PRESIDENT EISENHOWER, in his recent State of the Union message, declared that we now have it within our power to eradicate malaria, "the scourge of mankind," from the face of the earth. He called on the Soviets to join us in this great work of humanity which he cited as an example of "cooperation on projects of human welfare"—works of peace.

Surely, it is remarkable that in a country where malaria is a rare disease the President should give so much prominence to malaria eradication in a speech devoted to measures which he was recommending to the Congress in the interests of our own security. Remarkable, indeed, but logical in the light of present progress and problems in the age-old conflict between man and malaria, which is the subject of this address.

It seems to me very important that there should be widespread understanding of the history and present status of this insidious but devastating disease. Here in our own United States we now have so little direct evidence of malaria's power for evil that we tend to underestimate it and to forget its indirect damage to us. We fail to grasp the significance of a disease that in 1957 brought to an estimated 200 million persons, attacks of chills, fever, and debility, from the effects of which some two millions died. Who can evaluate the impact on the physical, social, and political health of the world of a disease that annually brings bodily weakness to approximately the same number of people as live in the United States, Canada, and Mexico combined?

Certainly, such an evaluation is not easily made by Americans, to most of whom this disease is practically unknown. For example, provisional data indicate that the remarkably low number of 144 malaria cases was reported to our National Office of Vital Statistics in 1957. The Public Health Service has surveyed 40 of these reports, confirming 24, of which only eight were found to represent infections contracted within the United States, four in California and four in Oklahoma (Dunn, 1957).

All but a few "old timers" have forgotten that malaria was once highly prevalent in this country. Moreover, only a few observers with special knowledge realize that although less than a dozen persons are known to
have contracted malaria in this country last year, yet during the same 12 months the disease probably cost us more than a third of a billion dollars, through higher priced imports and decreased exports, in our dealings with malarious countries.

So I thought it might be interesting to look for a few moments at malaria as once it prevailed here and in certain other areas around the world.

**Malaria Once Prevalent in the United States**

Just twenty years ago Williams (1938) one of the world's leading malariologists, estimated that the average incidence of malaria in the United States was four million cases a year, with as many as six or seven million afflicted in peak years such as 1935. Williams further stated that the average cost of malaria to the Southern United States was probably over half a billion dollars annually. This was the incidence and the economic importance of malaria after 30 years of active malaria control had greatly improved the situation.

In the 19th century, malaria was so common throughout the Mississippi Valley and much of the South that it was often accepted as a normal and inevitable part of life. Ague, *i.e.* chills and fever, as Ackerknecht (1947) has pointed out, although objectively dangerous and burdensome, had subjectively by social convention come to lose the character of a disease. "He ain't sick, he's only got the ager," was a typical comment of the period. For example, Petersen (1938) quotes an immigrant on the Mississippi in the 1830's, who wrote: "As we drew near Burlington [Iowa] in front of a little hut on the river bank, sat a girl and a lad—most pitiable looking objects, uncared for, hollow-eyed, sallow-faced. They had crawled out into the warm sun with chattering teeth to see the boat pass. To mother's inquiries the captain said: 'If you've never seen that kind of sickness I reckon you must be a Yankee; that's the ague. I'm feared you'll see plenty of it if you stay long in these parts. They call it here the swamp devil, and it will take the roses out of the cheeks of those plump little ones of yours mighty quick. Cure it? No, madam. No cure for it; have to wear it out. I had it a year when I first went on the river!"

This Mississippi Valley malaria made a deep impression on Charles Dickens when he traveled from Cincinnati to Saint Louis by river boat in 1842. In his *American Notes* he wrote of the place where the Ohio joins the Great River as follows: "At the junction of the two rivers, on ground so flat and low and marshy, that at certain seasons of the year it is inundated to the house-tops, lies a breeding place of fever, ague, and death, . . . a dismal swamp, . . . with rank unwholesome vegetation, in whose baleful shade the wretched wanderers who are tempted hither, droop, and die, and lay their bones." Later, in his novel *Martin Chuzzle-
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wit, Dickens described this area as “a marsh on which the good growth of the earth seemed to have been wrecked and cast away, that from its decomposing ashes vile and ugly things might rise; . . . where fatal mala-
dies, seeking whom they might infect, came forth at night in misty shapes, and creeping out upon the water, hunted them like spectres until the day. . . .”

