and 1997 in sub-Saharan Africa. To cope with this dangerous resurgence, public health workers carefully select prevention methods best suited to a

particular environment or area. In addition to medicines and insecticides, these include such standbys as draining swampy areas and filling them with dirt, and using window screens, mosquito netting, and insect repellents.

At the same time, scientists are intensively researching ways to develop better weapons against malaria, including

- Sophisticated techniques for tracking disease transmission worldwide
- More effective ways of treating malaria
- New ways, some quite ingenious, to control transmission of malaria by mosquitoes
- A vaccine for blocking its development and spread

MALARIA *Parasite*

Malaria is caused by a one-celled parasite from the genus *Plasmodium*. More than 100 different **species** of *Plasmodium* exist, and they produce malaria in many types of animals and birds, as well as in people.

Four species of *Plasmodium* infect humans. Each one has a distinctive appearance under the microscope, and each one produces a somewhat different pattern of symptoms. Two or more species can live in the same area and can infect a single individual at the same time.

Plasmodium falciparum is responsible for most malaria deaths, especially in Africa. The infection can develop suddenly and produce several life-threatening complications. With prompt treatment, however, it is almost always curable.

Plasmodium vivax, the most geographically widespread of the species and the cause of most malaria cases diagnosed in the United States, produces less severe symptoms. **Relapses**, however, can occur for up to 3 years, and chronic disease is debilitating. Once common in temperate climates, *P. vivax* is now found mostly in the tropics, especially throughout Asia.

Plasmodium malariae infections not only produce typical malaria symptoms but they also can persist in the blood for very long periods, possibly decades, without ever producing symptoms. A person with asymptomatic (no symptoms) *P. malariae*, however, can infect others, either through blood donation or mosquito bites. *P. malariae* has been wiped out from temperate climates, but it persists in Africa.

Plasmodium ovale is rare, can cause relapses, and generally occurs in West Africa.

LIFE *Cycle*

The human malaria parasite has a complex life cycle that requires both a human host and an insect host. In *Anopheles* mosquitoes, *Plasmodium* reproduces sexually (by merging the parasite's sex cells). In people, the parasite reproduces asexually (by cell division), first in liver cells and then, repeatedly, in red blood cells.

When an infected female *Anopheles* mosquito bites a human, she takes in blood. At the same time, she injects saliva that contains the infectious form of the parasite, the **sporozoite**, into a person's bloodstream.

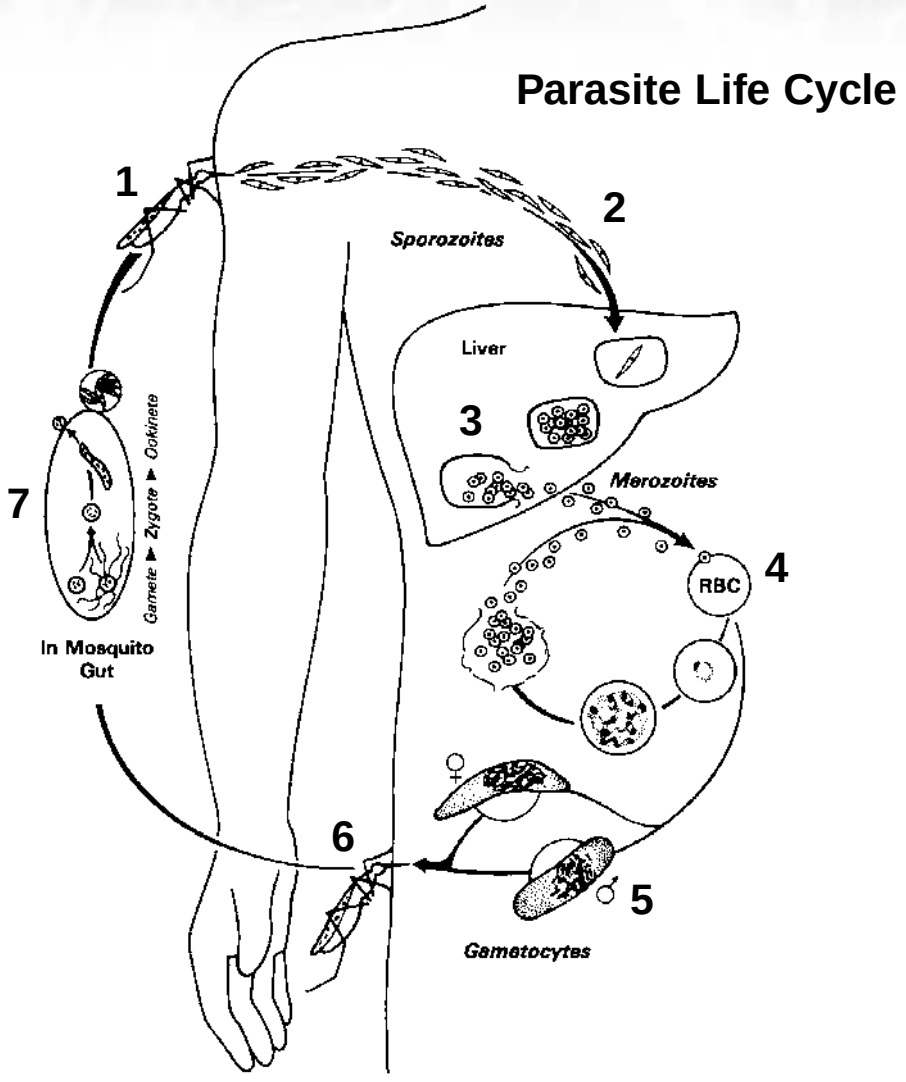
The thread-like sporozoite promptly invades a liver cell. There, during the next week or two (depending on the *Plasmodium* species), each sporozoite develops into a **schizont**, a structure that contains thousands of tiny rounded **merozoites** (another stage of the parasite). When the schizont matures, it ruptures and releases the merozoites into the bloodstream.

