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Malaria

Meeting the Global Challenge

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Contents

Foreword, *Nyle C. Brady* vii
Preface, *Alexanderina V. Shuler* ix
The Ballad of the Plasmodium, *Dr. Leonard J. Bruce-Chwatt* xi
1. Malaria: Ancient Scourge of Humankind 1
   Unraveling Malaria's Secrets 1
   Focus on Control 3
   Between Wars 3
   Era of Malaria Eradication 5
   End of the Eradication Era 6
   The Resurgence of Malaria 8
   Return to Control Programs 9
   Call for More Research 10
2. Early Modern Battles 13
   Turning to Malaria Research 14
   Drug Resistance Increases 15
   Search for Alternatives 21
3. A Regional Review of AID Malaria Efforts 23
   Latin America and the Caribbean 23
   Haiti and the Dominican Republic 27
   Ecuador 29
   Bangladesh 30
   India 31
   Indonesia 32
   Nepal 33
   Pakistan 35
   The Philippines 36
   Sri Lanka 37
   Africa 37
   Near East 40

4. Drug and Vector Control Research 47
Vector Control 49
5. AID's Support for a Malaria Vaccine 51
Vaccine Patents 57
6. Future Role in Global Malaria Programs 61
Tremendous Gain 66
Appendixes
A. Malaria Parasites of Humans 75
B. Role of AID Offices Other Than Office of Health in Malaria Programs 77
C. Status of Antimalarial Drugs 81
D. WHO's Role in Global Malaria Efforts 83
E. AID-Supported Vector Control Programs 85
F. AID Malaria Vaccine Research Network 91
Glossary 95
References 99
Index 107

Foreword

In August 1984, the Agency for International Development (AID) announced a major breakthrough in the development of a vaccine against the most deadly form of malaria in human beings. The vaccine should be ready for use around the world, especially in developing countries, within five years.

The vaccine could have a tremendous impact on human health; it could drastically reduce the 150 million malaria cases that occur each year. Its development was possible due to the Agency's investment of more than $35 million to support 43 malaria research projects over the past 20 years. That research, combined with U.S. financial and technical assistance, commodities and training, has saved perhaps hundreds of millions of lives.

The United States traces its participation in global eradication and control programs to the early 1900s. International efforts initially concentrated on controlling the mosquito that causes malaria. Many impressive successes were achieved; malaria was eradicated in several countries. But as circumstances developed, including increased mosquito resistance to pesticides, the disease incidence that had dropped to all-time lows suddenly began to climb. In some countries, they soared. It was apparent that alternatives had to be found.

In the mid-1960s, AID defied critics who said that a malaria vaccine was not worth the investment it required by supporting research on such. We now know several different vaccines are necessary to prevent the four malarias that affect humans in different parts of the world. The AID malaria vaccine research network continues its search for these vaccines.

Vaccines will be an extremely valuable tool in our arsenal against this terrible disease. With effective and efficient planning and coordination,

the vaccine will help prevent the debilitation and killing of millions of people every year.

But we are also wise enough to realize that vaccines are not a panacea. Research in other areas, including vector control, new drugs, improved operational methods and better equipment, needs equal attention. All these research efforts must be coordinated to mount a successful attack on malaria, and they must make full use of the capabilities of the private sector as well as research centers and universities in developing countries.

This book reviews the role research has played in seeking means to control malaria. It is the second in a series that focuses on science and technology as tools in economic and social development of the low-income countries of the world. It reminds us of the crucial role research must continue to play if we are to help these countries overcome their development constraints.

Special acknowledgment must be given to Alexanderina V. Shuler for her preparation of this volume. She researched existing material, interviewed several key persons substantively involved in malaria research and control and eradication programs, and wrote the manuscript. A preface by Ms. Shuler recognizes some of the principal actors who had a role in international, as well as AID, antimalaria efforts.

Nyle C. Brady
Senior Assistant Administrator for
Science and Technology, AID

Preface

June 4, 323 B.C. Alexander III of Macedon falls ill with high fever and chills. In his biography of the Greek conqueror, *Alexandre*, Jacques Benoist-Mechin (1964) reports that prior to lapsing into a feeble condition during which he could barely move, Alexander suffered sleepless nights and could hardly talk. On June 13, he died at age 33.

Alexander's symptoms "could be identical to those of falciparum malaria," world renowned malariologist Dr. Leonard J. Bruce-Chwatt of the University of London's Wellcome Museum of Medicine says. "Certainly, the guess of malaria is well justified."

The history of humankind reveals that malaria has played a major role in world events. Documentation of the debilitating effects of the disease appears in the early works of Chinese and Hindu writers as well as of Hippocrates, Plato and Pliny the Elder. Battles have been lost, civilizations have disappeared with blame laid to malaria.

Malaria evidently has been the world's no. 1 public health problem for centuries, but it was not until the early 1950s that it was officially labeled such by the World Health Organization. As late as 1981, malaria still was present in 104 countries and 1.4 billion people were exposed to infection. Malaria annually kills an estimated 5 million people and infects another 300 to 400 million, most of whom live in the developing countries in the so-called malarious zones of the world, extending from 64°N to 32°S.

Over the past 50 years, chemotherapy and vector control have made it possible to eradicate indigenous malaria in 37 countries, including the United States. In other countries, especially in South America and Asia, malaria incidence has dropped substantially. But the emergence of drug-resistant parasites and the increasing prevalence of insecticide-resistant mosquitoes, combined with administrative, financial and other

problems, have caused a resurgence of malaria in many areas. In many developing countries, the incidence of malaria has again reached alarming levels. The statistics that are known are warning enough. The problem must be addressed now to prevent the figures from reaching the levels of the early part of the century.

Political will and national commitment, in terms of money and people, are part of the solution. To achieve worldwide control of malaria, massive research programs are necessary to find new and better control techniques while other efforts are incorporated into national primary health care programs.

Only when policymakers, government leaders, program designers, researchers, administrative officers and development workers recognize the impact of malaria on their respective areas of work and the need for a self-sustaining, integrated antimalaria effort, will developing countries achieve economic and social development goals, and will the support for a long-term sustained effort be forthcoming.

Many individuals who have spent their lives working in the field of malaria provide the basis for this book. Some are active in positions in the public and private sector throughout the world; many are retired. But they have two basic things in common: an intense interest in malaria events and developments, and a remarkable dedication and determination to control and conquer malaria. These are the experts that can make the eradication of malaria possible.

My thanks go to James M. Erickson, Office of Health, AID; Albert E. Farwell, AID retired; Melvin Griffith, AID retired; and Edgar A. Smith, AID retired, for sharing their malaria expertise and experiences, and to Dr. Leonard J. Bruce-Chwatt, for granting permission to print his poem, "The Ballad of the Plasmodium," which wraps up this monograph in 63 lines.

Special appreciation goes to Larry Cowper, Office of Health, AID; Lee M. Howard, Pan American Health Organization; Donald R. Johnson, U.S. Public Health Service, retired; and John Daly, Office of the Science Advisor, AID, for their contributions of background information as well as considerable time spent reviewing the manuscript.

Alexanderina V. Shuler

viii

The Ballad of the Plasmodium

Plasmodium has a lot in store
And works in stages by the score.
Anopheles that probes your skin
Pumps many sporozoites in,

They lose no time, move into liver
And settle down before you shiver,
Some hypnozoites go to sleep
A late relapse intending keep.

But others grow, divide like mad
And move from liver into blood.
In red cells do their very worst
Expanding to make each cell burst

As merozoites they are vexed
By being greatly undersexed.
Their life is tedious, rather stale
Without a female and a male.

This truth they soon will realize
And change assuming larger size
So now, when a mosquito bites
It must suck up gametocytes

And microgametes being sucked
Can now perform the amorous act
When in the stomach of the gnat
They find a macrogamete fat.

Their love's great feat is now complete
As female forms ookinete
Then losing all her self-control
She goes through insect's stomach wall.

And there encysted feels more able
To raise a new plasmodial stable
When thousand sporozoites fit
Will prove that she has done her bit

To salivary glands they wend
And start again; there is no end.
The moral of this age-old story
Is that we can't aspire to glory

Until our principal objective
Will make control more effective
We try to fight Anopheles
With our weapons in a mess

Since DDT that was the norm
Is now refusing to perform
And most of new insecticides
Have some unwelcome costly sides

By now *Plasmodium falciparum*
Is causing very great alarum
Although this protozoan vulture
Can now be grown *in vitro* culture

Thus faced with chloroquine resistance
We must depend on more assistance
And find a new medicament
To solve our dire predicament
A compound that in all event
Is active, cheap, polyvalent

Perhaps we need a proper vaccine
With antigens that science mucks in
And adjuvants that will not itch
And antibody, God knows which

Or to develop other means
To fight those vicious little fiends
To fight those vicious little fiends
Which no one who is sound of mind
Can be defending from Mankind.

Dr. Leonard J. Bruce-Chwatt

1

Malaria: Ancient Scourge of Humankind

By the time man appeared on Earth, the *Anopheles* mosquito was a well-established form of life. Paleolithic and neolithic studies indicate that prehistoric man—at least in warmer areas—experienced malarial chills and fevers. It is possible that malaria originated in Africa, considered by anthropologists to be the cradle of the human race; migrants may have carried the disease to the shores of the Mediterranean, to Mesopotamia, to the Indian peninsula and to Southeast Asia.

Unraveling Malaria's Secrets

It was not until the 1600s that any significant scientific or medical advances related to malaria were made. In the mid-1600s, Europeans discovered that Peruvian or Jesuit bark, later known as cinchona, successfully treated intermittent fevers, specifically those associated with malaria. Another 200 years passed before quinine, the active ingredient, was extracted from cinchona bark.

Malaria got its name from Italian speculation that the disease came from the *mal aria* or bad air of marshes. The term was first used in scientific literature by John Mcculloch, a British physician, in 1829. Despite historical association between swamps, mosquitoes and fever, the precise method of transmittal of malaria remained a mystery until the late 19th century. It was Alphonse Laveran, a French army surgeon stationed in Algeria in 1880 who first observed (with a microscope) malaria parasites attacking human red blood cells. Patrick Manson, a Scottish physician, expressed a belief in 1884 that mosquitoes serve as hosts of human parasites found in the blood.

In 1897, England's Ronald Ross confirmed that a mosquito is the vector, or carrier, of malaria by observing malaria parasites of humans (see Appendix A) developing in a mosquito and by demonstrating transmission of a typical malaria parasite from infected birds to healthy birds. Italy's Giovanni Battista Grassi identified the female *Anopheles* mosquito as the vector of the parasites of human malaria and verified the life cycle of the human parasites in anophelines. No single species of *Anopheles* is universal and only 85 of 400 known species have been verified as spreading malaria (Herms et al. 1961).

All female *Anopheles* mosquitoes seek warm-blooded animals and humans to obtain blood for subsistence and to mature their eggs. Once the female has fed on a person infected with the malaria parasite, the parasite begins its sexual cycle, which takes place in the mosquito's gut (Figure 1). Immature male and female cells (gametocytes) of the parasite in the human blood are sucked into the stomach of the mosquito where they mature, fuse and form cysts. The infective stage of the parasites (sporozoites) develop in the cysts, which rupture and release the sporozoites. The sporozoites eventually enter the ducts of the mosquito's salivary glands and the mosquito is capable of infecting the next human it bites. The parasite enters a three-phase asexual cycle (blood or schizogonic cycle) in humans.

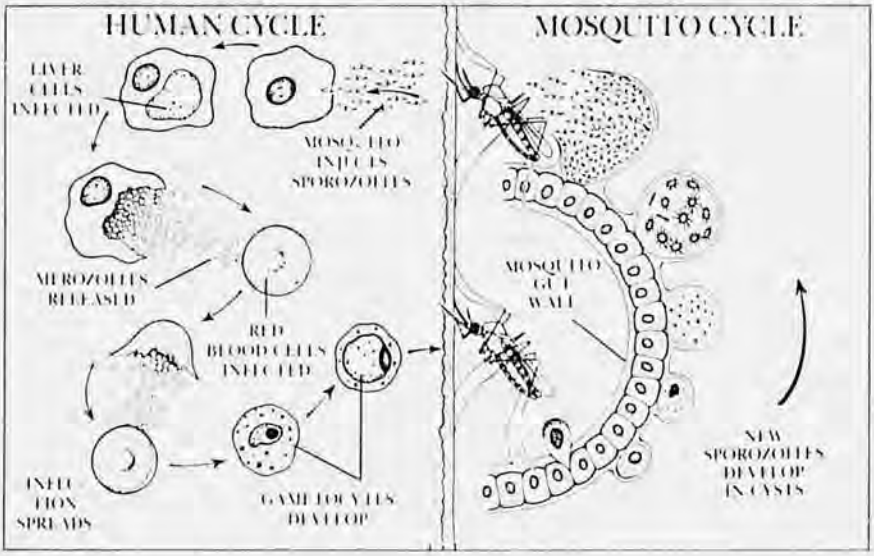


Figure 1. *The malaria parasite goes from a mosquito's stomach to its salivary glands and into the blood of a bite victim. Vaccines are aimed at three stages of its life cycle. (Drawing by Michael Reingold, courtesy of* Science Digest*)*

A human bitten by infected *Anopheles* mosquitoes will almost certainly contract malaria because as many as 1,000 sporozoites enter the victim's blood. Within an hour, the sporozoites reach the liver where asexual division (merozoite stage) begins. Six to 12 days later, merozoites are released and enter red blood cells. Here, the merozoites multiply and invade more red blood cells. For a female *Anopheles* to be infective, it must survive the time required for the parasite to complete its sexual cycle. The fact that many anophelines prefer to feed around dusk or at dawn, and usually seek an indoor surface on which to settle to digest the blood meal, is significant to control efforts.

Female anophelines will enter houses repeatedly for blood meals to mature successive batches of eggs. As long as mosquito resistance to an insecticide does not develop, spraying—under ideal circumstances—will kill mosquitoes before they become infective. An effective residual insecticide can reduce the numbers of mosquitoes enough to interrupt transmission of malaria.

Focus on Control

United States armed forces occupying Havana, Cuba, in the aftermath of the Spanish-American War (1898) were plagued by malaria and yellow fever. Surgeon General of the U.S. Army George Sternberg, who carried Laveran's discovery of parasites in human blood to the United States, sent an investigative team, led by Walter Reed, to Cuba. The army concentrated on fumigating contaminated houses, then on destroying mosquito larvae. By 1902, the two diseases were banished from Havana.

The malaria challenge to the U.S. Army resurfaced in 1904 in Panama. As many as one-third of the workers imported to build the Panama Canal were ill with yellow fever or malaria at any time. As in Havana, repeated fumigations were conducted and stagnant water receptacles were removed. By 1916, malaria had been reduced to a minor public health problem in the canal zone.

Despite the successes in Cuba and Panama, many experts continued to doubt the mosquito theory. Others forged ahead with programs to reduce malaria by eliminating the breeding places of mosquitoes.

Between Wars

During World War I, lack of action against malaria cost Allied and Central powers severe losses in the European and African campaigns. For example, the British army reported 160,000 cases of malaria in

Salonica, and another 107,000 cases in the East African campaign. Whole squadrons were assigned to clear mosquito-breeding sites.

United States involvement in international antimalaria activities dates to 1907 when the United States participated in the Third International Sanitary Conference of the Inter-American Sanitary Bureau, predecessor of the Pan American Health Organization (PAHO), founded to encourage, aid or enforce the destruction of mosquitoes and other vermin. One of the earliest large-scale organized U.S. efforts was initiated by the Rockefeller Foundation. By 1923, 26 countries had established national malaria research institutions thanks to Foundation assistance. The international tone of malaria work was further set in 1924 when the Malaria Commission of the League of Nations was established to investigate and report on the status of malaria and malaria control and to estimate world need for quinine.

Between World Wars I and II, many successes in at least partially controlling malaria were scored. The 1930s and 1940s witnessed increased emphasis on developing better engineering methods for mosquito breeding site reduction, continued development and exploitation of larvicidal methods, and an expansion of biological studies of vectors and their habits. Under the guidance of Drs. Fred L. Soper and D. Bruce Wilson, the Rockefeller Foundation eradicated *A. gambiae*, which had been introduced from Africa, from northeast Brazil by 1941. The United States provided its first foreign assistance to malaria programs in 1942 through the U.S. office of the Institute for Inter-American Affairs.

It took World War II to prompt a universal search for an answer to the malaria problem. The U.S. military hierarchy was dismayed to discover that, in certain areas, malaria caused more casualties than military action. Malaria control became an overnight necessity for U.S. troops stationed in malarious zones. Control campaigns combining antimalaria drugs and antilarval measures were successfully carried out by trained units, whose efforts outlasted the war and were responsible for introducing modern malaria control techniques in many parts of the world (Johnson 1964).

The single most important factor in triggering serious international control efforts was the discovery of the potent residual insecticide, dichlorodiphenyl trichloroethane (DDT). DDT had been synthesized by Viennese pharmacist Othmar Zeidler in 1874, but it was not until the U.S. Army obtained samples from Paul Muller, who was at the J. R. Geigy Co. in Switzerland searching for a chemical to kill the common clothes moth, that its full value was realized. By 1944, U.S. manufacturers were producing 9.5 million tons of DDT. More than 47 million tons were produced in 1947.

Era of Malaria Eradication

DDT provided the world with a new method to interrupt the transmission of infection. After the war, the Italian government expanded the antimalaria program using DDT as a residual spray on the walls of Italian homes. By 1949, there were only 81 reported malaria cases and no malaria deaths (Brown et al. 1976). In 1954, only five new cases of malaria were reported (International Cooperation Administration 1956).

DDT brought similar successes in malaria control to countries of Europe, Asia and South America. A U.S. program, which relied heavily on DDT—more than 1.36 million tons sprayed in 1948 alone—had eradicated malaria from the United States by 1951. Everywhere it was used, DDT was effective and inexpensive and had remarkably few adverse effects.

The introduction of DDT as an antimalaria tool, combined with the establishment of the World Health Organization (WHO) in 1948, had raised hopes that malaria might indeed be controlled. WHO placed priority on malaria and named an expert committee to set strategy and to investigate problems.

In 1955, 60% of the world's population still lived in malarious areas or regions that remained at risk of malaria. More than 200 million persons in 135 countries continued to suffer from the disease each year; an estimated 2 million died each year. In 1955, a global eradication effort of the World Health Assembly was endorsed by member governments, including the United States.

The objective of the global eradication effort was to break the malaria transmission cycle, eliminate sources of parasite infection and prevent the reintroduction of malaria into the human population. WHO's reasoning was that if malaria were merely controlled, the time would come when the disease would make a comeback. Insecticides, WHO emphasized, must be used to the maximum while still effective. The Eisenhower administration's U.S. International Advisory Board endorsed the eradication concept, and urged that the U.S. foreign aid program help make it possible.

The 1957 WHO Expert Committee on Malaria produced the Sixth Report that became the bible of malaria eradication (Bruce-Chwatt 1979). WHO and UNICEF, with the U.S. government providing 40% of their budgets, provided technical assistance and supplies to antimalaria programs in 29 countries. The United States, through the International Cooperation Administration (ICA), provided large-scale technical assistance to 19 national programs, and financial support to the malaria eradication efforts of WHO, PAHO and UNICEF. United

States contributions to WHO and PAHO Malaria Eradication Special Accounts from 1958 to 1970 totaled more than the contributions of all other countries combined.

Eradication of the malaria parasite does not necessarily require the eradication of the mosquito. If the number of infected *Anopheles* mosquitoes is reduced below the critical level of density that can lead to the elimination of the transmission of the malaria parasite (*P. vivax* and *P. malariae*) for two to three years, the disease could eventually disappear from the human host. (Some species of *Plasmodium*, such as *P. malariae*, remain viable for 20 years or longer in the human body.)

End of the Eradication Era

By the end of the global malaria eradication effort (1955–1969), the campaign had succeeded in protecting a billion people against the risk of malaria transmission. But despite many successes, the disease risk in 90 of the 143 originally malarious countries or areas remained moderate to high. Anopheline resistance to insecticides was increasing. By 1971, 224 species of insects were estimated to be resistant to DDT; 105 of them were of public health or veterinary significance (Howard 1971a). Dr. Lee M. Howard, former director of the Office of Health[1] in the U.S. Agency for International Development (AID), noted that "it is man himself who has often permitted pesticides to fail by expecting too much of them and by failure to adhere to the vigorous requirements of field performance."

In the mid-1960s, environmental and conservation groups, many inadequately informed, raised a public outcry against many pesticides, claiming they were safe to neither man, beast nor the environment. The 1969 Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health (U.S. Department of Health, Education and Welfare 1969), however, recognized the need and basis for continued use of pesticides, and recommended that DDT be used to prevent or control human diseases and other essential uses for which no alternative is available.

AID noted that developing countries relied on DDT to control vector-borne diseases such as malaria, as well as Chagas disease, plague and typhus. Furthermore, the United States was the only source of DDT at a price and in quality and quantity to make control of such

1. The Office of Health coordinates AID malaria projects. The role of other AID offices is outlined in Appendix B.

diseases technically and economically feasible in those countries. Howard (1971b) declared that "any act that directly or indirectly results in reducing or eliminating U.S. manufacture of DDT may be expected to have disastrous consequences for the health of populations in excess of a billion people in the less developed world."

Anti-DDT pressure increased, and, effective December 31, 1972, the U.S. Environmental Protection Agency cancelled all uses of DDT for crop production and nonhealth purposes in the United States, but permitted public health use. As U.S. aid to antimalaria programs decreased and as other pesticides were developed, DDT production in the United States gradually declined. In 1982, the United States stopped DDT production. Several other industrialized countries continue to manufacture DDT, but raw material and shipping costs may be prohibitive for developing countries.

Researchers sought alternatives. As of 1971, more than 1,400 pesticides had been tested through WHO's testing program for use in public health programs. But many were not usable as residual insecticides for antimalaria programs due to a variety of reasons, including expense and residual characteristics that may affect ecology, wildlife or human health.

One alternative to DDT is malathion. The residual effect of DDT 75% on wall surfaces is six months or more. Malathion 50%, on the other hand, is often effective for only three months. Final costs—exclusive of paying sprayers—is considerably greater than for DDT. For example, in 1977, a ton of DDT cost $950 compared to $1,350 for malathion. Because malathion has to be sprayed more often, the cost of DDT to protect a million people was $279,000; of malathion, $1.18 million (Phillips 1983). Propoxur, another alternative, also is much more expensive than DDT and, improperly used, is toxic to humans.