On his river trip, Dickens’ face and nose were “profusely ornamented with the stings of mosquitoes” but, of course, he did not equate, as we do, the insects and the misty spectres rising from the marshes “seeking whom they might infect.” Fortunately for Dickens his journey was made before the beginning of the malaria transmission season. The ague cases he saw and described were no doubt relapsing vivax infections.

Parenthetically, another aspect of American life that greatly impressed Dickens was the widespread use of chewing tobacco, that weed to which innumerable healing powers were once attributed, the herba panacea of the 16th century, the chewing of which, an Alabama farmer once told me, had given him freedom from chills and fever for many a year. In Washington, which Dickens considered a very unhealthy city, he noted in the Senate, “many honourable members with swelled faces.” He discovered “that this appearance is caused by the quantity of tobacco they contrive to stow within the hollow of the cheek.” Said Dickens: “It is strange enough too, to see an honourable gentleman leaning back in his tilted chair with his legs on the desk before him, shaping a convenient ‘plug’ with his penknife, and when it is quite ready for use, shooting the old one from his mouth, as from a popgun, and clapping the new one in its place.” Dickens added that he “was surprised to observe that even steady old chewers of great experience, are not always good marksmen.”

Not even Yankees in the 19th century were exempt from malaria. For instance, the late Alan Gregg (1956) wrote that his parents left Connecticut in 1882 for Colorado because of the frequency of malaria around their home in Hartford. Indeed, throughout the length and breadth of our country and spilling up into southern Canada, malaria in the 1800’s was the most common infectious disease. Quinine in large bottles stood on the clock shelf of countless homes, together with a tumbler of water containing slippery elm bark, used as a “chaser.” Barber (1929) noted that the taking of quinine for ague was a daily ritual—but not for prophylaxis, because the people were so rarely free from malaria that there was no question of anything but trying to cure it.

John Macculloch, an English physician (1829, p. 190) discussing those fevers in the United States which he believed were due to the noxious miasm he called “malaria,” wrote as follows: “What the fate of much of this new country may ultimately be in this respect, it is difficult to foresee,
when we reflect on the numerous circumstances already noted, which modify the production and propagation of Malaria, and where so much is yet to be done as to alteration; though it is to be suspected that no changes and no cultivation will ever bring into a state of salubrity, a country so abounding with alluvial plains, even in the interior, and so extensively the produce of its numerous and enormous rivers.”

Going back to Colonial times, we are uncertain whether or not malaria was indigenous in the Americas before the arrival of Europeans. But the disease undoubtedly became very common in the early settlements, in fact malaria not only plagued Colonial America but it also significantly delayed its development. The recurring spring and fall epidemics brought anemia and disability that seriously depleted the supply of labor. As expressed in a Boston news report of September, 1690 (Duffy, 1953) “Epidemical Fevers and Agues grow very common in some parts of the Country, whereof, tho’ many dye not, yet they are sorely unfitted for their imployments.” Another testimony is that of a Pennsylvania missionary in 1771 explaining why church construction in his parish was so slow: “In the beginning of last September the workmen fell sick of intermitting fevers, the epidemical distemper of this country, and the autumnal season was so far advanced before they recovered, that the utmost they could do was lay the floor” (Duffy, 1953).

One is tempted to speculate as to how different our history might have been had this country not been severely handicapped by malaria and other now preventable fevers during so much of its developmental period. So, too, we sometimes wonder how any progress at all was made in those days, or today in malarious underdeveloped countries, when we realize that to the now preventable fevers were added practically all of our own contemporary ills that press, radio, and T-V will not let us forget by day or by night.