Alternatively, some *P. vivax* and *P. ovale* sporozoites turn into **hypnozoites**, a form that can remain dormant in the liver for months or years. If they become active again, the hypnozoites cause relapses in infected individuals.

Merozoites released from the liver rapidly invade red blood cells where they fuel their activities by consuming **hemoglobin**, the oxygen-carrying part of the blood. Within the red blood cell, most merozoites go through another round of asexual reproduction, again forming schizonts filled with yet more merozoites. When the schizont matures, the cell ruptures and merozoites burst out.

The newly released merozoites invade other red blood cells, and the infection continues its cycle until it is brought under control, either by medicine or the body's immune defenses.

The *Plasmodium* parasite can complete its life cycle through the mosquito because some of the merozoites that penetrate red blood cells do not develop asexually into schizonts. Rather, they change into male and female sexual forms known as **gametocytes**. These circulate in the person's bloodstream, awaiting the arrival of a blood-seeking female *Anopheles*.



1. Female anopheline mosquito injects *Plasmodium* sporozoites into the bloodstream. 2. Sporozoites migrate to the liver and infect liver cells. 3. Sporozoites reproduce asexually to form thousands of merozoites, which ultimately rupture from the liver cells and re-enter the bloodstream. 4. Once in the bloodstream the merozoites invade red blood cells (RBCs). Parasites mature within those cells and are then released to infect even more RBCs. Disease and death in malaria is most commonly caused by this stage of infection. The common malaria drugs chloroquine and quinine also block the parasite's life cycle at this stage. 5. Some RBC parasites differentiate into male and female forms called gametocytes. 6. When a female mosquito feeds on an infected person, she ingests gametocytes from the blood. 7. Inside the mosquito midgut, the gametocytes differentiate into forms resembling sperm and eggs, allowing sexual reproduction to occur. The resulting parasites grow into sporozoites and migrate to the insect's salivary glands.

When she bites an infected person, the female mosquito sucks up gametocytes along with blood. Once in the mosquito's stomach, the gametocytes develop into sperm-like male **gametes** or large, egg-like female gametes. Fertilization produces an **oocyst** filled with infectious sporozoites. When the oocyst matures, it ruptures and the thread-like sporozoites migrate, by the thousands, to the mosquito's salivary (saliva-producing) glands. And the cycle starts over again when she bites her next victim.