In 1969, "the metaphorical crossroads in the history of malaria eradication" (Farid 1980), WHO reluctantly concluded that malaria control is valid and indispensable as an interim step where eradication is impractical. The organization recommended that eradication programs that stood a good chance of success be carried speedily to conclusion and that others should revert to control work until an opportunity for eradication could be developed. In essence, a control program should limit its efforts to areas with large populations or with the greatest prevalence of malaria. WHO suggested that countries undertaking new antimalaria efforts make certain they were based on adequate public health, financial and human resources, and that local epidemiological conditions existed to maintain gains achieved.

The ultimate goal might still be eradication where eradication was technically feasible. Control programs, on the other hand, have a more

modest objective. They aim to reduce death and illness, and to contain the disease at a level where it no longer is a serious public health problem in areas of greatest economic importance in a program not limited in time. Figure 2 outlines control measures.

The Resurgence of Malaria

The resurgence of malaria resulted from a variety of reasons that differed from place to place. Country after country had decided malaria was no longer a serious problem and reduced or cut their malaria budgets. Technical difficulties related to parasite resistance to drugs and resistance of vectors to insecticides were only partly responsible. The fact that each *Anopheles* species has unique habits, life cycle and breeding sites complicated the problem.

Inadequate funding was a serious constraint. Few malaria programs represented more than 5% of annual national health budgets. Weak operational units, or the lack of them, in national malaria programs helped increase malaria transmission. The failure to institute effective surveillance in coordination with other health services, or to integrate them into such services where workable, is considered a primary cause of failure by many malaria experts who insist that, had antimalarial activities been integrated into basic health services, program operations would have continued to make gains.

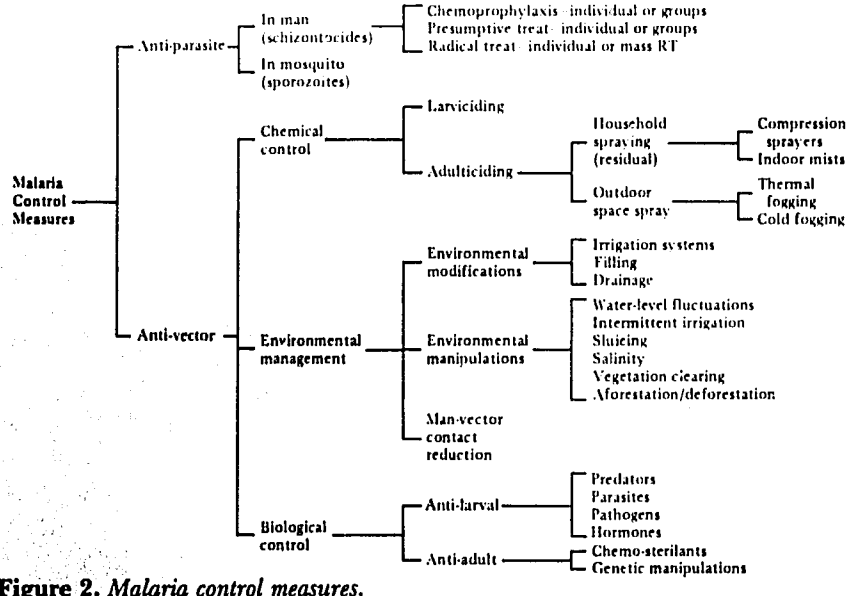


Figure 2. *Malaria control measures.*

Return to Control Programs

In the United States, public and congressional disenchantment with the foreign aid program led to the U.S. government decision to reduce U.S. staff in overseas posts. United States funding for economic and social development efforts previously under AID jurisdiction was increasingly channeled through multilateral organizations. A multilateralization policy was spelled out in an August 8, 1970, memo, "AID Policy for Malaria Eradication Multilateralization of Technical Services." The intent of the policy was to make the best use of worldwide WHO malaria personnel and resources. AID and HEW signed a new memorandum of understanding, in which AID agreed to help WHO assume increased in-country administrative, training and technical advisory services, while gradually reducing the number of U.S. technicians stationed overseas.

An underlying assumption of the new policy was that there were adequate trained personnel to carry out a decentralized malaria control program. It went substantially unchallenged for several years (Insect Control and Research 1983). Only two AID malaria personnel transferred to WHO; other experienced professionals left the program. The number of Agency technical advisors dropped to five in three countries by June 1973. Simultaneously, AID issued a policy statement instructing missions that multilateralization was to take place as soon as a specific timetable could be established. The guidance assured AID's willingness on a case-by-case basis to support country antimalaria programs, setting some carefully defined preconditions regarding country interest and resources and the existence of a feasible plan.

By the end of 1975, AID's bilateral assistance was phased out in 16 of the original 18 country programs. A generation of Agency malaria experts disappeared, many simply because their expertise was not called upon. With opportunities in malariology, specifically in the research area, limited or nonexistent, young scientists shied away. "A major mistake of the eradication era was the decision of the funding agencies to de-emphasize research; it was thought that additional knowledge of malaria was not required to successfully execute the eradication program," declared Chin (1977). Not only was it felt that no new information was needed, agreed Clay Huff, former president of The American Society of Tropical Medicine and Hygiene, "but it appeared that all we had learned in the past could now be ignored and forgotten." In 1964, he told Society members, "...the seeds of failure were sown when the nature of eradication took the form it did. It assumed that we knew enough to abandon basic research and the training of personnel along lines which had proved to be efficacious...I believe we cannot deny

that the eradication program greatly depleted the sources of support for a continuation of research and training in a highly complicated group of disciplines involved in the reduction of malaria" (Jeffery 1976).

Huff further noted that the U.S. Congress "could not be expected to provide financial support for basic malaria research when it was at the same time providing millions for malaria eradication with the virtual promise that in 5, 6, 7, or even 10 years the disease would be extinct" (Jeffery 1976).

The warnings were largely ignored. Even as health research scientists voiced concern about declining support for malaria research, both AID and WHO agreed during the early 1970s that there was no standard formula for malaria eradication. The 1968 World Health Assembly and subsequent Expert Committees on Malaria had made it clear that each country would have to design its malaria program around epidemiological conditions that might or might not permit eradication in the short term.

Except for the disappearance of malaria from Tunisia and a decline in affected areas in Algeria and Morocco, the distribution of malaria shows practically no major changes since the mid-1970s (Figure 3). Some 60% of the people in the world live in originally malarious areas, and 46% still are at risk of contracting malaria. However, the increasing incidence of malaria has led to a certain recognition of the magnitude of the unfinished task, prompting "the understanding of pressing needs for further research into methods of malaria control" (Bruce-Chwatt 1980).

Call for More Research

The fact that the *Anopheles* species may constantly evolve to meet changing environmental conditions, often one step ahead of man, is reason enough for vital and sustained research. New tools were needed but, unfortunately, during the era of eradication optimism, funds for the research that could develop those tools fell drastically as planners became overly optimistic about known methods.

AID's record exemplifies the funding problem. Between 1950 and 1972, only 0.1% of the $1.2 billion AID and its predecessors spent on controlling malaria problems went to research. In 1968, Paul Russell, a prominent malariologist with the Rockefeller Foundation who received the U.S. Legion of Merit for his malaria work in the U.S. Army Medical Corps in the early 1940s and later a consultant to an AID predecessor, noted that there did not appear to have been a logical or practical ratio between the funds spent trying to eradicate malaria and

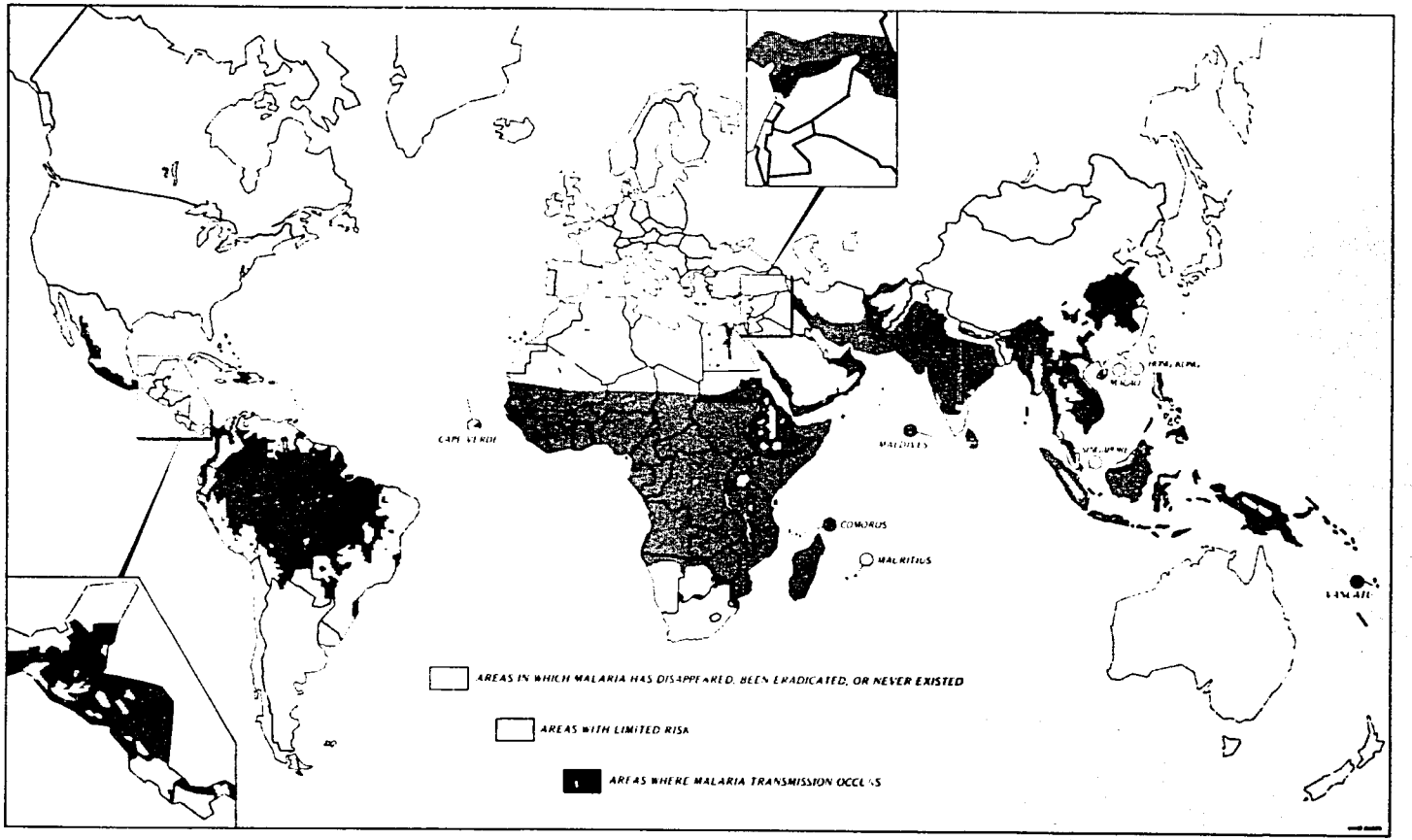


Figure 3. *Epidemiological assessment of the status of malaria, 1982. (Courtesy of World Health Organization)*

those spent on discovering how to do so effectively and economically. Research efforts focused on insecticides and related hardware and on the technical problems impeding eradication progress.

Despite the early imbalance of funds dedicated to malaria research, experts insist that "it is entirely possible that investment in research and development can play as great a role in malaria control as they can and do play in industrial development.... AID's major contribution to worldwide malaria control programs may well be the long-lasting effects of funds invested in research" (Insect Control and Research 1983).

In 1975, WHO Director General Dr. Halfdan T. Mahler said, "There are no miracle technical solutions to the problem (of malaria) and there is no prospect of such solutions being developed and becoming available for wide application for a number of years to come."

Ten years ago the bleak outlook may have indeed been justified. But increasing developing country consciousness, biotechnology developments and research advances, including the development of a vaccine, promise an encouraging future.

2

Early Modern Battles

Impressive initial successes in anopheline mosquito control were achieved by draining ditches, introducing larvivorous fish or applying Paris green and larvicidal oil to ponds, and weekly spraying of houses with pyrethrum. But while malaria was reduced in many countries, control seemed to be the best health experts could hope for. Eradication—the complete interruption of transmission of the malaria parasite—was another matter.

That is, until the advent of DDT. Residual spraying with DDT initially worked as well as it did because it attacked the place where most of the transmission of malaria infection takes place—in the houses where people live. The chemical's long-lasting residual effects interrupted the vector-parasite association—the weak link researchers focus on in their search for new drugs and immunological methods to control and eradicate malaria. And, most important, at least from the perspective of developing countries, DDT was an affordable solution.

Human malaria is caused by any of four species of blood parasite of the genus *Plasmodium* (*P. falciparum, P. malariae, P. ovale, P. vivax*) (see Appendix A), which develops alternately in female anopheline mosquitoes and humans. The species that affect humans are closely related to the species found naturally in monkeys and apes. Although Simian malaria can be transmitted to people, it is rarely known to happen.

Falciparum malaria, the most lethal of the human malarias, can be fatal if not treated promptly. It also is the easiest to cure if attended to in its early stages and in absence of drug resistance. In a nonimmune population, the death rate during an epidemic may exceed 10%; mortality reaches 50% in limited areas. In Africa, more than 25% of children between six months and seven years of age who contract falciparum malaria die (American Public Health Association 1977).

The acute symptoms of clinical human malaria are chills, fever, sweating, nausea, vomiting, anemia, an enlarged spleen, abdominal pain, headache and lethargy. Recovery takes weeks, leaving the victim physically and mentally exhausted. Falciparum malaria may also cause kidney failure and the accumulation of fluid in the brain and lungs.

Turning to Malaria Research

The 1955 WHO-stimulated malaria eradication program, which received strong support from AID predecessors, was credited by Paul Russell for eradicating malaria from most of Europe, much of the Middle East, important areas in the Caribbean and in South America. Russell also noted that two of the most malarious islands in the world, Taiwan and Mauritius, have been completely freed from malaria (Bruce-Chwatt 1980).

Third world countries receiving U.S. economic assistance reported encouraging figures and program results. India is a good example. The 75 million cases the country annually reported before World War II dropped to 100,000 by 1965. Not only did residual spraying with DDT eliminate malaria in the Chiang Rai Valley of northern Thailand, but the vector was not found in the area for nine years. Early successful campaigns in Italy, Cyprus, Greece, Guyana, Puerto Rico and Venezuela showed that the cessation of the transmission of malaria does not require the total disappearance of local vectors (Bruce-Chwatt 1979), and that *Anopheles* without malaria is possible, as proven in Sardinia in the late 1940s (Jeffery 1976).

Some experts tempered their enthusiasm with reality. AID malaria adviser Edgar A. Smith in a 1957 memo suggested that ICA, an AID predecessor, set up demonstration projects of available supplementary or alternative methods of malaria control so that the international community would be prepared "for the time when the single method of DDT residual spraying fails to do the job." But optimism over DDT overrode doubts.

For a decade, the optimists seemed to have the upper hand. Malaria incidence fell drastically—to the point where overconfidence set in. That, combined with U.S. congressional cuts in funding, contributed to the fact that of the $1 billion AID and its predecessors spent over a 30-year period to support operational malaria control and eradication programs, only $2 million went toward research. Limited as it was, the research made great contributions to control and eradication efforts, as well as to breakthroughs in the search for a human vaccine.

The first malaria research project supported by the U.S. bilateral

foreign aid program was with the Centers for Disease Control (CDC) to develop standards and specifications for spray equipment, insecticides and insecticide packaging. AID and WHO adopted the resulting standards, which are still in effect throughout the world. In the meantime, U.S. assistance reached its peak (1958–1962).

By the mid-1960s, doubt about the ultimate success of the DDT house-spraying campaign and drug treatment approach to eradicate malaria was on the rise. Resistance of some *Anopheles* to DDT was growing. Other insecticides, such as lindane, dieldrin, propoxur, malathion, fenthion and fenitrothion, were initially effective. Later, certain mosquito species developed resistance to a number of them (Table 1). By 1976, 42 species of *Anopheles* were resistant to one or more insecticides. Use of many of the insecticides for agricultural purposes increased the pace of the development of resistance.

While insecticides—including DDT—continued to be extremely effective in controlling malaria, AID decided to expand its CDC agreement to provide for the development and testing of alternative methods. A second CDC agreement was made by the Agency in 1966 to develop serologic methods to diagnose malaria, methods that are used in many parts of the world today.

Two more agreements followed, under which CDC conducted large-scale research in El Salvador and Thailand to determine why the residual spray program failed to interrupt transmission of malaria and to develop methods that would. While neither project achieved its main objective, both contributed information that would be valuable in later research.

In 1972, CDC assumed funding of the four agreements but developed funding problems. The Technical Development Laboratory was transferred from Savannah to Atlanta, Georgia; the 75-member staff dropped to 12. In El Salvador, the Central American Malaria Research Station was converted to a broader-scale public health research station.

Drug Resistance Increases

Drug resistance development has four important elements: the degree of drug pressure, the duration of drug pressure, the degree of host-parasite contact and the drug type. If drug pressure is maintained long enough, it may lead to the selection of resistant parasites. It is to be noted, however, that whenever chloroquine resistance has developed (Figure 4), it has been in areas where the drug was massively used for prophylaxis, "often in a haphazard way and as a palliative measure in the absence of vector control" (Wernsdorfer 1982).

Measures initially successful in reducing transmission and the malaria

New DDT Containers Cut Costs by Half

Research on the effect of pressure on the suspensibility of DDT powders showed the suspensibility is inversely proportional to the log of the pressure to which the powder is subjected. This ruled out DDT shipment in bags because stacking them produced pressure on the powder.

During the 1950s, DDT was shipped in metal or cardboard drums. The round drums were expensive, difficult to handle (the AID drum held 100 lbs. and the WHO drum 200 lbs.), took up valuable space and stacked poorly. Furthermore, they required two people to carry them. Breakage and spillage were additional problems.

CDC's Technical Development Laboratories, under contract to AID, designed a new rectangular container of cardboard lined with plastic. The container did not need banding; could be carried by one person; could be easily stacked, thus taking less cubic space in a ship's hold; and could withstand storage in humid climates.

Savings are tremendous. For example, during 1980–1982, 17,700 million tons of DDT powder shipped to the Far East in cardboard boxes saved $2.56 million. It is estimated that using the box for water-dispersible powders has resulted in savings of more than $20 million. Current savings made by shipment in boxes instead of fiber drums amount to $145.16 per metric ton.

DDT was once shipped in round drums (left), *which took up a great deal of room, stacked poorly, broke easily, and were very expensive. New, rectangular shipping containers* (above) *have remedied those problems. (AID photos)*

Table 1.
AID Contributions to Antimalaria Projects in Developing Countries, 1950–1981

	Contributions (Thousands of $)			
Region/Country (Number of Projects)	*Loans*	*Grants*	*U.S.-Owned Foreign Currency*	*U.S. Value*
Asia				
Cambodia (1)		$ 772		$ 772
India (3)	$ 38,000	83,269	$179,172	300,441
Indonesia (3)	28,300	37,643		65,943
Korea (1)		68		68
Laos (1)		1,052	99	1,151
Nepal (2)		6,770	11,847	18,617
Pakistan (5)	38,200	8,168	44,977	91,345
Philippines (1)		8,974		8,974
Sri Lanka (2)	16,000	1,004	599	17,603
Taiwan (1)		167	283	450
Thailand (2)	4,000	18,985		22,985
Vietnam (2)		8,596		8,596
Total (24)	$124,500	$175,468	$236,977	$536,945
Africa				
Ethiopia (4)	$ 22,500	$ 5,607		$ 28,107
Liberia (1)		509		509
Libya (1)		222		222
Zaire (1)		1,352		1,352
Total (7)	$ 22,500	$ 7,690		$ 30,190
Latin America/Caribbean				
Bolivia (1)		$ 931		$ 931
Brazil (3)	16,584	14,115	$ 1,696	32,395
Colombia (1)		1,762		1,762
Costa Rica (2)	1,600			1,600
Ecuador (3)	2,000	2,892	24	4,916
El Salvador (2)	2,665	10		2,675
Guatemala (1)	1,550	3,541	100	5,191
Haiti (3)		32,096		32,096
Honduras (2)	2,673	2,474		5,147
Jamaica (1)		71		71
Mexico (1)		27		27
Nicaragua (2)	3,934	2,125		6,059
Panama (1)	1,421			1,421
Paraguay (2)	1,900	272		2,172
Peru (1)		169		169
Total (26)	$ 34,327	$ 59,554	$ 2,751	$ 96,632
Near East				
Afghanistan (1)		$ 44		$ 44
Iran (2)		4,446		4,446

Table 1 *(cont.)*

	Contributions (Thousands of $)			
Region/Country (Number of Projects)	*Loans*	*Grants*	*U.S.-Owned Foreign Currency*	*U.S. Value*
Near East *(cont.)*				
Iraq (1)		31		31
Jordan (1)		1,923		1,923
Tunisia (1)		534		534
Turkey (1)		200		200
Total (7)		$ 7,178		$ 7,178
Total (64)	$181,327	$249,890	$239,728	$670,945
Technical assistance and training (12)		$ 6,408		$ 6,408
Total (76)	$181,327	$256,298	$239,728	$677,353

Source: Malaria Control in Developing Countries, U.S. General Accounting Office, April 26, 1982.

reservoir to a low level eventually cause the population's immunity to malaria to drop. Combined with high drug pressure and lack of vector control, drug resistance occurs and spreads. The failure of drugs is even more significant than the failure of insecticides because drugs frequently are cheaper and easier to use.

P. falciparum and *P. vivax* showed signs of resistance to such drugs as proguanil and pyrimethamine shortly after they were introduced into wide, especially prophylactic, use. Quinine, most commonly used by short-term travelers, remains an effective drug. But its scarcity and its high cost, as well as the problem of administering it on a broad scale, prohibit its use in most developing countries.

Of utmost significance, especially from an operational standpoint, was the detection of *P. falciparum* resistance to chloroquine, a widely effective, easy-to-use and relatively inexpensive drug to help reduce the malaria burden in many developing countries (Wyler 1983). Malaria workers and researchers are urgently trying to arrest the spread of chloroquine-resistant malaria and find countermeasures.