Malaria in Europe

In Europe, in the last century, no region was exempt from malaria, not even Scandinavia, where there were serious epidemics from time to time, the last one in Finland in 1902. As recently as 1920-21, a malaria pandemic swept northwards through Russia even to the 64th degree of latitude, not far from Archangel (Hackett, 1949). Southern European countries have for centuries been greatly affected. Macculloch (1829, pp. 7-8) described the malaria blight very clearly in the following quotation: “Let us turn to Italy: the fairest portions of this fair land are a prey to this invisible enemy, its fragrant breezes are poison, the dews of its summer evenings are death. The banks of its refreshing streams, its rich and flowing meadows, the borders of its glassy lakes, the luxuriant plains
of its overflowing agriculture, the valley where the aromatic shrubs regale
the eye and perfume the air, there are the chosen seats of this plague,
the throne of Malaria. Death here walks hand in hand with the sources
of life, sparing none: the labourer reaps his harvest but to die, or he
wanders amid the luxuriance of vegetation and wealth, the ghost of man,
a sufferer from his cradle to his impending grave; aged even in childhood,
and laying down in misery that life which was but one disease. He is
even driven from some of the richest portions of this fertile yet unhappy
country; and the traveller contemplates at a distance deserts, but deserts
of vegetable wealth, which man dares not approach, or he dies.

"Nor do even his homes and towns afford him a shelter against this all-
pervading pestilence. It enters with him into his chamber, and stalks
through his streets. Imperial Rome herself is its chosen victim: man flies
before it, but the enemy is behind him and around him on all sides:
every day sees the dominions of death extended, and the hour is impend-
ing when the Eternal City will cease to be, when it shall submit to that
fate, which has been the fate of proud Niveveh, and Babylon the queen
of nations.

"Such also is Sicily, such Sardinia, and such classic Greece."

If this vivid picture by Macculloch seems overdrawn, it should be
recalled that as recently as 1930 not a single permanent household existed
in all the Pontine Marsh area, one of the most fertile in Italy and within
easy access of the huge markets of Rome (Hackett, 1937).

**Malaria in Asia**

Asia like Europe has been afflicted with malaria for centuries. India,
for example, has suffered enormously. Sinton (1936), an expert malari-
ologist, concluded that malaria by its direct and indirect effects was
almost certainly responsible for at least two million deaths each year in
India, including what is now Pakistan. Sinton further concluded that
malaria was probably the greatest factor in lowering the health, vitality,
and physical development of 100 million persons who were attacked each
year, and that malaria caused financial losses of some 400 million dollars
a year to the families affected, and incalculable losses to agriculture,
industry, and commerce. Sinton concluded that the problem of existence
itself in many parts of India was the problem of malaria which constitu-
ted the most important cause of economic misfortune, engendering
poverty, diminishing the quality and quantity of the food supply, lower-
ing the physical and educational standards of the nation, and hampering
the increase of prosperity and economic progress in many ways.

India has been subject to epidemic as well as endemic malaria. In
the Punjab, for example, time and time again malaria has demonstrated
a ferocity that staggers the imagination. For instance, in 1908 in the two months of October and November, fulminant malaria killed more than 300 thousand persons in this one province. In some towns the deaths exceeded 400 per 1000 population; the mortality rate in Amritsar, a city of 160,000, was over 200 per 1000 population. The entire community was prostrated and all ordinary business, including train service, was interrupted. For many weeks labor for any purpose was unprocurable and even food vendors ceased to carry on their trade. Following the thought of Christophers (1911) who studied the epidemic, it was as though a sea of miasm had rolled in upon the community, submerging it and suffocating an incredible number of the inhabitants.

Numerous other dramatic episodes could be recounted, for example, the terrible epidemic in Mauritius in 1867 when "the living were scarcely able to bury the dead"; in Brazil in 1938, when there were 100,000 cases with 14,000 deaths in a six-month period; and in Ceylon in 1934-1935 affecting a million and a half and killing nearly 70,000 persons in about six months. But far more important even than such cyclonic epidemics has been the insidious, anemia-producing, stunting effect of endemic malaria century after century throughout much of the tropics and subtropics.

Make no mistake about it. Malaria has had in the past tremendous power over masses of mankind, killing millions and blighting tens of millions each year. Moreover, so long as malaria persists in large seed beds in the world it remains a potential threat. In the event of a serious breakdown in public services such as could occur in this atomic age, malaria might develop into epidemics that would compound disaster and greatly delay recovery from it.

So much for background. Now comes the pleasant task of discussing man's astounding and accelerating progress in mastering this mosquito-transmitted affliction. We have gone ahead so well that world-wide eradication of malaria seems possible in the foreseeable future.