SPREAD *of Malaria*

Many biological and environmental factors shape the character of malaria in a given location. Nearly all the people who live in **endemic** areas are exposed to infection repeatedly. Those who survive malaria in childhood gradually build up some **immunity**. They may carry the infection, serving as reservoirs for transmission by mosquitoes without developing severe disease. In other areas, where the infection rate is low, people do not develop immunity because they rarely are exposed to the disease. This makes them more susceptible to the ravages of an **epidemic**. An epidemic can occur when conditions, such as those discussed below, allow the mosquito population to suddenly increase.

Effects of Climate

Climate affects both parasites and mosquitoes. Mosquitoes cannot survive in low humidity. Rainfall expands breeding grounds, and in many tropical areas, malaria cases increase during the rainy season. Mosquitoes must live long enough for the parasite to complete its development within them. Therefore, environmental factors that affect mosquito survival can influence malaria incidence. *Plasmodium* parasites are affected by temperature—their development slows as the temperature drops. *P. vivax* stops developing altogether when the temperature falls below 60°F. *P. falciparum* stops at somewhat higher temperatures. This explains why parasites can be found in various parts of temperate areas.

Effect of Human Intervention

People have worked for centuries to control malaria and were successful in eradicating it from most of the New World early in the 20th century. Certain human activities, however, have inadvertently worsened the spread of malaria.

World Malaria Situation

Malaria is endemic to tropical and subtropical regions.

Malaria situation, 1999 (*source: WHO*)

Areas in which malaria has disappeared, been eradicated, or never existed

Areas with limited risk

Areas where malaria transmission occurs

City conditions can create new places for mosquito larvae to develop. Agricultural practices also can affect mosquito breeding areas. Although draining and drying of swamps gets rid of larval breeding sites, water-filled irrigation ditches may give mosquitoes another area to breed. In addition, because farmers use the same pesticides on their crops as those used against malaria **vector** mosquitoes, the problem of insecticide-resistant mosquitoes is growing. Modern transportation also contributes to the spread of the disease, moving travelers between malaria-endemic and non-endemic regions.

Blood

Malaria is transmitted occasionally by transfusions of blood from infected individuals, sharing of needles to inject intravenous drugs, or from an infected pregnant woman to her unborn child. In the United States, however, transmission rarely occurs through blood transfusions because blood donors are not allowed to donate for specified periods of time after traveling to or living in a malarious area.

SYMPTOMS *of Malaria*

Malaria typically produces a string of recurrent attacks, or **paroxysms**, each of which has three stages—chills, followed by fever, and then sweating. Along with chills, the person is likely to have headache, nausea, and vomiting. Within an hour or two, the person's temperature rises, and the skin feels hot and dry. Then, as the body temperature falls, a drenching sweat begins. The person, feeling tired and weak, is likely to fall asleep.

The symptoms first appear some 10 to 16 days after the infectious mosquito bite and coincide with the bursting of infected red blood cells. When many red blood cells are infected and break at the same time, malaria attacks can recur at regular time periods—every 2 days for *P. vivax* malaria and *P. ovale*, and every 3 days for *P. malariae*.

With *P. vivax* malaria, the patient may feel fine between attacks. Even without treatment, the paroxysms subside in a few weeks. A person with *P. falciparum* malaria, however, is likely to feel miserable even between attacks and, without treatment, may die. One reason *P. falciparum* malaria is so **virulent** is that the parasite can infect red blood cells in all stages of development, leading to very high parasite levels in the blood. In contrast, *P. vivax* parasites infect only young

red blood cells, which means the number of parasites in the blood does not reach the same high levels as seen in *P. falciparum* infection.

DIAGNOSING *Malaria*

A doctor or other health care worker should suspect malaria whenever a person who has been in the tropics recently or received a blood transfusion develops a fever and other signs that resemble the flu. A doctor will examine blood smears, taken from a finger prick, under a microscope. If parasites are present, the diagnosis is confirmed. A "thick" smear makes it possible for the health care worker to examine a large amount of blood. Then, the species of parasite can be identified by looking at a corresponding "thin" smear. This is important for deciding on the best treatment.

Mixed infections are possible. For example, a person can be infected with *P. vivax* as well as the more dangerous *P. falciparum*.

In the unusual event that parasites cannot be seen immediately in a blood smear, but the patient's condition and prior activities strongly suggest malaria, the doctor may decide to start treatment before being sure the patient has malaria.