Depending on the situation, three lines of attack are suggested by Wernsdorfer (1982):

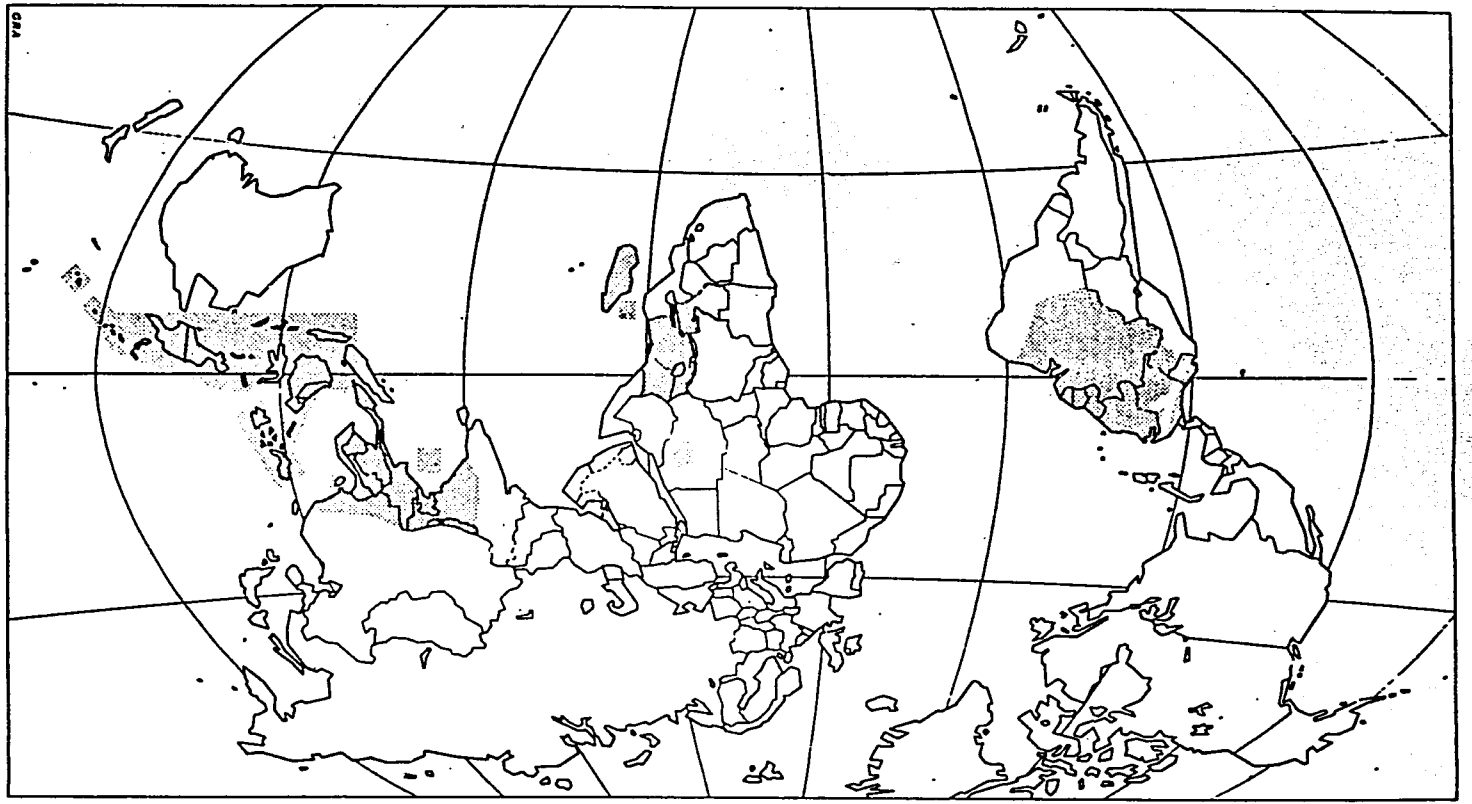


Figure 4. *Areas and countries with chloroquine-resistant* Plasmodium falciparum, *January 1983. (Courtesy of World Health Organization)*

In areas that continue to have chloroquine-resistant malaria cases, aim antimalaria activities toward early detection.

In areas where chloroquine resistance is confirmed, aim antimalaria activities toward intensive vector control efforts.

In areas where chloroquine resistance is widespread, aim antimalaria activities at minimizing the effects, establishing a national policy on the use of antimalaria drugs, using alternative treatment drugs and intensifying antivector measures.

Effective alternatives are combinations of sulfonamides and pyrimethamine, particularly for radical cures and for prophylaxis. However, *P. falciparum* already has indicated resistance to these drugs. Fortunately, chloroquine resistance in Africa, where falciparum malaria is rampant, is limited.

Drugs—proguanil, chlorproguanil, cycloguanil, trimethoprim, pyrimethamine—that have been effective in curing falciparum malaria, do little more than suppress vivax malaria. Moreover, resistance to these drugs also develops quickly. Some antibiotics, such as tetracycline and minocycline, alone or in combination with other drugs, are used to suppress acute attacks as well as to ward off malaria.

Search for Alternatives

Obviously, new antimalaria drugs are needed. The Vietnam conflict stimulated a large volume of research. Initial research aimed at finding a replacement for chloroquine. Later, researchers branched into basic immunology and drug studies. The WHO Special Programme for Research and Training in Tropical Diseases announced it had identified malaria as one of six major tropical diseases that desperately needed radically new tools. The announcement boosted research initiatives. WHO called for low-cost, safe and effective drugs to attack parasites at various stages of the cycle within the human host.

Toward this end, various chemical classes and compounds are being studied. Mefloquine is a relatively new antimalarial drug that shows promise against falciparum malaria. But malaria experts are being realistically cautious, recognizing the speed at which drug-resistant strains of falciparum malaria appear and spread. New candidate compounds, such as triazines, have been identified for preclinical treatment. The Chinese are studying diamino quinazolines and qinghaosu, the active ingredient of a Chinese herbal medicine used for the empirical treatment of malaria rediscovered in 1971 (Wyler 1983). The Walter Reed Army Institute of Research is searching for a tissue schizonticide.

The obvious question is, why are pharmaceutical companies not involved in finding alternatives? The answer is primarily economic. Drug firms must first meet stringent FDA requirements, then answer to their stockholders. Investors are not inclined toward committing the substantial financial investment needed to develop and market a product that does not promise an equally substantial profit. Antimalaria agents fall into this category. Because demand would be from poor people living in developing countries—people who cannot afford to pay for drugs or any other kind of treatment—the returns would not be great. The costs of developing new drugs and of proving their safety and efficacy are increasing rapidly. It is particularly difficult for a U.S. company to justify the high expense when U.S. sales for a new drug will be minimal.

"It appears quite certain that new drugs can be developed which are better than current ones," says Pick (1982). But he also warns, "It is important to remember that one new drug probably will not solve the problem. An armamentarium of drugs must be developed which, combined with other control measures, can support the world goal of reducing morbidity and mortality due to malaria."

AID's search for a cost-effective means of protecting people from malaria was aided by a 1978 world conference sponsored by WHO and UNICEF and held in Alma Ata, Soviet Union. The conference produced the Alma Ata Declaration, which endorsed a multiple services approach to improve health, with primary health care (PHC) as the context within which endemic disease could be prevented and controlled. The declaration further pointed out that when endemic disease is a problem, the public health care system should include endemic disease control.

The PHC approach endorsed at Alma Ata promotes eight basic services: education concerning prevailing health problems and methods to prevent and control them; promotion of food supply and proper nutrition; an adequate supply of safe water and basic sanitation; maternal and child health care; immunization against major infectious diseases; prevention and control of locally endemic diseases; appropriate treatment of common diseases and injuries; and provision of essential drugs.

While malaria programs and PHC functions have similar support requirements, some problems and differences need to be overcome before PHC systems can become effective vehicles for malaria control. Some experts argue that expanding the responsibilities of PHC systems to include malaria control can strengthen the appeal of PHC programs by making workers more effectively responsive to a serious health need of the public. Conversely, many PHC field workers already feel overworked and undersupported. But both agree that malaria requires immediate and serious action—action that should be taken within the context of PHC.

3

A Regional Review of AID Malaria Efforts

United States bilateral assistance to 76 malaria control and eradication projects from 1950 to 1981 totaled $677.3 million, with 79.3% to the Asia region, 14.3% to Latin America and the Caribbean, 4.4% to Africa and about 2% to other projects (see Table 2). Assistance to multilateral projects totaled $131 million. This chapter covers only a few countries that have received malaria assistance from the United States.

Latin America and the Caribbean

Until the mid-1940s, malaria treatment in the Latin America and the Caribbean region mainly consisted of quinine and atebrine; the vector was attacked using larvicides and source reduction, such as draining mosquito-breeding sites.

DDT was widely used in the region during the late 1940s and early 1950s. Countries there were among the first to accept the World Health Assembly's 1955 global challenge to eradicate malaria, having already approved a resolution calling for malaria eradication in the Americas. At the time, more than one-third of the population was at risk to malaria transmission.

Results were spectacular. Chile, Cuba, Dominica, Grenada, Guadelupe, Jamaica, Martinique, Puerto Rico, Saint Lucia and Trinidad and Tobago all succeeded in eradicating malaria by 1964. More than 56% of the population in malarious areas were freed of the disease.

But the successes led to complacency, and local government commitment to the task of malaria control peaked in 1969. AID ended its annual contribution to PAHO's Special Malaria Fund in 1970, an action

Table 2.
Insecticide Resistance in Principal Anopheline Vectors

Species	*DDT*	*Dieldrin/HCH*	*Organophosphates*	*Other insecticides*
A. albimanus	Colombia, Costa Rica, Cuba, Dominican Republic, El Salvador, Guatemala, Haiti, Honduras, Mexico, Nicaragua, Panama	Belize, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Haiti, Honduras, Jamaica, Mexico, Nicaragua	El Salvador (a,b,g,h,i,j,k) Guatemala (b,c,i,k), Honduras (a), Mexico (a,b), Nicaragua (a,b,i)	Costa Rica (l), El Salvador (l,m), Guatemala (l,m), Honduras (l), Nicaragua (l), Mexico (l)
A. aquasalis	—	Brazil, Trinidad, Venezuela	—	—
A. arabiensis	Senegal, Sudan, Swaziland	Chad, Ethiopia, Kenya, Nigeria, Malagasy Republic, Mauritania, Mozambique, Senegal, Sudan, Swaziland, Upper Volta, Zimbabwe	Sudan (a)	Sudan (m)
A. balabacensis	Sabah (Malaysia), Burma, Peninsular Malaysia	—	—	—
A. culicifacies	Afghanistan, Burma, India, Iran, Nepal, Pakistan, Sri Lanka, Thailand	Afghanistan, India, Nepal, Oman, Pakistan	India (a,b)	—
A. fluviatilis	India	Saudi Arabia, India	—	—
A. funestus	Mali	Benin, Central African Republic, Ghana, Kenya, Mali, Nigeria, United Republic of Cameroon, Upper Volta	—	—
A. gambiae	Benin, Central African Republic, Liberia, Niger, Nigeria, South Africa, Togo, United Republic of Cameroon, Upper Volta, Tanzania, Zaire, Zanzibar	Benin, Central African Republic, Congo, Equatorial Guinea, Gambia, Ghana, Guinea, Ivory Coast, Kenya, Liberia, Mauritania, Nigeria, Senegal, Malagasy Republic, Mali, Togo, United Republic of Cameroon, Upper Volta, Zanzibar, Tanzania	—	Nigeria (m—laboratory)

A. maculipennis	Greece, Iran, Turkey, USSR	Greece, Turkey	Turkey (b,g)	Turkey (l)
A. minimus	Thailand	Indonesia, Thailand	—	—
A. pseudopunctipennis	Mexico, Peru	Ecuador, Guatemala, Mexico, Nicaragua, Peru	—	—
A. sacharovi	Greece, Iran, Iraq, Lebanon, Syrian Arab Republic, Turkey, USSR, Bulgaria	Greece, Iraq, Lebanon, Syrian Arab Republic, Turkey, Bulgaria	Greece (b), Lebanon (b), Syrian Arab Republic (b), Turkey (b,f,g,h,i,j,k), Bulgaria (b,l,i)	Greece (l), Turkey (l,m) Bulgaria (m)
A. sinensis	China, Japan, Vietnam	Republic of Korea	China (a), Hong Kong (a,b), Japan (a,f), Republic of Korea (b,f)	—
A. stephensi	Afghanistan, Saudi Arabia, Arabia, India, Iran	Afghanistan, India, Iran, Iraq, Oman, Pakistan, Saudi Arabia	India (a,b,g), Iran (a,b,g,i,j), Iraq (a,b)	Pakistan (m)
A. sundaicus	Indonesia, Malaysia, Thailand	Indonesia, Malaysia	—	—

Source: World Health Organization.

Key: (a) malathion; (b) fenitrothion; (f) propoxur; (g) jodfenphos; (h) chlorpyrifos; (m) pyrethroids; (i) chlorphoxim; (j) phoxim; (k) parathion; (l) propoxur.

that required PAHO to severely restrict funding for malaria programs. Subsequently, AID's Latin America and the Caribbean Bureau lowered its priority for malaria, which led to the termination of many antimalaria programs in the region.

In 1984, the number of people at risk was up to 170 million; deaths had risen to 137.7 per 100,000. A third of the population at risk was exposed to falciparum malaria, the most lethal form. Malaria presents the greatest threat to Brazil, Colombia, El Salvador, Guatemala, Honduras and Haiti. Belize, El Salvador, French Guiana, Guatemala, Haiti, Honduras and Surinam have detected malaria morbidity levels between 13 and 16 cases per 1,000. Most of the falciparum infections are in Brazil and Colombia, where parasite resistance to chloroquine has been widely confirmed. In most of Central America, the vector shows resistance to every residual insecticide to which it has been exposed.

Although there is considerable anopheline and parasite resistance to insecticides and drugs, DDT remains effective in some countries after 25 years of continuous use while chloroquine generally is the chemotherapeutic drug of choice. But before additional progress in controlling malaria can be made, other factors need to be overcome. In some areas, the vector has been incorrectly identified, if at all. Another constraint is "manmade" malaria. Development projects alter the environment in such a way that the anopheline population explodes. For example, roadways and highways impound water, providing a perfect breeding site for the vector.

A recent review of antimalaria programs in the Latin American region found them "in a state of disarray" (Management Sciences for Health 1984). A "near-disastrous" increase in malaria incidence between 1979 and 1983 prompted Latin American governments to revise their malaria strategies as recommended by experts from AID, WHO and PAHO. The nations of the region realize they must develop stratified programs, ones that are tailored to epidemiological zones, that are affordable and that reduce malaria to a level where it no longer constitutes a public health problem.

The 1980 donor contributions for health-related programs in the Latin American and Caribbean region amounted to $727.8 million, with $26.7 million coming from the United States. Eighty-one percent of the total goes toward water and sanitation, leaving a minuscule amount for other health activities such as antimalaria activities. Some development experts suggested that the United States should increasingly concentrate on establishing cooperative agreements among donor countries. To this end, PAHO developed a guidance manual ("Guidelines on Mobilization of External Financial Resources for the Health

Sector in the Region of the Americas," 1984) to support government efforts in developing proposals.

In 1980, AID's Bureau for Latin America and the Caribbean reissued a regional malaria position, emphasizing that support to malaria programs should be considered in the context of rural health-care delivery goals, competitive (in terms of benefits to be attained) with other options for assistance. Three years later, the Bureau suggested that a regional initiative, in coordination with PAHO and other relevant institutions, could help bring malaria in the region under control.

A team of former AID malaria experts recommended three actions to establish country programs:

> In collaboration with PAHO, AID should evaluate national anti-malaria programs to identify training, research, operational and other needs of each country.
>
> Technical assistance should be provided to enable each country to develop programs that use a combination of control techniques appropriate to the country's situation.
>
> In countries where the malaria problem is so great that it cannot be tackled within budget allowances, aid should be provided to stratify the malaria situation so the country can direct resources where they will provide the most benefit to the greatest number of people.

Other recommendations addressed the research and training aspects of malaria control, including the establishment of a regional vector-borne disease research and training center with emphasis on malaria and other mosquito-borne diseases. The team noted that the location of such a center is "critical to its success," and specified factors to be considered in selecting a site. The only current AID-supported program specifically aimed at malaria control in Latin America is in Haiti, although malaria control is a component in several AID-assisted primary health care projects. Proposals are being considered for AID assistance to Ecuador and Belize in the field of malaria and vector-borne diseases.

Haiti and the Dominican Republic

Haiti and the Dominican Republic share the island of Hispaniola, the only Caribbean island where malaria remains a serious public health problem. Malaria cases in the Dominican Republic were reported to be about 3,600 in 1981. Numbers increased to about 5,000 in 1983, due in part to cases imported by migratory laborers and settlers from Haiti. Joint conferences and workshops have served as the impetus for the

Dominican Republic and Haiti planning joint antimalaria programs.

In Haiti, about 4.5 million people (75% of the population) live in potentially malarious areas. Malaria has long been a serious problem in Haiti. A 1928 survey revealed that 23.5% of workers and 50.5% of children under age 14 had malaria. A Rockefeller Foundation study of the period 1940–1942 showed that 31% of the school-age population had malaria.

In 1961, after several years of limited malaria control activities, the Haitian government asked AID to help plan a national campaign. Countrywide spraying with DDT started the next year. A massive drug program was initiated in 1964; by 1966, it covered 1.7 million people. Six years later, despite such problems as the destruction of sprayed houses by tropical storms, the number of malaria cases had dropped considerably. The drug program was discontinued in 1970 because, although malaria incidence was down, transmission failed to be interrupted.

Pleased with its success, the Haitian government made the same mistake other governments had—it cut back financial support of field activities and epidemiological surveillance at the same time that mosquito resistance to DDT was on the rise. Malaria cases rose to the current level of 50,000 annual reported cases, although actual cases are estimated to number more than 200,000.

In 1977, AID provided a $6 million grant to the Haitian malaria program for a five-year program, bringing the total U.S. financial commitment to antimalaria activities in Haiti to $32 million.

A 1982 U.S. General Accounting Office report criticized the Haiti program as hampered by an inadequate understanding of the effectiveness of various antimalaria measures. Officials were aware of vector resistance to DDT but lacked data about locations where the insecticide could be effectively applied. Furthermore, the GAO reported, antimalaria drugs were not being mass distributed to reduce prevalence of the disease. But AID insisted that some generally sound results, especially in institutionalizing effective field operations, had been achieved. In 1982, the Agency approved an additional $8 million as a followup project for 1982–1986, providing the program technical assistance, commodity support, operational research and training, and 35% of field operation costs. Fenitrothion, used in spray operations, has been provided by a Japanese government grant. *P. falciparum,* the dominant malaria parasite in Haiti, is treated with chloroquine distributed by volunteer collaborators and health institutions.

The current program is providing basic operational research in biological control, and is making progress in epidemiological stratification and in developing a responsive institution. AID has provided tech-

nical advisers, commodities, training opportunities, limited support to local costs and guidance in developing the nation's primary health delivery system. An example of U.S. technical input is a series of comparative trials of malathion and fenitrothion to determine relative effectiveness. If AID had not insisted on the trials, a serious mistake could have been made in insecticide procurement. The epidemiological system now in use was developed by an AID adviser and his Haitian counterparts. Plans are to computerize the information so malaria workers can respond rapidly to local malaria problems.

Haiti's national malaria control agency, with support from the health ministry, has taken the lead in reorienting primary health care medical and paramedical staff toward the seriousness and importance of malaria prevention, accurate diagnosis and appropriate treatment. This is being accomplished through workshops and seminars for physicians, nurses and laboratory technicians, radio messages to the general public, and increased contact with private practitioners and medical laboratories.

Ecuador

Between 1956 and 1965, AID provided support to the Ecuadoran malaria program through $3.2 million in grants that terminated in fiscal 1966. The government of Ecuador contributed $10.6 million during the same period. In 1968, another $2.7 million was provided in loan funds. Despite delays that diminished the potential effectiveness of the program, malaria was reduced to manageable limits.

Unfortunately, malaria cases started to increase in 1979. During 1983 and 1984, malaria incidence rose more than 154% over the previous two years. More important, the virulent *P. falciparum* species increased 284% between January–July 1982 and January–July 1983.

Despite the present discouraging picture, AID involvement in Ecuadoran malaria efforts has a positive carryover that may help future progress. Of special note is the training of malaria specialists capable of carrying out an effective antimalaria campaign—provided they receive financial support. The training program included alternative control methodology, one of the few programs in Latin America that did so. With U.S. encouragement, an excellent Health Education Section, later to become the Ministry of Health's Health Education Department, also was formed and trained. The malaria program was strengthened by the recruitment and training of a network of 6,000 volunteers who collected blood and provided treatment.

Asia

Although there has been a substantial overall improvement in the malaria situation in Asia, the disease continues to hamper development. Malaria is present in Bangladesh, Indonesia, Burma, India, Thailand, Sri Lanka, Nepal, the Java-Bali (Indonesia) areas, Pakistan and the Philippines. India's malaria cases dropped from 6.5 million in 1976 to 2.7 million in 1979. Pakistan's reported cases went from 1 million in 1975 to 12,285 in 1979. Indonesia's reported cases plunged 52%; Thailand's, 8%; the Philippines', 17% (Karam 1980).

Most of AID's malaria control activities are in Asia, specifically Pakistan, Nepal, Thailand, Sri Lanka and Indonesia. The AID-assisted India program recently ended; some residual spraying activities continue. AID malaria assistance to India over the years totals $330 million.

The policy of AID's Asia Bureau is that malaria control is part of national health planning and that PHC has a key role in program implementation. The Bureau recommends that integrated malaria control is the most effective way to reduce malaria and to maintain a low incidence in countries whose health resources are adequate to support commodity costs, technical and administrative needs, and requirements for trained personnel.

Bangladesh

For centuries, malaria has been a major disease problem in Bangladesh. During the 1950s, when the United States initially provided antimalaria assistance, the number of reported annual cases was 1.5 million and deaths 50,000. By 1970, the reported caseload for the entire country was 6,660.

The national eradication effort was converted into a control activity in 1976. Two years later, U.S. assistance was phased out and the program was integrated into the Thana Health Complex Scheme. Unfortunately, an adequate surveillance system was not devised; as a result, malaria remains a major health problem in the Chittagong Hill Tracts and in Sylhet and Mymensingh Districts along the Indian border. Experts considered epidemological activities inadequate to monitor the actual level of the disease. In 1982, Bangladesh reported 35,204 cases of malaria among its population of 87 million.