**MALARIA ERADICATION**

Malaria eradication is big news today! Seventy-six countries are planning, are carrying out, or have completed the eradication of malaria from their confines. Most authorities agree that eradication is preferable to conventional control because it sets a definite end-point, because it is cheaper in the long run, and because the growing phenomenon of *Anopheles* tolerance to residual insecticides indicates that the choice is either eradicating malaria or indefinitely enduring a disease transmitted by vectors that in increasing numbers are becoming resistant to control.

Malaria eradication implies both the complete interruption of trans-
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mission and the elimination of the reservoir of parasites by a campaign limited in time and carried out so thoroughly that at its end there will be no resumption of transmission. But malaria eradication definitely does not imply the eradication of malaria mosquitoes, a goal rarely attainable and usually not economically possible.

Current malaria eradication programs have four phases: preparatory, attack, consolidation, and maintenance. The phase of preparation includes initial survey, planning, and preliminary operations. It generally lasts from several months to a year. The phase of attack begins as soon as the preparatory phase ends and continues with total spraying coverage until malaria transmission has ceased and the parasite reservoir has been nearly emptied. It has generally been found that most falciparum and vivax infections will have died out in 2% to 3 years if there has been no reinfection. So three years is usually the minimum duration of an eradication attack phase. A few, not readily apparent, foci of residual malaria will generally remain at the end of the attack phase.

The phase of consolidation begins as the widespread spraying attack on the insect ends. During consolidation, residual pockets of transmission must be found and eradicated and the parasites remaining in man eliminated. Case-finding and the use of anti-malaria drugs have first importance. For this aspect of malaria eradication a new concept has arisen, that of surveillance, defined as that part of a malaria eradication project which is concerned with the discovery, the cure, and the prevention of such residual malaria infections in man as would delay the ending of transmission or threaten its resumption in a given area. Surveillance may be started in the attack phase but is most active in the phase of consolidation. This essential and rather difficult phase of consolidation ends when during three years of active surveillance no locally contracted infections have occurred. Because malaria mortality is so low during this key phase of an eradication project, it is sometimes difficult to obtain the necessary financial support from either governmental or international sources to carry the work through to completion. It is an important paradox in some areas that when malaria incidence becomes very low more money and attention than ever should be put into malaria eradication.

The final phase of maintenance begins when malaria has been eradicated from an area and lasts as long as malaria exists anywhere in the world. But maintenance is not difficult or expensive because it is carried out by regular health departments which add malaria to the list of exotic diseases against which they are always on guard.

In most large countries, time schedules will vary in different areas, some of the latter coming to the maintenance phase sooner than others.
WORLD STATUS OF MALARIA ERADICATION

Accurate vital statistics are unobtainable in underdeveloped countries. Malaria in particular is subject to much confusion. Sometimes most fevers in an area are classified as malarial, sometimes most cases of malaria are not reported at all. But, due to the increased emphasis on malaria eradication during the past few years, with wider and more detailed surveys by better trained personnel, it is possible to present figures that probably are not misleading, although certainly they are not to be considered as more than carefully prepared estimates.

Very likely, about 45 per cent of the world's total population of 2,677 millions live in communities in which they are now or have very recently been exposed to malaria transmission. That is to say, when we talk about world-wide malaria eradication we mean the removal of all threat of malaria infection from some 1.2 billion people. That is quite a contract! How far along is it?

On the basis of data from WHO, it appears that by the end of 1957, country-wide malaria eradication projects were operating or nearing completion in countries having a total exposed population of some 248 million (total population, 576 million). Moreover, by the end of 1957, officially adopted malaria eradication schemes were being prepared in countries with a total exposed population of 480 million (total population 580 million). Thus in 1958, some 728 million of the 1.2 billion exposed to transmission will be under malaria eradication projects, about 61 per cent.

Expressed another way, there are in the world, according to the 1956 UN Demographic Yearbook, 196 nations, territories, dependencies, or administered areas of which 58 are non-malarious, leaving 138 to be considered in world-wide planning for malaria eradication. Seventy-six already are operating or preparing eradication projects; 62 still have no plans. Some of the latter, like Australia, Japan, and Singapore, have little malaria; others, like Pakistan, have a great deal. From one large country, Communist China, we have no information as to the current malaria situation. But world-wide malaria eradication requires that even faint endemicity and even Chinese malaria must be eliminated.