TREATING *Malaria*

In most cases, malaria can be successfully treated, although the recuperating patient may find it takes several weeks to recover full strength. Before deciding on the best medicine to use, the doctor should try to identify the species of parasite responsible for the disease and where the patient got the infection. Up-to-date information on the geography of malaria, such as which species are present in which areas, whether chloroquine-resistant parasites are present, and which seasons of the year carry the greatest risk, is available at international travel clinics, CDC, and WHO.

In the United States, patients with *P. falciparum* malaria are usually hospitalized and treated as medical emergencies because their conditions may get worse quickly. Patients should talk with a doctor who specializes in infectious diseases and is knowledgeable about diagnosing and treating malaria and its complications.

Chloroquine, long considered the medicine of choice for treating malaria, is no longer considered the first-line antimalarial drug in many countries, and national malaria control programs are recommending alternatives. Because chloroquine-resistant parasites are becoming more widespread, doctors must carefully monitor patients who are treated with it.

If the number of parasites in the blood does not drop significantly during treatment, it may mean the parasites are resistant to the medicine. In addition, if a person develops any fever within a period of weeks to months after apparently successful treatment, the medicine may not have gotten rid of all the parasites. Additional treatment may then be required.

Health care workers should watch patients with *P. falciparum* malaria closely for potentially severe complications, including anemia, kidney failure, fluid imbalance, or respiratory distress. Brain damage can occur following cerebral malaria, which happens when large numbers of red blood cells containing parasites clog tiny blood vessels in the brain.

PREVENTING *Malaria*

Before leaving home, anyone traveling to a malarious area should consult CDC, WHO, a knowledgeable health care provider, an international travel clinic, or a local health department to get advice on what medicines to take before, during, and after the trip. Health risks for malaria vary with the destination and types of activities the traveler will undertake.

A traveler who spends even a single night in a malarious area risks getting infected. The first line of defense is to limit contact with mosquitoes by taking these measures.

- Use mosquito repellent
- Keep arms and legs covered
- Stay indoors beginning at dusk and throughout the night (when *Anopheles* mosquitoes like to feed)
- Sleep under mosquito netting

People traveling to malarious areas should also protect themselves by taking antimalarial medicines to prevent infection. CDC has current guidelines on antimalarial drugs.

Anyone who develops fever or other symptoms suggesting malaria, either while taking preventive medicines or after stopping them, should seek medical attention immediately.

MALARIA *and Pregnancy*

Malaria poses a serious threat to both the pregnant woman and her unborn child. Women who live in malarious areas are much more likely to develop acute *P. falciparum* malaria when they become pregnant. Infants born to mothers with malaria often will have low birth weights.

If possible, pregnant women from non-malarious areas should postpone travel to those regions until after their babies are born. Pregnant women who cannot postpone travel until after delivery should protect themselves from mosquito bites and take antimalarial medicines, if recommended by their doctors.

PROSPECTS *of Conquering Malaria*

Researchers in the fight against malaria have three major goals: new medicines, better methods of mosquito control, and a vaccine to prevent people from becoming infected.

Medicines

Medicines to treat malaria have been around for thousands of years. Perhaps the best known of the traditional remedies is **quinine**, which is derived from the bark of the *cinchona* tree. The Spanish learned about quinine from Peruvian Indians in the 1600s, and export of quinine to Europe, and later the United States, was a lucrative business until World War II cut off access to the world supply of cinchona bark. In the 1940s, an intensive research program to find alternatives to quinine gave rise to the manufacture of chloroquine and numerous other chemical compounds that became the forerunners of "modern" antimalarial drugs.

Chloroquine was the third most widely used drug in the world until the mid-1990s. It is cheap to manufacture, easy to give, and does not cause problems for most people. Unfortunately, chloroquine-resistant malaria parasites have developed and are increasing in numbers. From the 1950s to

the present, chloroquine resistance gradually spread to nearly all *P. falciparum* malaria-endemic regions. In the 1960s, the U.S. Government, WHO, and other agencies launched a massive search for new antimalarial drugs. In addition, many doctors treating people in Asia are using yet another new family of drugs based on the parent drug artemisinin, an extract of the Chinese herbal remedy qinghaosu.