AID's success in helping greatly reduce the number of cases of malaria as well as deaths is an administrative and logistic achievement. Thanks to U.S. commodity assistance, one of the best vehicle maintenance and

repair systems in Asia is in Bangladesh. An AID adviser assigned to the Agency's malaria program in the 1960s arranged for the training of dozens of mechanics and set up control and repair systems that continue to serve the country's current malaria and health services. The Bangladesh malaria program also had excellent census and mapping services.

India

India has had a widespread resurgence of malaria. Except for some mountainous areas and for some of the coastal plains, the entire subcontinent is at risk to malaria transmission in varying degrees. Prior to the organization of a comprehensive national malaria control program in 1953, malaria was estimated to infect 75 million people and to cause 800,000 deaths annually. The Indian malaria program is the largest single organized public health effort ever carried out in any country against a single disease. For some years, the program employed up to 150,000 people, and had an annual budget of as much as $22.5 million.

United States malaria assistance for India started in the early 1950s, when an AID predecessor supplied commodities, training and technical advisory services to the National Malaria Evaluation Program. Malaria cases as a percentage of the total number of cases due to all diseases reported to Indian hospitals and dispensaries declined from 10.8% in 1953–1954 to 0.7% in 1961–1962—a drop of 94%. Blood smears collected from fever patients throughout the country showed only 1 out of 400 to contain malaria parasites. By 1965, only 148,156 cases of malaria were reported even though the population had increased substantially since 1953.

AID phased out all assistance to India in 1973. Three years later, the country was reeling under the impact of a major epidemic that was the result of administrative neglect, budget cuts and government concentration on an integrated health effort that did not sufficiently incorporate antimalaria efforts. Reported cases in 1976 totaled more than 6.5 million; the actual number was estimated to be as high as 25 million. One of the first two projects reestablished when the United States resumed aid to India in 1975 was malaria control.

In 1976, the U.S. General Accounting Office reported that serious malaria resurgence "could negate the $300 million investment by AID in India's National Malaria Eradication Program as well as millions in other development programs of which agriculture was one of the biggest." Furthermore, "recurring malaria in India threatens AID's fu-

ture investments in antimalaria programs in Nepal and Pakistan" (U.S. General Accounting Office 1976).

The Indian government responded with a tremendous increase in its health budget and a revitalized national malaria effort that included a request for AID assistance. By 1980, India was spending 70% of its national health budget on the revitalized malaria program. Reported cases dropped to 2.5 million in 1983. Progress toward the goal of two cases or fewer per 1,000 people continues.

While AID provided the necessary immediate assistance to bring the disease under control, the government concentrated on improving Indian insecticide production and commodity supply. For example, India reportedly uses one-third of world chloroquine production but can produce only one-eighth of its needs.

Today, as for many years, India is a world leader in the field of malariology, with much credit going to the excellent professional relationships and rapport established by U.S. and Indian scientists. For example, the interchanges between U.S. advisers and Dr. A. D. Ray, one of India's and the world's leading malariologists, promoted the development of field surveillance procedures and field application standards followed throughout the world today. This professional relationship continues as negotiations move forward on joint operational and scientific research in the fields of parasitology, biological control and immunization.

Indonesia

The Indonesian government regards malaria as a major health problem and a deterrent to agricultural development. The government initiated efforts to battle the disease as early as 1919; in 1924, it established the Central Malaria Bureau.

The national program started expanding in 1951, by which time annual malaria cases numbered 20 million, with a malaria control demonstration project jointly sponsored and staffed by the Indonesian government with assistance from the United States and WHO. A National Malaria Eradication Service was set up in 1959, and, with U.S. assistance, made striking progress—freeing portions of Java and Bali from malaria—until 1965, when, due to political and economic turmoil leading to the termination of U.S. aid, it was disbanded. The usual scenario took place—malaria increased fourfold between 1965 and 1968, and fifteenfold between 1968 and 1973.

In 1974, a new malaria control effort was begun, with AID providing commodity assistance to supplement Indonesia's input. A year before

the scheduled five-year effort was up, malaria incidence was reduced to 127,590 cases on Java and Bali. Since 1980, U.S. aid for malaria control has been limited to a small project in Timor.

Nepal

For centuries, Nepal's fertile valleys of Rapti, Sinduli, Udaipui and Dang, and much of the western plains areas were economically unproductive because malaria incidence was so high as to make the areas virtually uninhabitable. After a vigorous AID-assisted national antimalaria program started in 1958, no fewer than 1.8 million people from the crowded hillsides resettled into the formerly neglected areas, creating a food export area. What was once *Kala Pani* (Blackwater Valley), a reference to the presence of severe malaria, is now Nepal's breadbasket. The importance of antimalaria activities is apparent when one realizes that as much as 90% of Nepal's labor force is employed in agriculture.

United States malaria assistance began with a series of pilot projects, which became the basis for the 1958 national program. United States-funded insecticides, drugs, sprayers and vehicles, technical assistance teams and an intensive training program led to a reduction in malaria cases—from 2 million in the 1950s to about 16,000 in 1983. AID assistance to Nepal's neighbor, India, also helped reduce Nepal's statistics. In 1982, as much as 70% of Nepal's malaria cases came from the nine districts along the Indian border. The effect of India's efforts to contain the problem was evident in the decreased numbers of cases attributable to migration.

In 1971, AID began withdrawing technical assistance to Nepal. The government of Nepal agreed to continue funding the National Malaria Eradication Organization (NMEO), considered by some U.S. malaria veterans to be the best organized and operated program in the Nepal Ministry of Health. Provision was made for the orderly transition from an eradication to a control program.

In 1973, the AID regional malaria officer assigned to Nepal reported that of the 6.8 million people living in malarious areas, 6.2 million were covered by the NMEO program. He also reported a slow but steady rise in malaria incidence and an increase in vector and parasite resistance to DDT and drugs. In 1975, AID and the Nepalese government signed an agreement for an Integrated Rural Health and Family Planning Project, which allocated $4.8 million for antimalaria efforts.

A significant aspect of U.S. malaria assistance to Nepal is the positive effect it has had on long-term economic and social development. More

What AID Left Behind in Nepal

• Malaria advisers took on a major census and mapping task, breaking tradition and the belief that work in Nepal could not be carried out on the Terai during the monsoon season.
• AID operations adviser Larry Cowper arrived in Nepal in the 1950s only to be told that the hill people were not trainable as spraymen. Cowper, dubbed "Malaria Sahib" by the rural Nepalese as he trekked more than 3,000 miles around the countryside, said "nonsense" and went about setting up training schedules and recruiting the hill people. Before they could read the markings on houses, he had to teach them numbers. But then, "they were the best spraymen ever seen by any malaria program," Cowper said.
• Rather than rely on often delayed and waylaid imported commodity orders, the program devised ways to produce sprayer spare parts in local blacksmith shops.
• As the advisers went about their business, villagers changed their preconceptions about malaria and became involved in planning and carrying out programs. Thanks to village specific programs—a kind of informal community health education effort—people soon realized that malaria was not a "visitation of the gods" and that eating fish from certain parts of a river did not cause the disease, nor did "walking in the dew" in early morning. Portable movie units presented malaria films; the projectionist threw in an entertainment film. The malaria program created songs and plays about malaria, and several of the songs became great favorites.
• Before the AID advisers arrived, many villagers had never seen a Westerner. The American presence opened a crack in the door for people to learn about the world and realize that people in foreign lands care about them and their problems.

than 1,000 senior and mid-level staff members have been trained in the technical areas of entomology, parasitology and operations, as well as in the supply, vehicle maintenance, and logistics areas. Furthermore, the recruitment of Nepalese at the local level and the encouragement of village volunteers, which broke traditional government patterns of centralizing activities in the Kathmandu Valley, has been so successful that the practice is being followed by other government offices.

The Nepalese government and AID believe that the success of the malaria program is one of the major U.S. aid program's accomplishments in that country. An AID malaria officer who served in Nepal said that not only was the health of the general population greatly improved, but the program reached millions of Nepalese citizens who previously had little or no contact with government services of any kind, setting a positive, responsive environment for other government programs.

Nepali malaria inspectors collect mosquitoes from a cattle shed during their training in the Terai of Nepal. (AID photo)

Pakistan

Pakistan received about $1 million in support of malaria control activities from the United States between 1952 and 1957. In 1958, WHO helped Pakistan develop an eradication program that initially proved very successful. The estimated 7 million cases of malaria in Pakistan in 1961 dropped to 9,500 by 1967. That same year, the malaria incidence rate began to rise. By 1975, malaria incidence was up so much that AID started a five-year malaria project in Pakistan with a loan for commodities and equipment and a grant to help meet local costs. Despite insecticide resistance, the project made progress. By 1981, the goal of

reducing malaria incidence to 500 cases per 1 million people had been met. While malaria continues to be a health problem in Pakistan, the situation generally is under control.

In 1982, AID provided Pakistan with a five-year, $41 million grant to support that government's malaria efforts. The grant is helping with the orderly transfer of malaria control responsibilities to a general health service organization, and in increasing urban malaria control activities.

The Philippines

The U.S. and Philippines association regarding antimalaria activities started in 1921, when the Rockefeller Foundation provided technical assistance. In 1926, a malaria control section was established in the Bureau of Health while the Philippines was under U.S. government authority. Post–World War II malaria control efforts are divided into four periods: national malaria control, 1953–1958; resurgence of malaria, 1959–1965; reorganization of malaria eradication, 1966–1973; and malaria control, 1974–present.

Conservative estimates put the annual case load at 2 million and deaths at 10,000 during the 1940s. U.S. assistance, which included Peace Corps volunteers carrying out field and laboratory as well as health education responsibilities, helped cut the figures to 40,000 cases and 1,000 deaths by 1972, with considerable economic benefits to the general population. Malaria today is confined to about 20% of the land area, compared to about 80% of the land area considered malarious in 1953. The Philippines reported 97,000 cases of malaria in 1981.

United States malaria assistance to the Philippines, phased out in 1973, has left a positive mark. United States epidemiological advisers shaped the direction of the program. At the AID-assisted Malaria Eradication Training Center, 1,302 participants from 43 countries took 56 courses and seminars between 1963 and 1972. Many center graduates today are in senior positions in the national malaria program and other health programs throughout the world.

Sri Lanka

Malaria continues to be the source of widespread suffering and death in Sri Lanka. The country is a natural incubator for malaria due to its year-round high temperatures, humidity and rainfall pattern, as well as population movements and vector potential. Explosive epidemics of malaria could occur at any time if the proper precautions are not taken.

Sri Lanka: Classic Example of How to Obtain Development Assistance

The Sri Lanka malaria program is a classic in regard to multidonor assistance and cooperation. When malaria reached epidemic proportions in the early 1970s, the government responded by preparing an operations plan. Next, with AID guidance, it called a multidonor meeting to present its case, stating the extent of the problem, what it was prepared to do and how much external assistance it needed. The result: the three donors (the United Kingdom, the Netherlands and the United States) were able to coordinate their inputs, eliminating duplication and covering all needs.

Sri Lanka, estimated to have more than a million annual cases of malaria in the early 1950s, nearly attained malaria eradication by 1963 when only 17 cases were recorded. DDT spraying was discontinued, and the program was integrated into general health services—as usual, without adequate advance preparation. Within 12 years, malaria incidence soared to 600,000 reported cases. The actual number of cases is estimated to be substantially higher, perhaps as much as four times.

The United States became a major donor to the Sri Lanka antimalaria program in 1977, when AID approved $12 million in training, commodities and construction and technical assistance. A health and environmental safeguard program developed by an AID adviser is in place. The safety procedures developed for Sri Lanka have been applied in programs in other countries with similar success.

Later, AID contributed another $4 million to the malaria project to cover operational costs of the Mahaweli Development Scheme, which moved about 1 million people into areas newly freed from malaria. By 1983, with coordinated assistance from the British, the Dutch and WHO, malaria was reduced to 127,000 cases.

AID assistance consists of support to biological control field trials and community participation to treat and prevent malaria and to use water management techniques to prevent mosquito breeding.

Africa

When an African gets a fever or becomes ill, the probability that the illness is malaria is high. The major problem area of the continent is the tropics, where each year a large percentage of the population is chronically affected by the disease. Every year, malaria kills an estimated 1 million Africans (90% of the population lives in malarious areas), mainly infants and children under age 14.

P. falciparum is endemic in virtually every country south of the Sahara Desert, excluding South Africa. Yet, other than drug distribution programs, little is being done to battle malaria in tropical Africa. Even during the eradication era, Africa was not included in the global effort. Pilot control projects and epidemiological studies supported by an AID predecessor and WHO concluded that eradication was not achievable within African countries' financial and logistical capability. One of the major contraints in any antimalaria undertaking in Africa is the poor infrastructure found in virtually every nation. Villages are spread out, many in remote, nearly inaccessible areas. The problem is compounded by the poverty of the people, a high rate of illiteracy and the lack of trained technicians and experienced administrators.

There were dramatic results in the 17 of the 40 African countries in malarious areas that did initiate eradication programs. Children in protected areas of Tanzania and Kenya had less anemia, presented fewer clinical symptoms and were taller and less undernourished than children from unprotected areas. Outpatient clinic attendance in Madagascar and Zanzibar was reduced ten- and fourfold, respectively. Infant mortality rates dropped in parts of Tanzania, Kenya and Senegal. Hospital deaths due to malaria in Madagascar and Zanzibar dropped (Graham 1979).

By 1964, most of the pilot malaria programs for Africa were discontinued. AID also reduced its global antimalaria program and expected that multilateral organizations would assume a greater role in global antimalaria efforts. But in a 1973 cable to AID missions, Administrator John Hannah noted that "in many country programs, the management/logistics advisors required to increase the (developing country) managerial capability have not been made available from multilateral sources." Three years later, AID's Office of Health commissioned a group of consultants to assess the potential of malaria control programs in Africa. The consultants' analysis showed that only 17% of the African population exposed to malaria received any protection. Most of those protected were in urban areas.

Furthermore, the report stated, "The malaria situation in Africa, as important as it is, cannot be evaluated without placing it in the context of the general health picture," which the experts considered bleak at best. The consultants called for the immediate development of basic health services, advising that any "real progress in malaria control must be coupled to an improvement in basic health services."

In 1977, the World Health Assembly drafted regional malaria program guidelines for Africa. Noting that organized antimalaria activities were yet to be initiated in most African countries, the Assembly in 1979 issued a resolution urging the international donor community to inten-

sify efforts to develop control activities and to coordinate international bilateral and private voluntary resources. To date, donors have made little progress toward this end, except for Japan, which has developed its own strategy in support of malaria control programs.

In the meantime, DDT and drugs were becoming less and less effective as the malaria vector and parasite developed resistance to insecticides and drugs. The most serious resistance levels were, and continue to be, in East Africa, with extension of the problem into central and southern Africa. The malaria parasite is widely resistant to chloroquine, especially in East Africa and parts of Central Africa. Mefloquine is the newest antimalaria drug being used.

In its search for the most cost-effective way to limit the impact of malaria on people in tropical Africa, AID's Africa Bureau has turned to the 1978 Alma Ata Conference's endorsement of a multiple services health approach, with PHC as a vehicle within which endemic disease could be prevented and controlled. The Bureau, recognizing the potential for improvement in the curative and preventive service capacity of PHC systems, developed a sector strategy that includes malaria control through existing PHC systems and other country health services. Bureau instruction to the field was that malaria control programs should be implemented within the framework of a national PHC system.

In mid-1982, 53 malaria experts from 10 countries, representing a wide range of international organizations and the U.S. private and public sector, met to advise the Africa Bureau on its malaria control efforts. The meeting was the culmination of a series of three. Among its conclusions was that PHC is an appropriate public health approach within which to control malaria. In fact, in some countries PHC is the *only* vehicle for control. The group also spelled out malaria control programs suitable for integration into PHC systems and defined program goals. These and other topics covered by the experts—constraints to program success, diagnosis and treatment, training, program continuation beyond external assistance, and preconditions—were incorporated into the Africa Bureau's "Manual on Malaria Control in Primary Health Care in Africa" (American Public Health Association 1982).

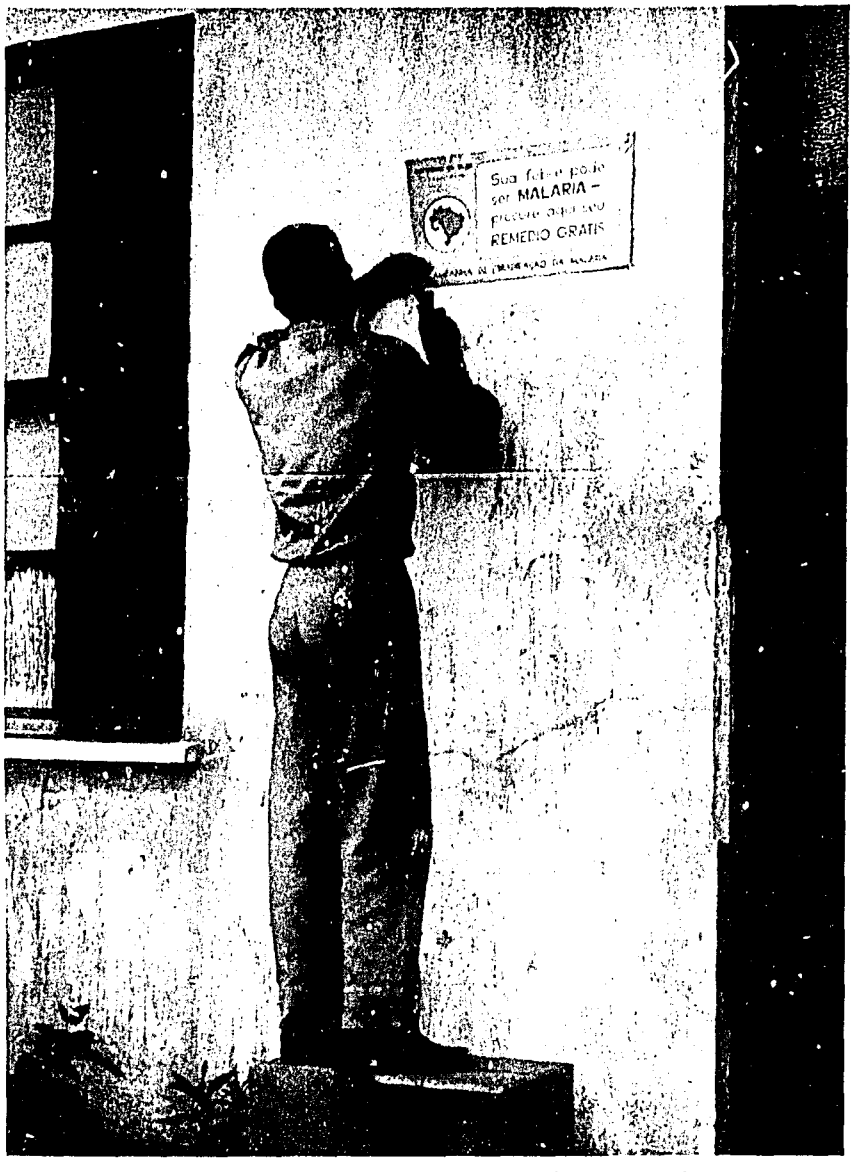
In effect, the most desirable program for African countries is the most affordable program, which generally limits antimalaria efforts to chemotherapy. The approach is feasible in a region where most malaria cases are caused by the *P. falciparum* parasite, an infection that can usually be cleared by a single dose of chloroquine. Limited vector control is encouraged, but, in fact, most African countries cannot afford major-scale vector control activities. Furthermore, such programs, if they did exist, would probably be effective only in urban and semiurban situations.

The Africa Bureau sponsors 22 PHC activities in 15 countries and a

regional activity in Central and West Africa, with most of the program in endemic areas where only rudimentary health delivery systems exist. The only specific malaria control project supported by the Bureau is on Zanzibar and Pemba islands, Tanzania.

Near East

AID's Near East Bureau has no specific malaria control projects. Several countries in the Near East have malaria problems, but some of them consider malaria a health problem not requiring external assistance (Insect Control and Research 1983). AID provides commodity support for chemotherapy programs through some PHC projects.



"Your fever could be malaria—get your treatment here free." (AID photo)

Serologic research conducted for AID by the Centers for Disease Control led to methods that are used worldwide today. Here a blood sample is taken from a youngster to determine whether he is carrying malaria. (AID photo)

Surveillance is a critical step in a successful malaria control program. (AID photo)

U.S. assistance to developing countries' antimalaria efforts included the training of thousands of spraymen. (AID photo)

Spraymen traveled to remote areas by elephant, dugout canoe, jeep bullock, mule and—if all else failed—foot. (AID photo)

An Indonesian technician collects mosquito larvae to study in the laboratory. (AID photo)

The Malaria Institute of India carried out extensive malaria research under the guidance of U.S. technicians. Here antimalaria drug is tested on a monkey. (AID photo)

4

Drug and Vector Control Research

AID generally has not invested in research on new drugs to fight malaria, but did, and continues to, finance programs based on control of vectors. Unfortunately, the introduction of chemical insecticides and reliance on residual spraying led to a deemphasis on vector control and field research in vector biology.

Most antimalaria drugs on the market were developed prior to 1950. While none is effective against all stages of the malaria parasite, they are essential to limit death and illness from malaria and to minimize the loss of human productivity. And where they are effective, drugs are difficult to apply on a large scale. Furthermore, parasite resistance to many drugs is increasing in many areas of the world.

WHO's Scientific Working Group on Chemotherapy of Malaria, which works in coordination with AID and other research programs, provides leadership in developing new drugs and related efforts, such as evaluation and delivery systems, for use in developing countries. AID does not directly fund drug research, but does coordinate and cooperate with public and private efforts.

Effective treatment of malaria originated with quinine. Although quinine still has some limited use in areas of severe chloroquine drug resistance, it is no longer widely used, mainly because it is expensive and more toxic than synthetic drugs. Instead, synthetic antimalarials, such as choloroquine, atabrine (mepacrine), pyrimethamine, chlorguanide and primaquine, are available to prevent or radically treat malaria (see Appendix C).

To determine the sensitivity of the parasite, it is important to choose a drug and to determine the length of treatment. Parasite species vary in virulence and response. For example, *P. falciparum* requires higher

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doses than *P. vivax* to achieve suppression of malaria. The most widely used drug to treat acute malaria attacks is chloroquine. But growing resistance is worrying many experts and scientists. The latest reports of resistance are from the Kenyan and Tanzanian coasts, part of Central and South America and much of Asia (including Bangladesh, Burma, eastern India, Indonesia, Kampuchea, Laos, Malaysia, Nepal, the Philippines, Singapore, Sri Lanka, Thailand, Vietnam and Papua New Guinea).