Countries now at or near malaria eradication are Argentina, British Guiana, Chile, France (Corsica), Cyprus, French Guiana, the Gaza strip, Italy (including Sardinia and Sicily), Martinique, Mauritius, Netherlands, Puerto Rico, Reunion, Romania, USA, and Venezuela.

A good example is Italy, the former malariousness of which I described earlier. The incidence of malaria in Italy in 1919 was over 300,000 cases and in 1945 it was over 400,000. In 1957, fewer than 100 cases were reported, mostly from a small overlooked Sicilian focus, now dealt with. Sardinia had not one case locally contracted and mosquito-borne.
I recall clearly my first visit to Sardinia in 1929, with Lewis Hackett. As we visited one poverty-stricken village after another, I became greatly depressed by the pitiable condition of the children, so many of whom were malarious. In the typical village street, almost always I would see sad little tots with huge bellies and pale faces, sitting listlessly in the doorways of their homes, seeming too weak to brush away the flies that ringed their eyes. My last visit was in 1950, at the close of the eradication project, and what a change I saw! The village children everywhere were playing vigorously, kicking balls and romping about in a normal healthy way, with rosy cheeks and no swollen bellies. Still some house flies but no longer able to linger about the eyes of the children. Sardinia is becoming a vacation resort and is rapidly erasing the evil name that malaria gave it from the time of the Caesars until some 10 years ago.

INTERNATIONAL COOPERATION

Time will not permit me to go very far into the history of international cooperation in malaria control and eradication. But among the many facets of this subject, as it developed prior to the end of World War II, may be mentioned the Pan-American Sanitary Bureau, which has been concerned with malaria control since 1907; the second Pan-American Scientific Congress, held in Washington in 1916, which adopted a resolution calling on the American Republics to join in an effort to eradicate malarial diseases from the Western Hemisphere; the Malaria Commission of the Health Organization of the League of Nations, which functioned from 1923 until the onset of World War II; the United Nations Relief and Rehabilitation Administration, which from 1943 to 1946 contributed to malaria eradication, especially in Greece and Sardinia; the Institute of Inter-American Affairs, set up in 1942, which carried out extensive antimalaria works in Latin America; and finally, The Rockefeller Foundation, which between 1920 and 1954 supported cooperative programs in many overseas areas. It seems to me fair to state that The Rockefeller Foundation through its world-wide cooperative support of basic preparatory work in (1) epidemiology; (2) practical control demonstrations; (3) training programs; and (4) the establishment of official organizations and institutes for malaria study and control, had a major part in laying the foundations for the remarkable acceleration in man's attack on malaria that we are now witnessing.

Since the end of World War II, international cooperation in regard to malaria has blossomed magnificently. In fact, the world never before has had an international sanitary effort that approached in magnitude and effectiveness that now existing in the world-wide cooperative attack on malaria. With justification we sometimes view the world scene these days with pessimism, wondering if mankind has made any progress except in
gadgetry and military hardware. As Bertrand Russell (1957) said, the really important question today is not "will it be possible for man to inhabit other planets?", but "will it be possible for man to continue to inhabit his own planet?" This philosopher thinks that a favorable answer is possible only if we can learn to think in terms of the welfare of mankind and not in terms of the welfare of one's own nation or group. Social progress, however slow, has been made and it seems to me that the international aspect of the present world-wide drive against malaria is evidence of such progress.

Several bodies have sparked this international attack on malaria. First, great credit should go to the World Health Organization for its effective leadership in the amazing acceleration of world-wide malaria eradication since 1947. The Malaria Section, with the help of five WHO Regional Offices, has stimulated nation-wide projects, demonstrated the feasibility of residual spraying in many areas, provided fellowships and training courses, organized regional malaria conferences, fostered inter-country and inter-regional unanimity in regard to malaria eradication, and financed basic research.

WHO has set up a Malaria Eradication Special Account (MESA) to which have been invited contributions from governments, non-governmental organizations, and private sources. Monies from this account may be spent in direct aid to national eradication projects. The United States in December, 1957, made a gift of $5 million to this account, the first sizeable contribution it has had.