Unfortunately, malaria parasites in many geographic regions have become resistant to alternative drugs, many of which were discovered only in the last 30 years. Even quinine, the long-lived mainstay of malaria treatment, is losing its effectiveness in certain areas.

To address the problem of drug-resistant malaria, scientists are conducting research on the genetic devices that enable *Plasmodium* parasites to avoid the toxic effects of malaria drugs. Understanding how those devices work should enable scientists to develop new medicines or alter existing ones to make it more difficult for drug resistance to emerge. By knowing how the parasite survives and interacts with people during each distinct phase of its development, researchers also hope to develop drugs that attack the parasite at different stages.

Mosquito Control

The appearance and spread of insecticide-resistant mosquitoes, as well as stricter environmental regulations, now limit the effectiveness of the insecticide DDT, the mainstay of the 1950s and 1960s malaria eradication programs. More recently, researchers have found that mosquito netting soaked with other insecticides, which prevent mosquitoes from making contact with humans, significantly reduce malaria transmission. Therefore, as part of its Roll Back Malaria program, WHO is promoting widespread use of mosquito netting in endemic areas. Still, in some parts of Western Africa, mosquitoes have become resistant to the pyrethroid insecticide used to treat mosquito netting. Although scientists do not think this is a serious limitation yet, it points out the need to continue research to identify new tools for mosquito control.

Vaccines

Research studies conducted in the 1960s and 1970s showed that experimental vaccination of people with **attenuated** malaria parasites can effectively immunize them against getting another malaria infection. Current methods to

develop vaccines based on weakened or killed malaria parasites are technically difficult and do not readily lend themselves to commercialization. Therefore, much of the research on vaccines has focused on identifying specific components or **antigens** of the malaria parasite that can stimulate protective immunity.

In 1997, the National Institute of Allergy and Infectious Diseases (NIAID) launched a 10-year Research Plan for Malaria Vaccine Development based on four cornerstones.

- Establishing a resource center to provide scientists worldwide with well-characterized research reagents
- Increasing support for discovery of new vaccine candidates
- Increasing capacity to produce vaccine candidates at the quality and quantity that will be required for clinical trials
- Establishing research and training centers in endemic areas where potential vaccines may undergo clinical trials

Under these and other programs, scientists are conducting research to understand the nature of protective immunity in humans and how to induce protective immune responses with malaria antigens.

Genome Sequencing

Genome sequencing, the process that allows scientists to determine an organism's genetic blueprint, is accelerating the discovery of new targets for drugs, vaccines, and diagnostic tests for malaria and other infectious diseases. By examining those blueprints, researchers can determine the genes that control a broad range of an organism's biological properties, such as feeding, reproducing, and adapting to its environment.

The complete genome sequences for the *Anopheles* mosquito and the *P. falciparum* parasite were published in 2002. Researchers are sequencing other *Plasmodium* species. These advances mark a milestone in malaria research. Combined with the recently completed human genome sequence, scientists have the complete genetic blueprints for the malaria parasite and both of its animal hosts. Researchers are now using that information to learn more about how *Plasmodium* survives within people and mosquitoes, and to discover new ways to diagnose, prevent, and treat the disease.

M A L A R I A

The conquest of malaria is a top priority for many international and government organizations, philanthropic foundations, and research institutions. In 2001, the NIAID published the *Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis*. That plan highlighted the serious toll exacted by malaria and reinforced its position as one of the three biggest infectious global health problems. As the lessons of the past decades have so convincingly demonstrated, however, conquering malaria is difficult. No one anticipates a quick victory even if new malaria drugs hit the market or a vaccine proves highly successful. Rather, researchers and health planners expect their best chances lie in a many-sided attack, drawing upon a variety of weapons suited to local environments. Skillfully combining several approaches, both old and new, may at last make it possible to outmaneuver the persistent and deadly parasites.

As with all diseases of worldwide importance, a critical aspect of our future ability to control malaria will depend on the skills and expertise of scientists, health care providers, and public health specialists working in endemic regions. Therefore, strengthening the research capability of scientists in these areas is another major focus of these efforts. NIAID works closely with national and international organizations involved in malaria research and control. The Institute was also a founding member of the Multilateral Initiative on Malaria, which emphasizes strengthening research capacity in Africa.