Biochemical studies are providing clues about metabolic pathways of malaria parasites that may be candidates for drug action. Biological screening of several chemical compounds promise potential new drugs. But because development of new drugs (such as qinghaosu, halofantrine and pyronaridine) takes a long time, work to improve already known drugs continues. One example is mefloquine, which was the only drug found effective out of the more than 100,000 compounds screened during the Vietnam War (Nickel 1983), and was used to treat or suppress malaria.

The Walter Reed Army Institute of Research, which discovered mefloquine 15 years ago, is cooperating with a major U.S. pharmaceutical company in clinical trials to determine the drug's efficacy and safety with hopes of making it available for use in the next few years. Trials have shown the compound is well tolerated by humans and is safe. It also has a cure rate of 95% with a single dose, an important logistical feature especially for use in remote areas.

Qinghaosu, the active agent of the plant *Artemisia annua*, has been used by the Chinese for more than 1,000 years to treat malaria. Qinghaosu-derivatives, artemether and artesunate, appear to have strong possibilities to treat cerebral and other complicated forms of falciparum malaria.

Research on primaquine is helping reduce the toxicity of the drug so that it can be used by humans and administered only once. Other drug research centers are concentrating on understanding the genetics and spread of drug resistance.

The search for new drugs and for other malaria control methods is never ending and increasingly urgent as drug resistance increases, especially in the case of falciparum malaria. The situation is particularly critical in tropical Africa, where current vector control methodology is considered too expensive and logistics difficult, factors that make antimalaria drugs generally the only feasible existing means of preventing death from malaria.

Vector Control

AID support of vector control programs has largely been in the form of commodities, such as insecticides, antimalaria drugs, pesticide application equipment, laboratory equipment, and vehicles. It also has included technical advisory services and training and some local currency support. During 1958–1972, vector control assistance amounted to $570 million in loans and grants to some 36 countries in Asia, Africa and the Americas.

AID coordinated its worldwide malaria eradication program with WHO (see Appendix D) and UNICEF, following the technical guidelines set by the WHO Expert Committees on Malaria. From 1956 until 1969, all antimalaria programs concentrated on residual spraying of interior walls of houses, case detection and treatment of detected cases through administration of antimalaria drugs. As noted in Chapter 1, initial success of this approach was spectacular in many countries. By the mid-1960s, however, progress toward eradication of malaria had peaked.

In response, WHO organized fact-finding teams in 1968 to study factors affecting progress, and to consider the need for a revised strategy. Recommendations based on visits to 12 countries, together with those of the Eighth International Congress of Tropical Medicine and Malaria, and views of the WHO Expert Advisory Panels and the Advisory Group on Malaria Eradication Strategy, provided the basis for the Director-General's report, "The Reexamination of the Global Strategy of Malaria Eradication," presented to the 22nd World Health Assembly in 1969.

An Assembly resolution cited the need for country-by-country strategy reviews by independent multidisciplinary teams, and, as an important feature, called for intensification of research and development of alternative vector control methods.

During the 1950s and early 1960s, when DDT residual spray campaigns were so successful in reducing the incidence of malaria, AID and WHO concentrated their research efforts on developing specifications for insecticides and spray equipment and on finding and testing new insecticides as alternatives. An annotated chronological list of significant AID-supported vector-borne diseases control research and development and related activities (excluding immunological research and development) is provided in Appendix E.

51-

5

AID's Support for a Malaria Vaccine

Geneva, Switzerland: 1965. An American physician and a scientist board a plane bound for the United States. The pair was returning home, having spent a week discussing global health problems with hundreds of colleagues. One of the subjects that occupied them during the flight was the alarming resurgence of malaria in developing countries.

Malaria remained endemic and epidemic in those parts of the world that housed the poorest and most susceptible people. The traditional tools, drugs and insecticides obviously were not as effective as when introduced. As drug and insecticide resistance increased, so did incidence of the disease. Scientists pressed for support of research to develop new methods and alternatives.

By the time the plane landed in the United States, Dr. Paul H. Silverman of the University of Illinois had convinced Dr. Lee M. Howard, health director for the Agency for International Development, that the time had come to explore intensively the possibility of a vaccine to help break the grip of malaria. Silverman, a pioneer in developing concepts of immunological responses to parasitic diseases and former adviser to WHO's Expert Committee on Malarial Immunology, noted that of all the research reports presented at the conference, not one addressed the possibility of a vaccine. Silverman believed this was a serious oversight; a vaccine could be the "missing link" in the arsenal of weapons to fight malaria.

Those who believed that a malaria vaccine was possible were few. They stood against those who insisted that a vaccine was not just impractical but impossible; the critics said AID would be throwing its money away by supporting malaria vaccine research, their skepticism founded

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in the fact that while vaccines against bacterial and viral infections were common, biological complexities thus far had prevented the development of vaccines against any parasitic disease. Up to this time, the protozoan that causes malaria had defied science and technology.

Those who did believe insisted it was worth the gamble. After all, the optimistic scientists argued, the disease has a devastating and debilitating effect. Also, there were known encouraging factors in natural and experimental immunity. In 1965, the year Silverman and Howard had that fateful conversation, an estimated 500 million people were struck by malaria, causing economic and social losses that could only be guessed at. As many as 2 million died, most of them children.

While some immunity does develop in infected individuals naturally, constant exposure to malaria does not produce partial protective immunity for 10 or so years. Hence the high death rate among children, especially infants.

Silverman conjectured that, with proper consideration of the changes of the malaria parasite in its human victim, infection could be overcome by artificial means. He ventured that "it appears that it is possible to induce a better immunity to malaria by artificial means than that which normally occurs as a result of exposure to natural infection." He based his theory on the fact that scientists had found that, in a laboratory, a high degree of immunity can be artificially induced by the infective sporozoite after it enters the blood stream.

Animal experiments in the 1940s demonstrated the principle that malaria could be prevented by vaccination. The vaccine, however, used complete Freund's adjuvant, which cannot be used for humans due to adverse effects. The challenge was to develop a safe, efficacious vaccine for people. Vaccines effective against one species of malaria parasite may not be effective in another system. "Until faithful models of human malarias have been indentified—and this can only come about after vaccination trials in human subjects—the net should be cast wide and all proven safe vaccine preparations . . . should be considered for trial in man," Silverman insisted.

One requirement of a human vaccine for use in malaria areas is that it be polyvalent: that it cover more than one part of the complex life cycle of the malaria parasite and contain elements to protect against all of the four species of human malaria. Other requirements are that the vaccine produce an effective immune response for at least a year; that it be fairly easy to manufacture and store; and that it be appropriate for mass administration in tropical countries (Bruce-Chwatt 1979). Finally, the vaccine should be inexpensive. While this represents the ideal and proper goal, it does not prevent effective use of less perfect products, alone or in combination, as with other drugs.

AID set out to meet the challenge. On July 1, 1966, a study on the feasibility of developing a human vaccine began at the University of Illinois. The Malaria Immunity and Vaccination Project proposed studies to determine which of the stages of the life cycle are potentially useful as sources of antigens and which are susceptible to the immune response. Emphasis was on sporozoite (mosquito stage) antigens, with provision for work on erythrocytic (blood stage) antigens, *in vitro* (in a laboratory) cultivation of all stages of malaria parasites, and development of a test to assess protection in an animal model.

Initial progress was slow. Several technical breakthroughs were required. The most significant achievement during the first five years was the demonstration of the biological feasibility of artificial immunization against malaria, a step that stimulated other scientists to undertake research along the same lines. The question then was not so much *whether* a vaccine was possible but *when*, and whether a malaria vaccine could be developed on a commercial scale with appropriate mass production.

Using rodents and monkeys, the Illinois scientists showed that antigens prepared from the mosquito stage (sporozoites) can be used to prevent monkey malaria in *Rhesus* monkeys, and that antigens prepared from blood-stage parasites (trophozoites, schizonts and merozoites) can be used to suppress the erythrocytic phase of malaria. Other laboratories working independently produced similar results. The immunological protection provided in some of these preliminary antigen studies lasted approximately three years.

To more carefully select research projects to meet the goal of developing a malaria vaccine, AID established priority research goals. The Agency decided to tackle the malaria problem with a two-pronged approach: a sporozoite vaccine would attack the parasite's mosquito stages; a merozoite vaccine would attack the parasite in a more susceptible stage—the blood stage.

The project was moved, along with key personnel and equipment, to the University of New Mexico in 1972. The new three-year contract included a work plan emphasizing antigen production and primate studies. A subcontract with the University of Illinois through 1973 provided an advantageous phasing of activities between the two universities. The University of New Mexico also subcontracted with Rush Memorial Institute (Chicago, Illinois) to develop a primate (monkey) model for human malaria species.

An AID-sponsored malaria vaccine workshop was held in June 1974 to examine the problems related to the development of a malaria vaccine, and to review the state-of-the-art of malaria immunology and vaccine research. Apparently, considerable skepticism about the possi-

bility of developing a malaria vaccine still existed. But there were some who appreciated the worthiness and timeliness of the effort. Dr. Philip Russell of the Walter Reed Army Institute admitted that the meeting "has converted me from a disbeliever to a skeptic.... I am impressed with the possibility of eventually being able to prevent malaria in man by immunization" (National Academy of Sciences 1974).

AID's Howard and Edgar A. Smith convened a small, select group of international malaria parasitologists and immunologists to assess the design of vaccine research. Their conclusion: there were no specific designs for research. Instead, the experts called for young professionals to work with more senior scientists to concentrate exclusively on *in vitro* cultivation of malaria parasites.

In August, a small group of experts in the field of immunology and parasitology convened to advise AID in terms of research priorities, institutional facilities and scientists interested and willing to collaborate on malaria immunity research. *In vitro* production of erythrocytic antigens was identified as the number one priority.

AID called for additional research proposals. Four more contracts were signed—with Rockefeller University, the University of Hawaii, Parke-Davis Co., and New York University (NYU). Within six months of the AID/Rockefeller contract, a dramatic breakthrough, the dream of all scientists, was made in 1975 by Drs. William Trager and James Jensen when they succeeded in continuously cultivating red blood cell stages of the human malaria parasite, *P. falciparum*, in the laboratory. Dr. David Haynes at the Walter Reed Army Institute for Research in Washington achieved parallel results the same year.

Because the project had achieved its goal well under its three-year contract schedule, Trager proposed a revised and expanded project with seven objectives, all exploiting the continuous culture system and aimed at facilitating the development of a human vaccine. Within two years, the two principal objectives were met with substantial progress on the remainder. The project was again revised.

The *in vitro* culture technique, which eliminates the need to cycle malaria parasites *in vivo* (in living animals), meant that scientists would have enough parasites to work with in the laboratory. It was the first major step toward producing large quantities of parasite material for isolation and characterization of potential protective antigens. The feat was hailed as the greatest advance in malaria research and technology in 25 years; Dr. Sidney Cohen of Guy's Hospital in London said it "translated malaria vaccination to the realm of practical feasibility" (Cohen 1979).

The Trager-Jensen technique also was the basis for accelerated progress in many aspects of malaria immunization research. For example,

a malaria vaccine using inactive disease organisms, which traditional vaccines use, does not work because the parasite is so complex, changing form several times during its life cycle. Each form has different antigens. It may be that several vaccines to suit specific needs of different parts of the world will be necessary.

As the Rockefeller work progressed, AID sought additional scientists to join its collaborative malaria vaccine reseach network of U.S. universities and private laboratories (see Appendix F). Those who joined the network were the Walter Reed Army Institute of Research, the Gorgas Institute in Panama and the National Institue of Health in Bogota, Colombia, each working on different aspects of vaccine development.

Other workshops followed, including one in 1978 to review the AID collaborative network. The problems and priorities identified three years earlier were still considered valid. But, because of the Rockefeller University's development of a continuous culture system and the progress on associated problems, a reordering of priorities and delineation of the problems were considered necessary.

Other breakthroughs followed. In 1982, Dr. Michael Hollingdale of the Bio-Medical Research Institute in Rockville, Maryland, another institution in AID's colloborative network, achieved the *in vitro* culture of the exoerythrocytic (liver) stage of *P. falciparum* and *P. vivax*. It was now possible for scientists to get *P. vivax* merozoites not obtainable by normal red blood cell *in vitro* culture methods. This tissue culture technology also has great potential for testing antimalaria drugs and, in fact, is being used for that purpose.

In the meantime, NYU Medical Center researchers, concentrating their work on the parasitic development in infected mosquitoes' salivary glands (sporozoite stage), brought the malaria vaccine one step closer to reality. Led by Drs. Ruth and Victor Nussenweig and basing their efforts on previous success in protecting rodents and primates against malaria with radiation-attentuated whole sporozoites, the NYU scientists in late 1982 isolated the protective antigen that is a component of the surface peptide, or coat, of the sporozoite. It is this peptide that prevents the host from recognizing the sporozoite as a foreign organism, thus protecting the sporozoite against attack by antigens. When test animals are injected with this protein alone, their immune defenses are mobilized to produce antibodies against it, thus providing protection against malaria.

Other advances were made by other members of the AID collaborative network: Scripps Institute, the University of Missouri, the University of Hawaii and the Uniformed Services University of the Health Sciences. The successes included the isolation of attenuated live malaria strains that may offer protection against the blood stage forms of malaria, and

the isolation of several potential antigenic molecules from the merozoite (blood) stage of the malaria parasite.

Large amounts of sporozoites are necessary to produce antigens for a vaccine. But sporozoites cannot yet be produced *in vitro*. Alternative ways to synthesize key parasite antigens therefore are the basis for a candidate malaria vaccine. In 1983, the NYU researchers announced that by using genetic engineering (recombinant DNA methodology) they were able to identify an *Escherichia coli* clone expressing the surface antigen of *P. knowlesi*, a malaria parasite of monkeys. As a result of the isolation of the *E. coli* clones secreting the antigen, large-scale production of the antigen is possible.

The stage was set for the next step—to isolate the *E. coli* clones with the surface antigen for the human malaria parasite, *P. falciparum*. To no one's surprise, the Nussenzweigs made that announcement August 2, 1984, promising that the same isolation for *P. vivax* would shortly follow. A vaccine produced by a combination of synthetic peptide immunotechnology and recombinant DNA studies is imminent.

The sporozoite vaccine is seen as but one piece of the puzzle. It should be suitable for people going to malarious zones and to prevent malaria infection for short periods. However, because the parasite spends most of its life within cells and goes through several stages, the human host requires different recognition mechanisms for each stage.

The sporozoite vaccine is effective only against the first stage of the infecting organism, and, if through continued exposure a colony escapes the initial immune response and moves into the next stage, clinical disease will probably result. Neutralization of the malaria parasite by most antibodies and cells is complex. The ideal vaccine—the one needed by people who live in developing countries—would be polyvalent, containing antigens from all the stages of the parasite's life cycle to attack each of the parasitic stages as well as all four species affecting humans. Such a vaccine might have as many as eight components. Adjuvants to enhance antigens also will probably be needed.

The AID network continues to work on the many possibilities. To date, the Agency has spent $17.4 million on its quest for a vaccine. Until now, the state of the science in malaria vaccine research has been the limiting factor on how quickly a prototype vaccine could be developed. With the recent scientific breakthroughs, it now appears that stable funding is the limiting factor.

The next step is limited human volunteer trials in the United States and limited clinical field trials in several tropical countries. "Technically speaking," says Dr. James Erickson, AID manager of the malaria vaccine research project, "a vaccine may be available for human testing as early as 1985." AID could put the first new major, effective antimalaria

weapon since DDT to use in developing countries by 1990. Meanwhile, the research on polyvalent vaccines continues.

Before proceeding to clinical field trials, however, the Food and Drug Administration (FDA) requires background epidemiological data to be collected at the overseas field trial sites. That takes time and money. Two-thirds of the more than 1.4 billion people who live in malarious areas are not covered by any antimalaria efforts (AID 1980). AID fully realizes the potential impact of its research, and in early 1984 doubled its financial commitment to $22.7 million over a three-year period, anticipating that the increase will cut in half the time to prepare the vaccine for FDA approval for human testing.

Malaria vaccines will not be a panacea for the malaria problem. However, they should be a giant step toward wiping out the dreaded disease, an important component of a strategy for more effective malaria control and, it can be hoped, eventual eradication of malaria.

Much depends on the type of vaccine—whether it attacks the initial stage of infection (preventing illness) or the later stages (preventing transmission). Where malaria transmission is low, vaccines could have a tremendous impact. In tropical Africa, where malaria is hyperendemic in virtually every country south of the Sahara Desert, a combination of vector control, drugs and vaccines are almost surely necessary to contain the disease. The largest number of deaths in Africa are suffered by children six months to four years old. It is unknown whether a malaria vaccine will induce immunity in children.

Experts do not expect a vaccine will eliminate malaria from Africa, nor anywhere else for that matter. To do so would require practically all people to be vaccinated, an extremely difficult task, unless the vaccine is one that needs to be given only once versus repeated inoculation (such as was the case with smallpox). The least a malaria vaccine would do is reduce morbidity, a feat not to be scorned. At the same time a vaccine is being given to people, considerable attention must be directed at controlling the vector.

Vaccine Patents

Several of AID's contractors in its collaborative malaria vaccine research network have made significant breakthroughs in their search for a vaccine to prevent malaria. The breakthroughs have prompted the researchers and their respective institutions to consider applying for patents, raising an important legal issue in contract research: Who is entitled to patent rights? The funding agency? The researcher's institution?

The situation is complicated by changing U.S. policies on patents for

federally funded research, new laws on the intellectual property rights for the products of biotechnology, and developing country distrust of the international patent rights system. Prior to March 1982, AID contracts were governed by U.S. government-wide patent policy that gave AID the first option on the principal rights in any invention resulting from work it funded. The contractor was permitted to petition AID for greater rights and demonstrate reasons for giving the contractor more rights in the invention.

In 1982, there was an overall change in U.S. government patent policy. To encourage private sector businesses to develop government-funded research into commercial products and to market new products, the U.S. government changed its overall patent policy and procedures to give domestic, nonprofit, research organizations the right of first refusal to title of inventions made under government contract. The research institutions could then, in turn, transfer some or all of the patent rights to industrial partners seen as a vital part in the further research and development of the invention into a product.

Before the 1982 U.S. government patent policy became effective, New York University filed a patent application for an invention funded under an AID contract. WHO and the National Institute of Health also had contributed to NYU research efforts, although in much lesser amounts than AID.

Several months after filing its patent application, NYU indicated it intended to petition AID for greater rights under previous U.S. patent policy. NYU entered negotiations with Genentech, concentrating on a proposed license that would give the California-based bioengineering company exclusive rights to develop, manufacture and sell a malaria vaccine incorporating the subject matter of the NYU patent application. At that time, Genentech had no experience conducting clinical trials, obtaining FDA clearance, or manufacturing and distributing pharmaceutical products.

During the negotiations over patent rights, WHO reminded NYU of its policy regarding inventions developed as a result of WHO-supported projects—that WHO has a claim to a nonexclusive, royalty-free license for member countries. At the same time, AID requested detailed information on the NYU-Genentech plan to manufacture and distribute the vaccine.

NYU subsequently carried out the developmental genetic research it anticipated would be conducted by Genentech, and NYU-Genentech collaboration become moot. The AID-WHO-NYU-Genentech negotiations focused sharply for AID the importance of pharmaceutical company expertise to the ultimate production of a safe and efficacious vaccine. AID realized that such expertise would be helpful in engaging

in clinical trials that meet FDA standards and in the manufacture and marketing of safe drugs.

However, only a few U.S. drug companies produce vaccines. Moreover, as Marcell Hommell, genetic engineer at the Institute Pasteur in Paris, points out, "many of the available vaccines against infectious diseases are still not extensively used in the areas where they are most needed, because the affected nations cannot afford their purchase and do not have the medical infrastructure for their distribution" (Hommell 1983). Thus, how do you attract an appropriate industrial partner?

Patent protection for the pharmaceutical firm is one helpful attraction but such protection should not bar continued coordinated research by the AID network of researchers. In 1983, AID maintained that its malaria vaccine program, which had a limited potential market and required highly coordinated research, justified a modification of the federal patent policy. The 1982 policy permits modification "when it is determined by the agency that restriction or elimination of the right to retain title to any subject invention will better promote the policy and objectives of this chapter" [35 U.S.C. 202(a)(ii)].

No one research institution is working to develop a polyvalent vaccine; each of the research institutions in the AID network is concentrating on developing a vaccine for a particular stage of the malaria parasite—either the sporozoite or merozoite stage. Furthermore, there are several species of malaria parasite and different vaccines may be required for each. It is important that no barriers (including possible patent barriers) be in the way of developing polyvalent vaccines through scientific and commercial collaboration among the institutions developing components of such vaccines.

Because there are other donors in this area, notably WHO, there is considerable likelihood that patent policies will conflict. One U.S. drug company already has expressed its view that the WHO stance taken during the NYU-Genentech negotiations may be an impediment to its participation in the manufacture of the vaccine. AID, working collaboratively with WHO and other donors, can achieve a coherent position on the disposition of invention rights acceptable to all donors, the contractors and the industry. For AID to be successful in this objective, it must be able to demonstrate to WHO that its program is set up in such a way as to ensure that the vaccine becomes available quickly and at a reasonable price to the world.

In 1983, AID Administrator M. Peter McPherson approved a special patent policy relating to malaria vaccine research. The policy restricts contractors' rights to title to inventions arising from their AID-funded work. The restriction leaves considerable room for collaboration between commercial concerns and AID contractors to develop and pro-

duce a vaccine. It also assures AID of sufficient rights to meet the needs of its malaria vaccine program.

In turn, contractors have full rights to their inventions for a period sufficient to allow them to collaborate with an industrial partner. The grant of these rights would be on the condition that contractors satisfy certain obligations designed to promote overall objectives of AID's malaria vaccine program.

6

Future Role in Global Malaria Programs

Initial AID malaria policy was set in 1973 in a cable to AID overseas offices that reassured them that, while AID did not advocate resumption of the major external support role it earlier provided, support to antimalaria programs should be flexible "under certain specified conditions" (AID 1973). The Agency has periodically reexamined its malaria policy, strategy, programs and research efforts.

Basically, AID's regional bureaus have adhered to the Agency's malaria policy while following their own strategies. In 1976, an AID internal audit summarized the global malaria situation, noting that there was a resurgence of malaria in countries where antimalaria programs had made tremendous successes; that the program machinery to battle malaria essentially had been disassembled; that many countries had failed to integrate malaria services into their general health systems; that declining AID inputs threatened development gains. The report also noted the Agency's entry into immunology research and declared that the undertaking merited high priority.

The report suggested that the time was right for a task force review of the global malaria situation and for modification of AID strategy. The Asia and Africa Bureaus convened expert panels to determine what AID's role should be in specific countries. The Asia region had the most to lose from a resurgence of malaria because most of the early successes were scored in that part of the world.

The Asia and Africa panels issued reports in 1977 and 1982, respectively, each emphasizing that public health care (PHC) systems are the potential focal point for antimalaria efforts. The Asia Bureau report concluded that malaria control operations can be devolved to the local

health infrastructure where basic health services are adequate; the Africa Bureau report declared that the PHC system can play a key role in antimalaria programs by distributing drugs. Both reports insisted that program success depends on ministries of health having a core group of malariologists, epidemiologists, entomologists, logisticians and administrators to carry out planning, supervision, training, supply, backstop and evaluation functions.

Integrated malaria control, the most effective way to reduce malaria and to maintain low incidence, is recommended for countries where health resources are adequate to support commodity costs, technical and administrative demands, and requirements for trained staff. The Asia Bureau emphasizes that malaria coantrol is part of national health planning, not an independent program. The Africa Bureau strategy emphasizes curative measures.

The approach of chemotherapy and limited vector control may be feasible in Africa because most malaria cases are caused by the falciparum parasite, which can be treated by a single drug dose. Elsewhere, malaria may be caused by any one of several parasite species that are less susceptible to single-dose treatment. Hence, there is a need to tailor antimalaria programs to specific epidemiological situations.

A statement by the Latin America and Caribbean Bureau in 1980 directed that support to malaria programs be considered in the context of rural health care delivery goals and that support be competitive with other options for development assistance.

The most recent review of AID's malaria policy was held in Columbia, Maryland, in June 1983. Attended by 27 of the world's leading malaria experts, the group took a hard look at AID strategy supporting country malaria control programs and discussed the implications of new ways to control mosquitoes or parasites, or both, and of vaccines anticipated to be ready for human use in the next decade.

The workshop convened, in part, in response to a 1982 General Accounting Office (GAO) report that noted U.S. financial and technical support to antimalaria efforts was declining at the same time malaria was reclaiming ground gained by earlier global control and eradication programs. While U.S. aid generally had been successful in meeting the immediate needs of many antimalaria activities, reported the GAO, progress toward achieving long-term goals has been hampered.

In light of the resurgence of malaria, the provision of antimalaria drugs to people via general primary health care services, and the development of regional approaches by AID geographic bureaus, the GAO suggested a reexamination of Agency policy on malaria programs was warranted.

AID officials recognized the value of an updated policy paper. Not

only would it provide AID officers guidance against which proposed antimalaria programs could be reviewed and approved, but it would serve as an approved AID position to be shared with other U.S. departments and agencies, foreign governments and international organizations.

Finally, a revised policy would formally incorporate the elements of economic assistance projects as mandated by Congress: a sound policy framework, private sector participation, transfer of technology and institutional development—elements critical to achieve self-sustaining economic and social change.

But changes and developments—specifically, the emergence of PHC as an approach to deliver health services, and the scientifically proven feasibility of a malaria vaccine for human use—prompted another Agency policy review.

The Columbia workshop opened with participants noting that while a well-defined, up-to-date strategy is important, it is virtually "worthless" unless industrialized and developing country government leaders and policymakers are willing to make a long-term commitment of international financial support. The reference, of course, was to the problems of the 1960s.

The Agency's strategy is basically sound, the experts agreed. But they added that it and the accompanying criteria "are excessively rigid with respect to insistence on a purely economic rationale for AID support of malaria programs; pay inadequate attention to the need to identify and anticipate constraints to successful long-term malaria control; and are silent on the relationship between malaria control and an increasingly important but widely variant mechanism for the delivery of health services, PHC." The group suggested revisions so the Agency would "have a coherent worldwide approach" (AID 1984).

The workshop resulted in proposed revisions that were submitted to AID health and other officers in Washington headquarters and overseas missions for review. In July 1984, AID Administrator M. Peter McPherson approved a new AID malaria policy paper.

The paper declares that AID malaria program assistance activities will concentrate on flexible control programs designed to reduce malaria incidence "to a level at which it is no longer considered a serious public health problem" (AID 1984).

AID malaria assistance will concentrate on cost-effective control programs that make the most use of existing PHC systems. AID will emphasize:

the design process, so projects have clear objectives and priorities;

a choice of control tactics keyed to epidemiological conditions and to

technical and administrative capacity within a framework of indigenous self-sufficiency;

increased support for biomedical and applied research and training to enable development, adaptation and transfer of cost-effective malaria control technologies;

continued support for evaluation on ongoing antimalaria programs;

coordination and collaboration with WHO and PAHO in the planning, evaluation and support of research, training and operational malaria programs;

use of technical resources available through U.S. government agencies and appropriate public and private organizations and institutions.

Training, research and high-quality technical assistance "are absolutely critical elements" of any AID guidelines or strategy, said the malaria experts at Columbia, who drew on their experience during the global control and eradication eras to respond to one of the most serious consequences of the international decline in malaria control programs—the drop in the number of professional staff with malaria experience. The experts called the inadequacy of AID's malaria staffing in Washington and in the field "of grave concern." The staff, they added, "lack both the numbers of personnel and the technical capacity to discharge its responsibilities" (AID 1984).

The scientific community has been concerned with the manpower needs and career opportunities in the field of vector biology for some time. In a 1981 letter to Victor Rabinowitch, then director of the Board on Science and Technology for International Development, Dr. Franklin A. Neva, NIH chief of the Laboratory of Parasitic Diseases, said: "Several of us have become increasingly concerned about the dwindling number of individual experts in the field... especially with respect to entomologists knowledgeable about malaria" (National Research Council 1983).

A start at remedying the situation, the 1983 Columbia workshop participants suggested, would be for AID to cooperate with U.S. educational institutions to establish training programs. Furthermore, AID "must reconsider its overseas staffing priorities" to emphasize technical skills. Indeed, the policy paper declares a modification of overseas staffing priorities, which now "stress managerial skills to the virtual exclusion of malaria technical skills," is required. One remedy is to provide malaria-trained advisory capacity to each AID-supported malaria program.

Training was singled out by the Columbia workshop as "the single most important requisite for the institutional development, which is

essential to the generation or improvement of national capabilities needed to plan and execute malaria control programs," and added that it is equally important to ensure the development, adaptation and transfer of new technologies of malaria control.

The policy paper provides for the cooperation with U.S. educational institutions to address the problem, declaring that "only with the expansion of training programs for AID staff, as well as for national staffs, will malaria programs be adequately designed and implemented." Furthermore, each region should have a U.S. malaria specialist as coordinator and technical backstop to country-level malaria advisers and as consultant in forming initial plans to establish malaria programs. Malaria control expertise also should be strengthened in headquarters. For technology transfer to be most effective, the capabilities of research workers in developing countries should be strengthened, mainly through coordination with WHO.

All malaria programs, the experts advised, should take advantage of existing and potential PHC systems. The policy paper states that in countries where malaria is a major threat to economic development or quality of life, "AID may provide selective support of malaria control using the most satisfactory available vehicle. In many countries this will be the PHC system; in some countries, support of vertical malaria programs may be necessary until the PHC system is more fully developed." However, the policy paper continues, "the presence or absence of a PHC system should not determine whether or not support should be given to an antimalaria program."

Community participation, a key element of PHC efforts, is equally important to the success of antimalaria efforts, the Columbia workshop report stated (AID 1984). The new policy paper addresses the issue, declaring that while "AID cannot profitably try to assume responsibility for developing community participation, a strategy of supporting efforts to stimulate the AID-assisted country to take the leadership in developing community participation is appropriate." AID will support national training for PHC and malaria workers towards this end.

Workshop participants said AID malaria policy should recognize the need for increased biomedical research and support, and for research on malaria vaccines as well as other antimalaria tools, such as drugs and insecticides, "necessary if the PHC system is to play its full role." Specifically, "not less than 10% of funds allocated to malaria control should be devoted to research—exclusive of vaccine research." AID support of a malaria vaccine research should continue "at a level which will ensure completion of this extremely important project." Until long-term answers are found, the workshop report continued, commodity

assistance "will continue to be vital to early success of antimalaria efforts."

The policy paper provides for continued support of malaria vaccine research but states that this potential tool for control "should not lead to the abandonment of other cost-effective forms of malaria control." New research activities should be initiated to simplify malaria diagnostic and survey methods; to identify, evaluate and test new antimalaria drugs; to identify and test new insecticides and alternatives; to further investigate comprehensive vector control and epidemiological determinants of the malaria problem; and to develop test methodology for use in specifications necessary to ensure delivery of high-quality insecticides, application equipment and packaging.

Finally, workshop participants noted that the annual levels of international concessional aid to developing countries was $35 billion in 1981, with about 10% going to health programs. The participants anticipated that the international donor community would not increase its support of malaria control activities unless AID took action to encourage cooperative efforts with potential donors and formulate proposals for multisource external financial and technical support.

The new policy paper encourages continued collaboration and coordination with other international agencies and organizations, especially WHO, at the country, regional and international levels, and to maintain regular contact with financial and technical agencies regarding research and program efforts.

Tremendous Gain

Although certain aspects of the global situation of malaria may appear to be negative, control and eradication efforts have achieved tremendous economic and social gains, saved millions of lives and relieved much human suffering.

Less noted, but of equal significance, are the auxiliary benefits. Examples include mapping and census taking where neither existed previously; development of health departments or ministries and health programs; strengthened images of respective governments; the development of a cadre of health professionals and other technically skilled persons; improved government-to-government relationships; cooperation between countries having malaria as a common problem; and control of other vector-borne diseases.

The prospects for control and eventual eradication are in the hands of policymakers, health administrators and malaria specialists. Thirty years of lessons provide world leaders, policymakers, project designers,

program managers, researchers, technicians and workers with a wealth of warnings and guidance.

"Realism," implores Tibor Lepes, retired chief of WHO's Malaria Action Program, "must prevail over emotions and malaria and its control should be considered within the overall health priorities and within the overall possibilities of countries to support such programs until the endpoint, i.e., malaria eradication, is achieved" (Lepes 1981). Furthermore, recognizing that malaria has an "almost infinite ability to evade whatever man throws against it," as noted by Robert O. Pick of the Walter Reed Army Institute of Research in Washington, D.C., malaria experts have developed more realistic biological and administrative approaches to antimalaria programs, providing optimism that new success stories will have a long-term effect.

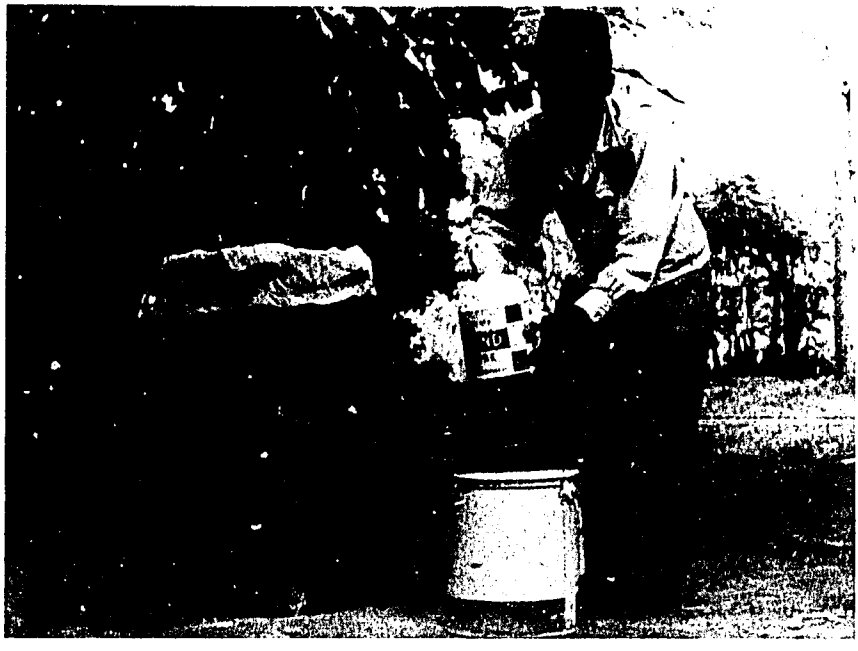
AID has invested considerable time and money in the search for a vaccine. Is it worth it?

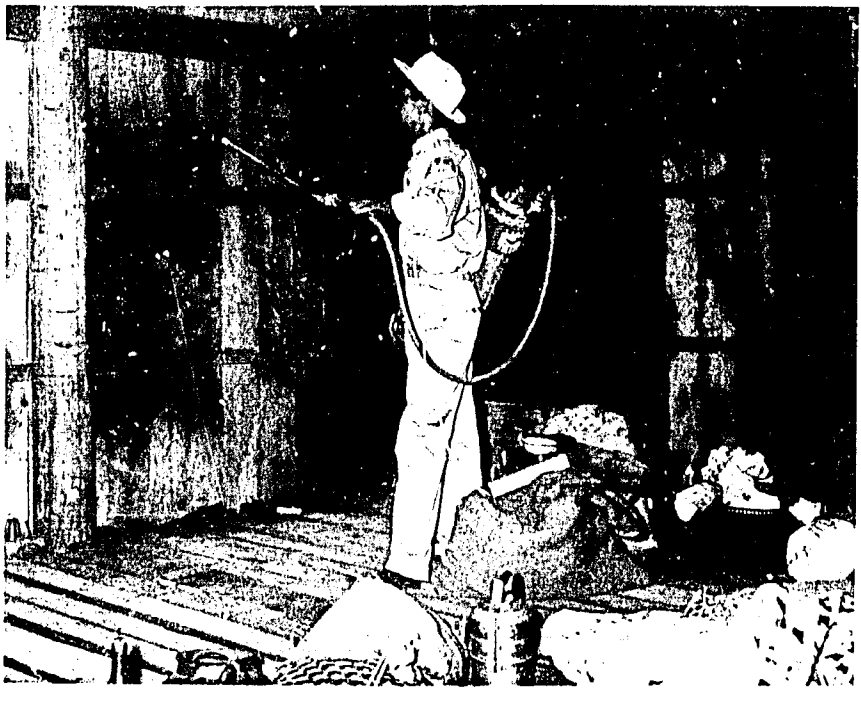
Yes, say many scientists who've served on the Agency's Research Advisory Committees in the last dozen years.

Yes, say scientists and experts all over the world—many who were most vocal about their reservations and doubts a dozen years ago.

At the same time, nearly everyone involved agrees that future malaria control strategy must use *all* available tools. Specific answers to individual areas based on a clear definition of the specific problems in those areas must be provided. Experience, say the experts, plus realistic control activities, taking into account and utilizing scientific progress, make for a good prognosis.

The United States continues to participate in worldwide malaria control activities. The Agency for International Development has endeavored to formulate an effective policy to meet the malaria challenge, not just of today but tomorrow.



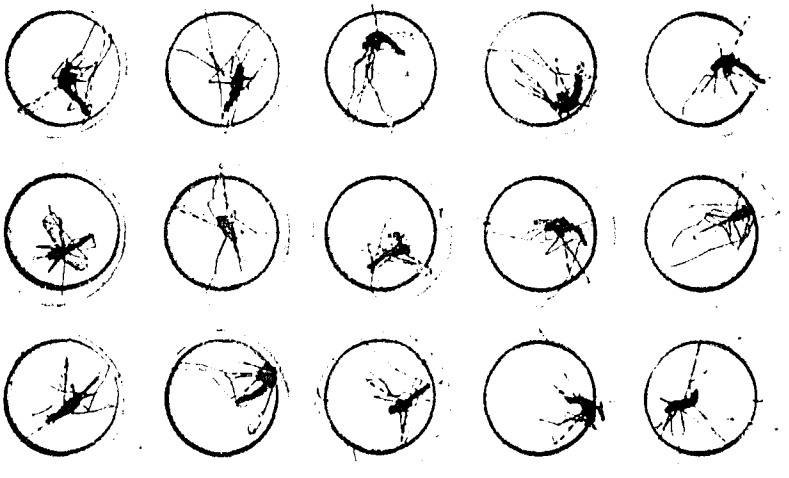


The late Haile Selassie of Ethiopia was a strong supporter of his country's antimalaria program in the 1960s. (Photo courtesy of D.R. Johnson)

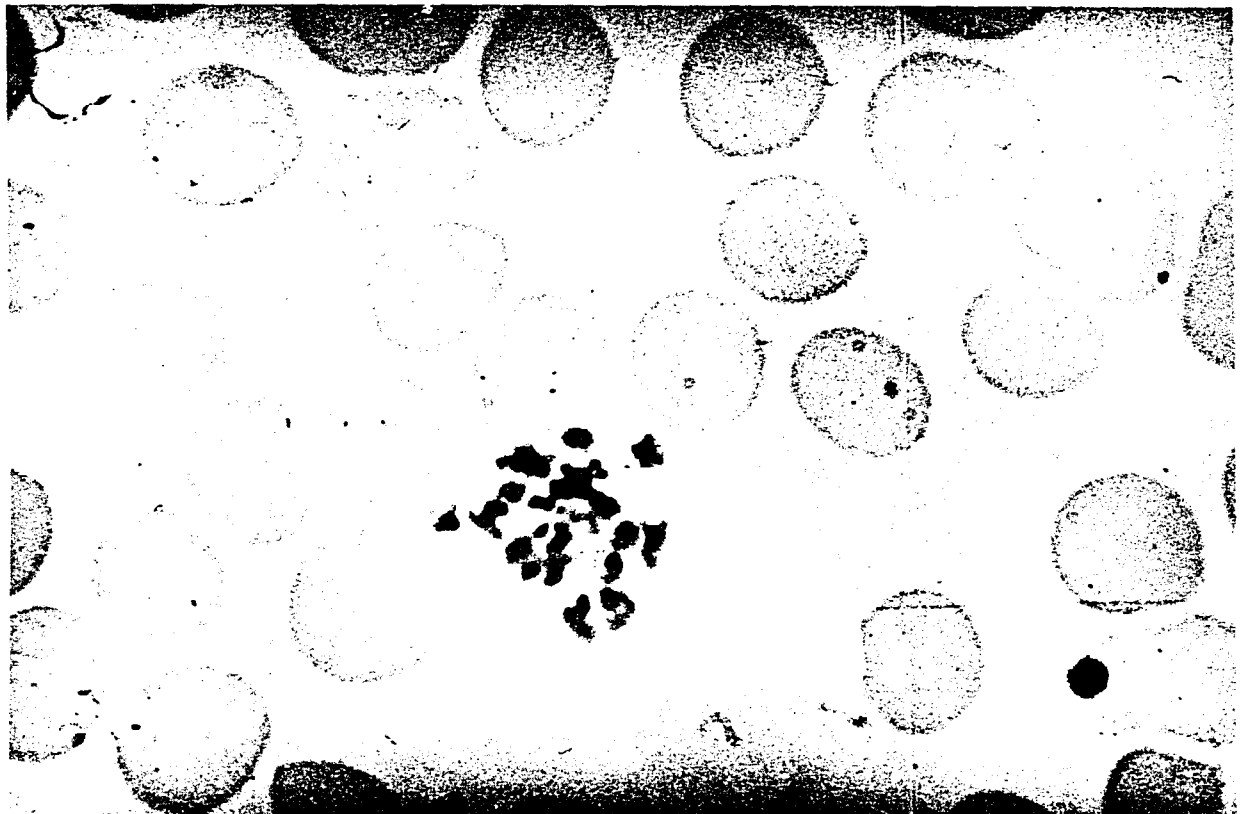
Facing page: *The U.S. government, through the Agency for International Development and its predecessors, supplied large amounts of commodities and equipment to antimalaria programs in developing countries.* Top: *DDT 75% wettable powder is transferred from a 100-pound drum into mixing cans.* Bottom: *A sprayer marked with the insignia of the U.S. International Cooperation Administration, an AID predecessor, is used to spray a home with DDT. (AID photos)*

Drugs help control the spread of malaria. But new drugs must be found as resistance continues to develop to existing ones. (AID photo)

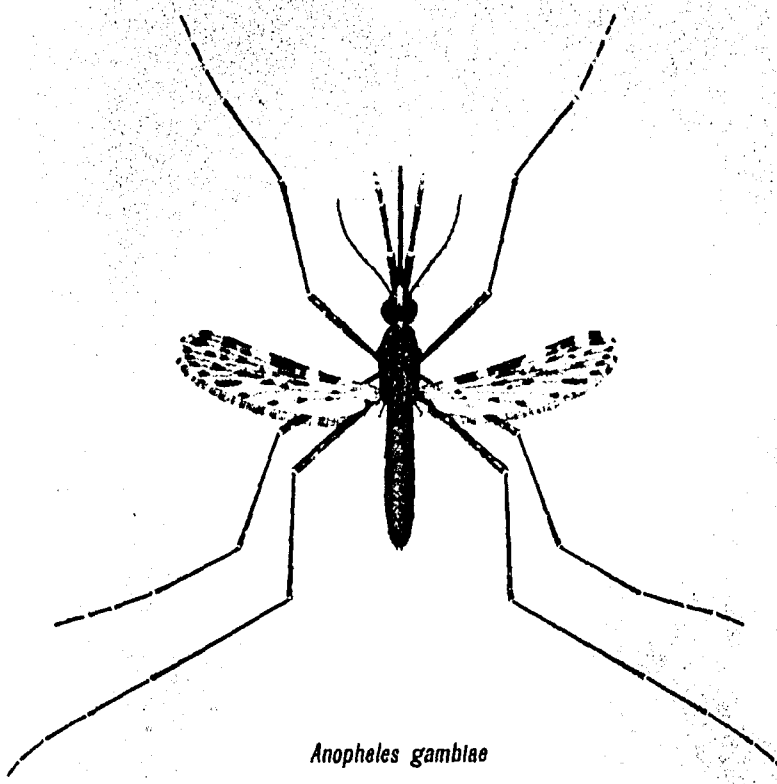
The AID malaria vaccine research network includes the New York University Medical Center. Studying electrophoretic gels for clues about the malaria parasite are (left to right) *Drs. Ruth S. Nussenzweig, Fidel Zavala, Victor H. Nussenzweig, Joan Ellis and Alan H. Cochrane. (Photo courtesy of Al Geise/The NYU Physician, New York University Medical Center)*



The study of dead mosquitoes in the wells of a microtiter plate has replaced the time-consuming microscopic examination of individual mosquitoes. (Photo courtesy of Al Geise/The NYU Physician, New York University Medical Center)



The host develops symptoms when parasites rupture blood cells. (Photo courtesy of The NYU Physician, New York University Medical Center)



Anopheles gambiae, principal vector of malaria in Africa. (Photo courtesy of Centers for Disease Control, Atlanta, Georgia)

Appendix A

Malaria Parasites of Humans

Plasmodium falciparum—Malignant Tertian Malaria. This, the most deadly of the human malarias, is confined to the tropics and subtropics. In Africa it is responsible for more deaths than any other single parasitic disease. The pre-erythrocytic cycle usually lasts 5½ days, each liver schizont releasing about 30,000 merozoites. During the last 12 hours of the 48-hour asexual erythrocytic cycle the parasitized red cells sequester in capillaries of internal organs, attaching through 'knobs' on the red cell. The crescent-shaped gametocytes are mature in 10 to 12 days. Most patients surviving the acute phase of the infection, when 25% or more of red cells may be infected, remain infected for 7 to 9 months.

Plasmodium vivax—Benign Tertian Malaria. Although once common in temperate countries, such as southern England, *P. vivax* is now found only in the subtropics. The pre-erythrocytic cycle lasts 8 days, each schizont producing about 10,000 merozoites. Some sporozoites on entering the liver become dormant, as hypnozoites, which resume their development months later to cause true relapses. Merozoites preferentially invade young red cells with parasitaemias rarely exceeding 1%. The asexual erythrocytic cycle lasts 48 hours. Gametocytes take 4 days to become infective to the mosquito. Relapses in *P. vivax* infections are common.

Plasmodium malariae—Quartan Malaria. Eradicated from temperate countries, *P. malariae* is now relatively uncommon. The pre-erythrocytic cycle takes 15 days, each mature liver schizont containing approximately 15,000 merozoites. Merozoites are said to prefer mature red cells although parasitaemias usually remain less than 1%. In red cells the asexual cycle is complete in 72 hours. After the primary attack the infection may become chronic and persists for more than 50 years.

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Plasmodium ovale. *P. ovale* is rare, most cases occurring in West Africa. The liver cycle lasts 9 days and each liver schizont produces about 15,000 merozoites. The asexual erythrocytic cycles takes about 48 hours. The patent parasitaemias always remain low. In blood smears the infected cells are oval rather than round and hence the specific name *ovale*.

Source: Reprinted by permission from R.S. Phillips: *Malaria*, Studies in Biology, published by Edward Arnold (Publishers) Ltd., London and Baltimore (1983).

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Appendix B

Role of AID Offices Other than Office of Health in Malaria Programs

The Office of Health in the Bureau for Science and Technology and the Health, Nutrition and Population Offices in the four regional bureaus have primary responsibility for backstopping and supporting AID-assisted country programs.

The Africa Bureau, for example, is funding a radioimmunoassay against the sporozoite stage of malaria, conducting field tests in The Gambia. The Near East Bureau has an agreement between Israel, Egypt and the United States to study arthropod-borne diseases with emphasis on malaria.

Another Agency office that plays an important part in U.S. antimalaria efforts is the Office of the Science Advisor (SCI), an important AID funding source for innovative disease research projects in the United States and in developing countries. The Office annually screens as many as 500 proposals, some of which are related to malaria biotechnology and immunology and to vector control.

The National Academy of Sciences (NAS), with funding from the SCI-managed Program of Scientific and Technological Cooperation (PSTC), has a research program on Biological Control of Mosquito Vectors, including malaria vectors. An explicit objective of the program is to develop a worldwide network of field researchers. As of mid-1984, 13 research projects totaling $1.5 million had been approved. It is likely that about another $1 million of grants will be added to the program, which is funded through 1988. The grants are to institutions in developing countries to fund research in those countries.

The majority of the projects deal with malaria. A common theme is the study of mosquitoes using biochemical information to distinguish different varieties. Such work is being funded in Colombia, Malaysia, Thailand and Uganda. Historically, most studies of mosquitoes were based on morphological characteristics for identification. However, recent work has demonstrated that some groups of morphologically indistinguishable mosquitoes include several different species, and that the species are behaviorally and biochemically distinct. This

raises the possibility that the confusion between species has resulted in squandering control resources on sibling species that are not serious public health threats, while the species most incriminated in the transmission of the disease breeds in relative safety. Field studies to reaffirm or challenge the belief that groups of incriminated mosquitoes are homogeneous is the first order of business. If more careful identification of vectors is required for field control programs, the development of DNA probes and other biochemical techniques for rapid and accurate identification of mosquitoes may greatly simplify field programs.

Two other projects, in Guatemala and Kenya, are investigating plant-mosquito interaction and the effect of plant chemicals on mosquitoes, respectively. If planting specific water plants or if using simple plant extracts instead of manufactured chemical pesticides were effective, such approaches might bring down the cost of vector control programs, or bring down the costs of imported inputs to such programs.

Other projects deal with more general field studies in relatively understudied ecolological situations. A project in Senegal, for example, is studying the ecology of malaria vectors in a zone that is being improved agriculturally through desalinization. A second project, in Sri Lanka, focuses on the impact of agricultural development (and urbanization) on malaria vectors. Some experts note that land improvement efforts involved in agricultural modernization sometimes also improve the land from the point of view of the mosquito. Detailed studies seldom have been carried out, however, and there are few guidelines for agricultural engineers for approaches to agricultural-sound water management that also are sound for malaria control.

An NAS project in Mexico deals with the identification of pathogens of anopheline mosquitoes. Four similar projects are funded directly by AID's Office of the Science Advisor. One of the projects is run by Dr. Joel Margolit of Ben Gurion University (Israel). Dr. Margolit discovered *Bacillus thuringiensis israelensis* (BTI), a bacillus found in the Israeli desert that produces a toxin fatal to mosquito larvae and to many other insects. The toxin also can be produced through *in vitro* culture of BTI and applied as a chemical insecticide. Dr. Margolit and colleagues at Harvard and Hebrew Universities are studying the chemical and pathological processes involved in the action of BTI. Other researchers in Thailand and Florida are applying novel biotechnological approaches to improve malaria control through the use of insect pathogens.

In a comparative field trial, Dr. Milan Trpis is studying the effect of BTI and the use of three species of mosquito-larvae eating fish to control malaria vectors. The work, being done in Liberia under a grant to Johns Hopkins University, will test the four control measures separately and in combination in rice fields. Ideally, Dr. Trpis will develop a strategy by which the habitat provided by the flooded rice fields will not be attractive to malaria vectors, and the fish used in the control will be an edible source of protein.

Based on advice from an SCI-funded National Academy of Sciences workshop on the applications of biotechnology to development and other experts, the Office of the Science Advisor decided to concentrate $1 million annually on

biotechnology and immunology in animal systems (including humans). In collaboration with AID's Office of Health, several projects complementary to the malaria vaccine development effort have been funded to compare two *in vitro* techniques for the cultivation of *P. falciparum* to increase the supply of parasites for research. Dr. Michael Stek of the United States Navy has been funded to work with Zambian colleagues to develop and test sensitive new assays to qualify and quantify circulating antigens to malaria. Researchers in Papua New Guinea have been funded to carry out research preparatory to the availability of malaria vaccines.

PSTC also funds work applying the techniques developed in malaria research to the closely related disease of cattle, babesiosis. University of Missouri researchers are studying populations of clones of individual parasites to try to identify those that do not produce symptoms of the disease, but that induce immunity against the pathenogenic varieties.

AID generally has not invested in research on new drugs to fight malaria, leaving that field to other agencies and the private sector. However, the Office of the Science Advisor recently initiated some particularly innovative efforts in this area. For example, it is funding researchers at Rutgers University to use the new *in vitro* techniques for culturing sporozoites to develop and use an assay to evaluate the effect of different therapeutic agents on malaria.

Dr. Gary Simpson of the Lovelace Medical Foundation (Albuquerque, New Mexico) is using *in vitro* cultures of *P. falciparum* and sophisticated chemical instrumentation to study the surface processes in drug-sensitive and drug-resistant organisms. Chloroquine and quinine affect *P. falciparum* through a process that involves attachment to the surface protein. Researchers recognize that such chemical reactions involve the specific forms and chemical properties of the drug and of the specific receptor protein. It is likely that drug resistance involves the natural selection for plasmodia that have surface proteins that do not bind to the drug, that do not allow the toxic transfer from the drug to the *Plasmodium* or that secrete other substances that interfere with the processes. If successful, the Lovelace work may lead to the more efficient development of new drugs, or to the development of adjuvants to increase or restore the efficiency of existing drugs.

Appendix C

Status of Antimalarial Drugs

Chloroquine and Amodiaquine (4-Aminoquinolines). The therapeutic value of this group of drugs is seriously reduced in areas with chloroquine-resistant *P. falciparum* and no benefit can be derived from the standard 4-aminoquinolines in the hard-core areas of *P. falciparum*. However, *P. vivax*, *P. malariae* and *P. ovale* still respond normally to these drugs.

Proguanil and Pyrimethamine (DHFR Inhibitors). Widespread resistance of *P. falciparum* and *P. vivax* renders the prophylactic use of these drugs alone obsolete.

Sulfonamides (DHPS Inhibitors). These are not used alone but in combination with pyrimethamine (potentiating synergism) for the treatment of chloroquine-resistant falciparum malaria as drugs of the second line. Sulfonamides matching the half-life of pyrimethamine (e.g., sulfadoxine) promote drug resistance probably less than ill-matched sulfonamides. These combinations should not be used in areas with chloroquine-sensitive *P. falciparum*. They are not adequately effective to pyrimethamine-resistant *P. vivax*. Resistance of *P. falciparum* to sulfonamide/pyrimethamine combinations is already widespread on the Indochina Peninsula and in Brazil.

Sulfones (DHPS Inhibitors). These are not used alone but in combination with pyrimethamine in malaria prophylaxis as drugs of the second line. However, the half-life of the available sulfones does not match that of pyrimethamine. Their use has similar limitations to those of the sulfonamide/pyrimethamine combinations.

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Quinine. It is essential as a first-line drug in severe and complicated manifestations of falciparum malaria (to be followed by effective radical treatment), and as a third-line drug in infections with multiresistant *P. falciparum* (here usually in association with or followed by tetracycline for radical cure). Quinine resistance is still quite rare.

Tetracyclines. These are not used alone as antimalarials, but in association with or following a course of quinine. They are only for treatment purposes, not for prophylaxis.

Primaquine (8-Aminoquinoline). This is an important tissue schizontocidal drug for the radical cure (antirelapse treatment) of *P. vivax* and *P. ovale.* It is also increasingly important as a gametocytocidal drug against *P. falciparum,* especially in areas with chloroquine or multidrug resistance. There is no indication of primaquine resistance as yet.

Advanced Candidate Antimalarials. Mefloquine (quinoline methanol) and derivatives of Qinghaosu (sesquiterpene lactones) are the most advanced blood schizontocidal candidate drugs for the treatment of chloroquine and mutidrug-resistant falciparum malaria. Their introduction into wider use may be expected within a few years. Other advanced candidate drugs are pyronaridine (aminoacridine) and phenanthrene methanols. Various antibodies—already used in the treatment of other infections—may qualify also as alternative antimalarial drugs.

Source: Wernsdorfer, Werner H. Drug resistance, current studies and future prospects. Scand. J. Infect. Dis., Supp. 35, 29–30; 1982.

Appendix D

WHO's Role in Global Malaria Efforts

Malaria has occupied a dominant place in the World Health Organization's list of health priorities since the organization was established following World War II. WHO seeks to coordinate the policies of organizations supporting global antimalaria efforts, such as AID, the U.S. Public Health Service and UNICEF; promotes research; and provides technical assistance and training to requesting countries.

WHO programs are guided by the World Health Assembly (WHA) and its Executive Board. The first WHA (1948), following recommendations of the WHO Expert Committee on Malaria of the Interim Commission, sent demonstration teams to countries that requested assistance setting up malaria control programs. Malaria has featured in all subsequent assemblies. The eighth WHA meeting (1955) launched the global malaria eradication program that focused world attention on the disease.

Today, the Special Program for Research and Training in Tropical Disease, the Malaria Action Program and the Vector Biology and Control Program are the WHO activities most specifically concerned with malaria and other vector-borne diseases. The Special Program, cosponsored with the United Nations Development Program and the World Bank, strengthens national capability to carry out research related to the six major tropical disases responsible for high morbidity and mortality in developing countries. It receives financial support from more than 30 donors, most prominently the United States. In 1982, AID contributed $5 million to the program. Other WHO programs, such as Primary Health Care and Tropical Disease Research, also contribute to global antimalaria efforts.

U.S. officials serving on WHO working groups and special committees influence WHO policy and programs, promote cooperation and encourage information exchange. United States malaria assistance is coordinated with WHO

through joint planning and assignment of technical assistance, field evaluations and research and training, thus avoiding duplication and overlap with efforts by other donor countries and organizations. From 1957 to 1967, WHO provided more than $87 million in international assistance to global malaria eradication efforts.

Although the Malaria Action Program, headquartered in Geneva, Switzerland, provides worldwide policy and program guidance, WHO malaria programs are carried out through the regional offices (ROs) in the Americas (Pan American Health Organization), the Eastern Mediterranean (EMRO), Southeast Asia (SEARO), the Western Pacific (WPRO) and Africa (AFRO). The regional offices, in turn, work with requesting countries on specific malaria problems, assigning country advisers or intercountry teams, or both. The regions vary considerably in their approach. For example, AFRO countries carry out efforts through existing and developing health infrastructure. In the Southeast Asia region, countries have developed effective vertical national malaria control services.

WHO's Seventh General Program of Work (1984–1989) calls for "the attainment of specific targets by national antimalarial programs and for the development of WHO-supportive actions in technical collaboration, training, research and the exchange and dissemination of technology and operational information."

85

Appendix E

AID-Supported Vector Control Programs

Centers for Disease Control (CDC) Participating Agency Service Agreement (PASA), 1955–1966. Research at the Technical Development Laboratory in Savannah, Georgia, sought and tested alternative insecticides as replacements for DDT where the mosquito vector had developed DDT resistance. The project responded to the needs of the global malaria program as identified in the field and made many invaluable contributions through the development of improved specifications for insecticides, packaging for insecticides, compression sprayers and nozzle tips, and provided quality control testing for individual country programs.

Worldwide Malaria Eradication Research, CDC PASA, 1966–1972. This agreement expanded the earlier one, with the additional objectives of developing and testing alternative methods of mosquito vector control that involved a wide range of biological and biochemical investigations.

Central America Research Station, CDC PASA, 1966–1972. A malaria research center was set up in a tropical area (El Salvador) to address a variety of special problems, define the problems of malaria eradication and develop practical solutions through new, improved or combined methods.

While the primary objective of the project was not fully achieved, numerous baseline studies on malaria and the biology and ecology of the vector were conducted. Collected data supported later research. The project also collaborated with the U.S. Department of Agriculture (USDA) and provided epidemiological services for the Alternative Malaria Control Methods project conducted by the USDA Laboratory for Research on Insects Affecting Man and Animals (Gainesville, Florida).

Thailand Malaria Research Unit, CDC PASA, 1967–1972. A malaria operational research unit was established in Thailand to determine the causes of persistent transmission of malaria and to develop methods that would interrupt transmission.

Serologic Diagnosis of Malaria, CDC PASA, 1968–1972. The objective was to develop simple, rapid and accurate methods for the serologic diagnosis of malaria. Following the project's completion, CDC field-tested the methods in eight countries in Africa, Asia and Central and South America.

Intensive Review of Malaria Research, June–July 1971. AID conducted an intensive review of its malaria-related research activities. Each project was reviewed against AID malaria policy and prospects of productivity and in terms of organization, facilities and competence to achieve objectives. Activities were appraised as essential, marginal or additive in terms of achieving the objectives as defined in the project agreement. The review team was charged with establishing relative priorities of each project in terms of the prospects of achieving AID objectives.

The team based its review on performance and accomplishments, facilities and staff and the continuing responsive relationship to WHO and country malaria programs. There was unanimous agreement that the prospects for future contributions to the worldwide malaria eradication effort was excellent. Continued support was recommended.

The team considered overall project accomplishments to be largely academic and suggested a more practical field orientation. To achieve this, it was recommended that all AID-supported CDC malaria research be combined as a single project and that a malaria research planning board with membership consisting of AID, WHO, PAHO, CDC, Walter Reed Army Institute of Research and other outside experts be established.

The team's third area of review was on the serologic diagnosis of malaria. The members concluded that such methods would supplement but not replace conventional methods, and would be of particular value in delineating malarious areas and monitoring surveillance in the maintenance phase. The team recommended completing the project, but felt that further epidemiological evaluations should be done on a collaborative basis in the field.

After reviewing the University of New Mexico's malaria immunity and vaccine work, the team reported it was impressed with early results. But because immediate contributions were not in the offing, the team recommended continuation at a lower funding level.

AID's Office of Health agreed with all but the last of the team's recommendations. The Office felt that because of the potential for a breakthrough in technology, the Malaria Immunity and Vaccination Project deserved a higher priority. An office memo stated that the project, "admittedly a long shot," has "a much greater payoff potential than any of the others in terms of revolutionizing the approach to malaria control and eradication." The project was elevated to priority number one.

The upshot of the review was that the vaccine research project was continued, albeit at a lower level; the Thailand unit was closed; CDC's serologic diagnosis was funded through completion of the laboratory phase; and CDC's Technical Development Laboratory and Central America Malaria Research Station were funded at a reduced level while other funding sources were found with CDC.

CDC informed AID that it was prepared to take over funding of the two projects. However, CDC experienced budget problems the next year, and the laboratory at Savannah was moved to Atlanta with a greatly reduced staff. The El Salvador station was converted to a general disease research facility that deemphasized malaria.

By June 1972, AID annual support of malaria research was reduced from five projects totaling $1.7 million to one—the malaria vaccine project—at $428,000. Several factors were responsible for the change in emphasis, but the foremost one was the overall reduction of the AID budget and the subsequent reordering of development priorities to make the most of limited resources. The $1.7 million malaria research program represented nearly 20% of the maximum legislative authorization for all AID research, with no reassurance that the full authorization of $9 million would be available. There was substantial pressure on the Office of Health to find other sources of funding, or else to reduce or eliminate projects.

Panel on Perspectives in Mosquito-control Methods Suitable for Developing Countries, 1972–1973. The National Academy of Sciences with funding from AID's former Bureau for Technical Assistance, organized a panel charged with:

deciding whether there are worthwhile alternatives to conventional pesticides for mosquito control in developing countries;

selecting approaches that seem particularly promising;

evaluating the state of knowledge and potential of selected approaches;

recommending areas in which further research and development funding could have particular impact.

The panel's report, issued in March 1973, was entitled, "Mosquito Control—Some Perspective for Developing Countries." The title may have been inappropriate in that of the nine methods discussed, only one was suitable for operational use; the other eight were in various stages of research and development. The report stimulated and guided mosquito control research along lines that could eventually lead to practical application in operational mosquito control programs.

Stage VI and VII Testing of Fenitrothion, AID Grant to WHO, 1973–1976. The grant was to complete testing of fenitrothion as an alternative to DDT. The test site was Kisumu, Kenya. WHO had supported preliminary testing through stage five but requested AID assistance to carry the final entomological and epidemiological evaluations to completion. The project paved the way for use of fenitrothion in many AID-supported malaria programs.

Development of Environmentally Acceptable Replacements for DDT, Contract with University of Illinois and Grant to WHO, 1975. The activity started in 1972 as a small (under $25,000), one-year project for laboratory and field testing of biodegradable analogues of DDT already synthesized at the University of Illinois. Several analogues tested as very effective in the laboratory and in simulated field huts proved ineffective when tested in village huts in tropical countries.

In view of the need for field testing of alternative insecticides under tropical conditions and the necessity for approval under the WHO Stage Testing System, the second phase (1975–1983) of the project was carried out under a new project by the WHO Vector and Rodent Control Research Unit in Indonesia. This project was developed in response to requests from WHO and the Indonesia government with the immediate objective of finding an alternative to DDT in Central and East Java, where the mosquito vector, *A. aconitus*, had developed resistance to DDT.

The project more than paid for its cost in its first year by demonstrating that malathion was not effective against the vector whereas fenitrothion was, thus avoiding the possible waste of millions of dollars on the wrong insecticide. Field tests of several of the biodegradable analogues of DDT developed by the University of Illinois had discouraging results. The project was expanded to cover testing of other insecticides, different application techniques and other methods, such as biological control.

During the eight-year life of the second-phase project, the Research Sub-Unit at Semarang in Indonesia made numerous contributions to malaria programs in tropical countries, including the testing of new insecticides (the team was the only one in the world with the competence and experience to conduct Stage IV and V trials of new insecticides); innovative use of insecticide and spray equipment; and progress in developing supplementary and alternative methods of malaria control.

Vector-borne Disease Consultant Workshop, 1975. The workshop identified malaria in Africa and control of the *A. gambiae* as a high priority, and suggested field visits so recommendations for demonstration programs in a self-help attack on vector-borne diseases could be made. Consultants urged that AID support additional research on the vector, seek innovative methods for vector control, study the effectiveness of a combination of self-help methods for malaria control, and conduct operational research on malaria control methods in urban areas. AID, the consultants also suggested, should consider the same elements in other areas of Africa, specifically identifying Tanzania and French-speaking countries.

Literature Review, National Institutes of Health PASA, 1978. G. G. Blevins and R. J. Davis published "Malaria Vector Control, A Review," a review of malaria vector control methods, including those being developed.

Low-cost, Self-help Village-level Malaria Control Methods, 1978. AID's Office

of Health proposed a low-cost, self-help project for the testing of various methods of malaria control on a local level. Although considerable interest was expressed in the concept, funds were not made available.

Alternative Malaria Control Methods, U.S. Department of Agriculture PASA, 1978–1979. The overall objective of the project was to develop alternative malaria control methods that are not dependent on pesticides. Specific objectives were to demonstrate the ability to induce high levels of sterility and population reduction of *A. albimanus* in El Salvador by releasing sterile males, to determine the competitiveness of the released insects in relation to the existing population and the effect of migration on total population control, to test various combinations of control methods to reduce mosquito populations prior to the release of sterile male mosquitoes, and to evaluate, in collaboration with CDC, the effect of the reduced mosquito population on the incidence of malaria.

The project developed operational approaches in the field testing of the results of many years of USDA research and provided considerable valuable scientific information for future use. In reference to the specific objectives, the studies revealed a high level of competitiveness in the genetically sexed strains of *A. albimanus*. Mosquito population reductions were observed in the experimental area, but migration of fertile insects from outside the experimental zone prevented complete population control. Indications were that results would be better with a larger test area or one with more effective natural geographic barriers.

Comprehensive Vector Control, 1979. Following the Asia Malaria Strategy Study and a renewed concern over the resurgence of malaria, the Health Office proposed a "Comprehensive Vector Control Project." The project would integrate established vector control methodologies, such as source reduction, water management, larviciding and adulticiding with new approaches in biological, genetic and chemical control that would be environmentally stable and reduce dependence on residual insecticides. Highly acclaimed by reviewers and strongly endorsed by the technical offices of AID's three regional bureaus having countries with serious malaria problems, the project finally was included in the fiscal 1982 budget submission, but still has not been implemented.

Vector-control Research Workshop, U.S. Department of Agriculture PASA, 1982. A state-of-the-art workshop to set the stage for the proposed Comprehensive Vector Control Program was held in Gainesville, Florida, just as the AID-sponsored National Academy of Sciences Workshop in Problems Related to the Development of an Antimalaria Vaccine launched the AID-expanded Malaria Immunity and Vaccination Research Program. The participants made recommendations and established priorities for the research needed in each of the key aspects of vector control including insecticides, source reduction, water and weed management, surveillance, attractants and repellents, environmental problems, genetic control and sterile insect techniques, biological control, population dynamics and computer simulations.

Funds for the program were never obligated and none of the recommendations of the several consultant teams or the workshop has ever been carried out. Considering the increasing incidence of malaria worldwide and the compounding of technical problems, the need for research on vector biology and control is greater than ever. The lack of support can be attributed, at least in part, to inadquate appreciation of the difficulties and incomplete understanding of WHO's Reexamination of the Global Strategy for Malaria Eradication and the 1970 AID Policy for Malaria Eradication Multilateralization of Technical Services, as well as the erroneous impression that a malaria vaccine would soon be ready and that it would obviate the need to improve or replace control methods.

Appendix F

AID Malaria Vaccine Research Network

Project Institution	*Project Objectives*
1. Bio-Medical Research Institute 1211 Parklawn Drive Rockville, MD 20852 Investigator: Dr. Mike Hollingdale	To achieve the full *in vitro* cycle of development of the exoerythrocytic stage of *P. vivax* and *P. falciparum* in suitable culture systems and the molecular characterization of the human hepatocyte receptor for plasmodial sporozoites.
2. Bio-Medical Research Institute 1211 Parklawn Drive Rockville, MD 20852 Investigator: Dr. Werner Zolg	To take a 10-step approach to the development of an effective red blood cell (merozoites) specific malaria vaccine using DNA techniques (genetic engineering).
3. Case Western University Cleveland, OH 44106 Investigator: Dr. Masamichi Aikawa	(a) To consider the causes and effects of renal syndrome on *Aotus* monkeys; (b) to characterize protective antigens of human malarias, especially *P. falciparum* and *P. vivax*, against the sporozoite stage.
4. University of Hawaii, School of Medicine 3675 Kilanea Avenue Honolulu, HI 96816 Investigator: Dr. Wassim Siddiqui	(a) To produce and enrich segmenters/merozoites of *in vitro* cultured *P. falciparum*; (b) to purify *in vitro* cultured *P. falciparum* segmenter/merozoite antigens; (c) to characterize *P. falciparum* merozoite antigen obtained through purified saponin treatment and its comparison with that of natural-released merozoites; (d) to do vaccination studies in *Aotus trivirgatus griseimembra* using a standardized *P. falciparum* antigen derived from long-term *in vitro* cultured *P. falciparum*.

5. Uniformed Services University of the Health Sciences Department of Microbiology 4301 Jones Bridge Road Bethesda, MD 20014 Investigator: Dr. Susan Langreth	(a) To locate the surface and the internal malaria antigens to which immune animals produce antibodies; (b) to characterize those antigenic components structurally, cytochemically and immunologically; (c) to develop assays to assess purity of blood-stage antigen preparations and to screen for interstrain antigenic differences and variations *in vitro*; (d) to determine the structure and function of the knobs (alterations on the infected erthrocyte surface produced by *P. falciparum* infection).
6. University of Missouri Department of Veterinary Microbiology Columbia, MO 65211 Investigator: Dr. Theodore Green	(a) To identify, isolate and characterize merozoite surface coat immunogens; (b) to test the immunosensitivity of candidate immunogens *in vitro* and *in vivo*; (c) to assess vaccination procedures and/or adjuvants with immunogenic antigen, including safety /toxicity testing in *Aotus* and rabbits; (d) to establish baseline prevaccination reference data for *Aotus* subjects, including interval of activity data.
7. University of Illinois 225 Veterinary Medicine Annex 1101 West Peabody Drive Investigator: Dr. Miodrag Ristic	Research on the intra-erythrocytic protozoan agent, *P. falciparum*, to develop a vaccine based on soluble antigens released by the parasite during infection.
8. New York University Medical Center Department of Microbiology 550 First Avenue New York, NY 10016 Investigator: Dr. Ruth Nussenzweig	(a) To immunize with purified antigens of *P. berghei* sporozoites; (b) to characterize and isolate protective antigens of *P. knowlesi* sporozoites; (c) to characterize plasmodial antigens of sporozoites from different malaria species including *P. berghei*, *P. knowlesi*, *P. cynomologi*, *P. falciparum* and *P. vivax*; (d) to do sero-epidemiological investigations of sporozoite-induced immunity in Thailand.
9. Michigan State University Department of Microbiology East Lansing, MI 48824 Investigator: Dr. James B. Jensen	(a) To identify, isolate and characterize "naturally elaborate" soluble exoantigens in the exhausted culture medium used to grow *P. falciparum*; (b) to identify and characterize soluble exoantigens from cultured *P. falciparum* that may play a role in protection against malaria and thus may be a vaccine candidate; (c) to use electron microscopic immunolabeling techniques, determine the subcellular position of those antigens that show promise as potential vaccine candidates.
10. Scripps Clinic and Research Foundation 10666 N. Torrey Pines Road La Jolla, CA 92037 Investigator: Dr. Robert Reese	To identify, isolate and begin chemical characterization of one or more macromolecular components of the asexual erythrocytic forms of *P. falciparum*, which can be used to induce protective immunity in owl monkeys.

11. Centers for Disease Control
Infectious Disease Center
Atlanta, GA 30333
Investigator: Dr. Kent Campbell

(a) To store, produce and partially characterize selected isolates of *P. falciparum* and their derived clones, which would be distributed upon request to investigators within the AID malaria vaccine network; (b) to prepare various MABs against human malarias for use of AID network laboratories; (c) to determine the susceptibility of *Saimiri sciureus* monkeys to *P. falciparum*; (d) to determine antigenic characterization of geographically diverse strains of *P. falciparum*; (e) to determine the susceptibility of different types of *Aotus* monkey to infection with different strains and species of plasmodium.

12. American Institute for Biological Sciences
1401 Wilson Boulevard, Suite 701
Arlington, VA 22209
Program director: Dorothy Jordan

(a) To develop and manage models for network implementation, review and evaluation; (b) to develop models for *Aotus* and related primates for biochemical/husbandry parameters and the standardization-centralization of data analysis; (c) to develop and manage guidelines for FDA-mandated data and laboratory management; (d) to conduct research on the various species of *Aotus* to include distribution of range in South America, kariotyping and testing their applicability as a human malaria model; (e) to develop and manage patent/legal support of network research program; (f) to conduct research at Institute Nacional de Salud, Bogota (Dr. Carlos Espinal): identify protective antigen(s) of *P. falciparum* merozoites by using serum from *Aotus* monkeys in which varying degrees of immunity have been induced by different immunication schedules, and serum from infected patients; evaluate putative merozoite immunogens in *Aotus*; and breed *Aotus* monkeys.

13. Battelle Memorial Institute
Pacific Northwest Laboratories
P.O. Box 999
Richland, WA 99352
Investigator: Dr. Richard Weller

(a) To modify data entry software for Systematized Nomenclature of Pathology (SNOP), Systematized Nomenclature of Pathology (SNOVET) and/or related programs to primates within AID's program; (b) to coordinate exchanges of primate data, analyze all data and provide statistical backstop for all aspects of primate data required by the U.S. Food and Drug Administration.

Glossary

adjuvant In immunology, a substance that, when mixed with an antigen, enhances antigenicity and gives a superior immune response.

antigen A substance, usually protein in nature, introduced into the body to stimulate the body's immune system to produce antibodies.

Annual Parasite Incidence (API) The proportion of malaria cases detected on an annual basis in relation to a unit of population (usually per 1,000).

Anopheles Genus (or subgenus) of mosquito of the subfamily Anophelinae, which includes all vectors of human malaria.

chemoprophylaxis The use of a chemotherapeutic agent (drug) to prevent the development or progression of a specific disease. Primary chemoprophylaxis is the prophylactic use of a drug before infection has occurred; secondary chemoprophylaxis is the prophylactic use of a drug after infection has occurred but before disease has become manifest.

chemotherapy The treatment of disease by chemical agents.

endemic Term applied to malaria when there is a constant measurable incidence both of cases and of natural transmission in an area over a succession of years. There are four levels of endemicity: hypoendemic, mesoendemic, hyperendemic and holoendemic (highest).

entomology The branch of zoology that deals with the study of insects.

epidemic Term applied to malaria when the incidence of cases (other than seasonal rises) in an area increases rapidly and markedly above its usual level or when the infection occurs in an area where it was not present before.

epidemiology The study of the various factors that determine the frequencies and distributions of disease and infectious processes.

erythrocyte Red blood cell.

erythrocytic Developing within red blood cells; applied to stages of the malaria parasite.

exoerythrocytic Outside the erythrocyte; a term applied to stages in the development of malarial parasites that takes place in tissue cells instead of in red blood cells.

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gamete Mature sexual form, male or female. In malaria parasites, gametes normally develop in the mosquito.

gametocyte The sexual stage of the malarial parasite in the blood which may produce gametes when taken into the mosquito host.

host, definitive Host in which sexual reproduction of the malaria parasite occurs. The mosquito often is described as the definitive host; invertebrate host is preferred.

host, intermediate Host in which asexual forms of the malaria parasite develops. Man often is described as the intermediate host of human malaria parasites; vertebrate host is preferred.

hybridoma technique If lymphocytes sensitized to certain antigens are fused with mouse cancer cells, the new cells (hybridomas) multiply rapidly and indefinitely, and produce an antibody targeted for the original antigen. Selecting the progeny for a single hybridoma cell, a genetically uniform colony of clones can be found. The antibody produced by this colony is known as a monoclonal antibody. Application of the hybridoma technique provided a breakthrough in the methods available for analysis of the antigenic composition of microorganisms, for rapid diagnosis and to aid in the development of vaccines. It is simple and straightforward, and can be readily developed and made available for use in developing countries.

incidence Number of cases of disease occurring during a given period in relation to the unit of population in which they occur. Not to be confused with prevalence.

in vivo In living animals.

in vitro In a test tube or other laboratory container.

malaria A disease characterized by intermittent febrile paroxysms, anemia and splenic enlargement, caused by infections with parasites, generally assigned to the genus *Plasmodium*, class *Sporozoa*.

malaria control An operation aimed at reducing the prevalence to a level at which the disease no longer is a major public health problem. The ultimate goal may be eradication of the malaria. Control campaigns are not time limited.

malaria eradication An operation aimed at ending the transmission of malaria and at eliminating the reservoir of infected cases. Eradication campaigns are limited in time and carried out until there is no resumption of transmission.

merozoite One of the young forms derived from the splitting up of the schizont in the human cycle of the malarial plasmodium. It is released into the circulating blood and attacks new erythrocytes.

monoclonal antibodies Highly specific disease-fighting molecules produced in artificially created hybrid cells. These molecules act by combining with antigens, with the combined molecules triggering the body's defense system. These antibodies also can be combined with enzymes or radioactive markers to produce laboratory markers for their antigens.

oocyst The encysted or encapsulated ookinete in the wall of a mosquito's stomach.

parasite rate The percentage of persons showing malaria parasites by blood smear examination.

paroxysm Cyclic manifestation of acute illness in malaria characterized by a rise in temperature with accompanying symptoms.

Plasmodium Generic name of the parasites of human malaria. The four species that cause malaria in humans are: falciparum (the most frequent and virulent); malariae (causes quartan malaria, which has an intermittent fever with paroxysms recurring on every fourth day); ovale (causes tertian malaria—intermittent fever with paroxysms recurring on every third day, found in the Congo and adjacent areas, tends to end in spontaneous recovery); and vivax (causes the mildest form, with paroxysms occurring every other day—although they may occur daily if there are two broods of parasite segmenting on alternate days).

prophylaxis Any method of protection from or prevention of disease.

recurrence Renewed manifestation of infection (long-term relapse) believed due to reinfection of erythrocytes from exoerythrocytic forms.

residual insecticide An insecticide which, when suitably applied on a surface, maintains insecticidal activity for considerable time either by contact or by fumigant action.

schizont Intracellular asexual form of the malaria parasite, developed either in tissue or in blood cells.

sporozoite Final stage of sporogony of *Plasmodium* in the mosquito. The infective form of the malaria parasite occurs either in a mature oocyst before its rupture or in the salivary glands of the mosquito.

stratification An analytical technique to help select the most appropriate intervention and to determine the areas where intervention is most needed. Stratification enables the identification of areas with similar epidemiological characteristics so that a single set of control tactics can be applied to similar areas. Subdivisions include drug sensitivity, insecticide susceptibility, high mortality and parasite species.

subspecies Population of organisms originally belonging to the same species but so isolated by geographical barriers from other populations of the species as to have undergone taxonomically significant genetic divergence.

vector From the Latin, "one who carries." Any species of mosquitoes in which the *Plasmodium* completes its sexual cycle in nature and is thus able to transmit the disease.

vector-borne disease A disease that cannot be directly transmitted from human to human but requires obligatory maturation of the disease-causing organism within the body of an intermediate host.

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107

Index

Africa, 10, 37–40, 77, 88
Agency for International Development (AID), 6; Africa Bureau, 39–40, 61–62, 77; Asia Bureau, 61–62; Columbia, Maryland, workshop, 62–67; financial contributions by, 18–19 (table), 28–37 *passim*, 77–79, 83; Latin America and Caribbean Bureau, 26, 27, 62; Near East Bureau, 40, 77; Office of the Science Advisor's Program of Scientific and Technological Cooperation, 77–79; policy statements of, 9, 27, 61–67; regional programs of, 23–40; withdrawal of services by, 9–12, 23–26, 31, 32, 33, 36, 63, 87
Algeria, 10
Alma Ata Declaration, 22, 39
American Institute for Biological Sciences, 93
Anopheles mosquito, 1–3, 6, 8, 13, 77–78. *See also* Vector control
Asia, 14, 15, 30–37, 48

Babesiosis, 79
Bangladesh, 30–31
Battelle Memorial Institute, 93
Belize, 26, 27
Bio-Medical Research Institute, 55, 91
Brazil, 26
Brown, A.W.S., 5
Bruce-Chwatt, Leonard J., 5, 10, 14, 52
Burma, 30

Caribbean, 3, 14, 23–29
Case Western University, 91
Centers for Disease Control, 15, 85–87
Chile, 23
Chin, William, 9
Chloroquine, 15–21, 26, 39, 47–48, 81
Cinchona bark, 1
Cohen, Sidney, 54
Colombia, 26, 77
Community participation, 34, 65
Cowper, Larry, 34
Cuba, 3, 23
Cyprus, 14

Diagnosis, serologic, 15, 86, 87
Dichlorodiphenyl trichloroethane (DDT), 4–7, 28; alternatives to, 7, 15, 28, 88, 89; containers for, 16–17; effectiveness of, 6–7, 13, 26; resistance to, 6, 15, 26
Dominica, 23
Dominican Republic, 27–29
Drugs, 1, 28, 81–82, 93; other than chloroquine, 1, 19, 21, 47, 48, 81–82; research on, 21–22, 47–48, 79; resistance to, 15–21, 26, 39

Ecuador, 27, 29
El Salvador, 15, 26, 85, 87, 89
Epidemiological stratification, 26, 27, 28
Eradication programs, 5–6, 14, 23, 38, 49; versus control, 7–8, 9–12; overoptimism of, 9–10, 14, 23–26, 28
Erickson, James, 56

Falciparum malaria, 13–14, 19, 21, 26, 29, 38–39, 48, 75
Farid, M.A., 7
Fenitrothion, 15, 28–29, 87, 88
Field surveillance, 28, 30, 32
Food and Drug Administration, 57
French Guiana, 26

Gametocytes, 2
Genentech, 58–59
Gorgas Institute (Panama), 55
Graham, Betty J., 38
Grassi, Giovanni Battista, 2
Greece, 14
Grenada, 23
Guadelupe, 23
Guatemala, 26, 78
Guyana, 14

Haiti, 26, 27–29
Hannah, John, 38
Haworth, J., 5
Haynes, David, 54
Health services: and malaria control, 8, 27, 38; primary health care, 22, 29, 30, 39–40, 61–63, 65
Herms, William B., 2
Hispaniola, 26, 27–29
Hollingdale, Michael, 55
Hommell, Marcell, 59
Honduras, 26
Howard, Lee M., 6, 7, 51, 54
Huff, Clay, 9–10

Incidence, of malaria: global, 3–4, 5, 10, 52; regional, 14, 26–37 *passim*
India, 14, 30, 31–32
Indonesia, 30, 32–33, 88
Insecticides, 3–7, 49; DDT, 4–7, 13, 15, 16–17, 26, 28; other than DDT, 7, 15, 28–29, 87, 88; resistance to, 6, 15, 24–25 (table), 26, 39
In vitro culture techniques, 53–55
Italy, 14

Jamaica, 23
James, Maurice T., 2
Japan, 28, 39
Jeffery, Geoffrey, 10, 14
Jensen, James, 54
Johnson, Donald R., 4

Karam, Jalil S., 30
Kenya, 38, 48, 78, 87

Latin America, 3, 14, 15, 23–27, 29, 48, 85, 87
Laveran, Alphonse, 1
League of Nations, 4
Lepes, Tibor, 67
Lovelace Medical Foundation, 79

Mcculloch, John, 1
McPherson, M. Peter, 59, 63
Madagascar, 38
Mahler, Halfdan T., 12
Malathion, 7, 15, 29, 88
Malaysia, 77
Manson, Patrick, 1
Margolit, Joel, 78
Martinique, 23
Mauritius, 14
Mefloquine, 21, 39, 48, 82
Merozoites, 3, 53–56
Mexico, 78
Michigan State University, 92
Morocco, 10
Mortality rates, 5, 13–14, 26, 36, 37, 52. *See also* Incidence
Muller, Paul, 4
Multilateralization, 9

National Institute of Health (Colombia), 55
Near East, 40, 77
Nepal, 30, 33–34
Neva, Franklin A., 64
New York University, 54–56, 58–59, 92
Nickel, Peter, 48
Nussenweig, Ruth and Victor, 55, 56

Pakistan, 30, 35–36
Panama, 3
Pan American Health Organization (PAHO), 4, 5–6, 23–27, 64
Parke-Davis Co., 54
Pharmaceutical companies, 22, 58–60
Philippines, 30, 36–37
Phillips, R.S., 7
Pick, Robert O., 22, 67
Plasmodium: life cycle of, 2–3, 6, 52–57; species of, 6, 13–14, 75–76
Plasmodium falciparum, 13–14, 19, 21, 26, 29, 38–39, 48, 75
Primaquine, 48, 82
Primary health care (PHC), 22, 29, 30, 39–40, 61–63, 65
Puerto Rico, 14, 23

Qinghaosu, 21, 48, 82
Quinine, 1, 19, 47

Rabinowitch, Victor, 64
Ray, A.D., 32
Reed, Walter, 3
Research, 14–15; de-emphasis of, 9–12, 14; on drugs, 21–22, 47–48, 79, 81–82; early, 1–4; recommendations for, 12, 27, 49, 65–66, 87; vaccine, 51–60, 65, 67, 86–87, 91–93; vector control, 49, 77–78, 85–90
Resurgence, 8, 61; regional, 26–37 *passim*
Rockefeller Foundation, 4, 36
Rockefeller University, 54–55
Ross, Ronald, 2
Russell, Paul, 10, 14
Russell, Philip, 54

Saint Lucia, 23
Sardinia, 14
Scripps Institute, 55, 92
Senegal, 38, 78
Silverman, Paul H., 51–52
Simpson, Gary, 79
Smith, Edgar A., 14, 54
Soper, Fred L., 4
Sporozoites, 2, 53–56
Sri Lanka, 30, 36, 37, 78
Staff and training, 9, 29, 34, 36–37, 64–65
Stek, Michael, 79
Sternberg, George, 3
Surinam, 26

Taiwan, 14
Tanzania, 38, 40, 48, 88
Thailand, 14, 15, 30, 77, 86, 87
Trager, William, 54
Triazines, 21
Trinidad and Tobago, 23
Trpis, Milan, 78
Tunisia, 10

Uganda, 77
UNICEF, 5–6, 22, 49
Uniformed Services University of the Health Sciences, 55, 92
United States: control and eradication efforts of, 3, 4, 5; financial contributions by, 5–6, 15, 18–19 (table), 23, 26, 28–37 *passim*, 77–79, 83; technical assistance from, 5–6, 28, 29; withdrawal of aid by, 9–12, 14, 23–26, 31, 32, 33, 36, 63, 87. *See also* Agency for International Development
University of Hawaii, 54, 55, 91
University of Illinois, 53, 88, 92
University of Missouri, 55, 92
University of New Mexico, 53, 86
U.S. Agency for International Development. *See* Agency for International Development (AID)

Vaccine: patents, 57–60; research, 51–60, 65, 67, 86–87, 91–93
Vector control, 3–4, 13, 29, 39; versus eradication, 7–8, 9–12; research on, 49, 77–78, 85–90
Venezuela, 14

Walter Reed Army Institute of Research, 48, 55
Wernsdorfer, Werner H., 15, 19–20
Wilson, D. Bruce, 4
World Health Organization (WHO), 5–6, 9, 15, 58–59, 64, 83–84; recommendations by, 7, 10, 21, 22,

26, 49; and research, 21, 47, 88
Wyler, David J., 19, 21

Zahar, A.R., 5
Zambia, 79
Zanzibar, 38, 40
Zeidler, Othmar, 4