The Pan American Sanitary Organization with its own funds, and also as the Regional Office of WHO for the Americas, has had a key rôle in pushing forward the attack on malaria in the Americas. It is now coordinating and assisting a booming hemisphere-wide project that will drive malaria completely out of North and South America and the West Indies. The PASO also has a special malaria eradication fund to which the United States, Venezuela, and the Dominican Republic have made sizeable contributions. In December, 1957, the United States increased its support by putting an additional $2 million into the account.

The United Nations Children's Fund (UNICEF) has had a tremendous impact on malaria. Since 1947, this organization has put some $26.4 million into insecticides, equipment, and transport for malaria control and eradication in 56 countries. The 1958 malaria budget of UNICEF is $8 million. Here have been the sinews of war without which the impressive gains of the last few years would have been impossible.

The United States, as already implied, has also had a vital part in the world-wide attack on malaria. In addition to its relatively large share of the budgets of WHO, UNICEF, and PASO, an annual share totaling over $11 million, the United States through the International Cooperation Ad-
ministration (ICA) and its predecessors, has spent a total of $8.9 million for malaria control and eradication in some 30 countries. The 1958 budget of ICA for malaria eradication in $23.3 million. The Division of International Health of the United States Public Health Service has had a major part in many policy decisions relating to malaria eradication and in providing personnel for ICA projects. This Division has been a powerful factor in recent world-wide victories over malaria.

Finally, it must be emphasized that very large sums have been and are being spent by national governments for malaria eradication within their borders. The monies that individual governments have provided for this purpose have equaled about 60 per cent of the total spent. Great credit must go to political leaders in those countries that have decided to budget national funds for the eradication of malaria.

**Problems**

Three resistance problems threaten to delay the accomplishment of world-wide malaria eradication. These are (1) resistance of anophelines to residual insecticides; (2) resistance of plasmodia to synthetic antimalarials; and (3) resistance of malaria in Central Africa to eradication.

**Resistance to Insecticides**

The problem of *Anopheles* resistance to residual insecticides is of prime interest to malariologists today. Among the fifty or more species that are significant vectors of malaria, behavioristic or physiologic resistance has been detected since 1951 in some part of the geographic range of seven, *viz.* *A. albimanus, gambiae, quadrimaculatus, sacharovi, stephensi, subpictus* and *sundaicus*. In one area, Greece, such resistance has clearly delayed a malaria eradication project.

This resistance phenomenon is not yet well understood but a brief account of some aspects of the subject may be of interest. To begin with, what we describe as a normal *Anopheles* mosquito will not habitually avoid contact with residual insecticides; if it does it is said to exhibit behavioristic resistance. Moreover, so-called normal anophelines (1) will freely absorb BHC, Dieldrin, or DDT; (2) will not detoxify or excrete these insecticides or store them as inactive deposits in tissue; and (3) do not have nerve axons or myoneural mechanisms that are unaffected by these toxicants. In other words, the so-called normal anopheline is susceptible to the residual insecticides and is killed by them. If the insect does not absorb the insecticide, or it can block or neutralize the usual lethal effects of such absorption it is said to exhibit physiologic resistance.

On the basis of studies by Macdonald (1957) and others it is apparent that physiologic resistance is hereditarily transmitted from parent *Anopheles* to offspring and that this inheritance follows the pattern associ-
ated with a single pair of genes, described as monofactorial. It also appears that specific physiologic resistance divides into at least two classes; in the first there is group resistance to BHC, Dieldrin, chlordane, and closely related compounds; in the second group the resistance is to DDT, methoxychlor, and near relatives. Within the group, resistance to one insecticide is accompanied by resistance to the others. But resistance to one group does not imply resistance to the other. So DDT is effective against Dieldrin-resistant *A. gambiae* in Northern Nigeria, and Dieldrin against DDT-resistant *A. sundaeicus* in north Java.

Techniques are being developed to make it possible to determine on a practical scale in the field, in advance of a spraying program, what sort of physiologic resistance is present in a given species of a given area and, more than this, to find out the proportions of wholly resistant, hybrid, and wholly susceptible anophelines of a given species in a given area.

The problem of *Anopheles* resistance to insecticides is a real one although so far such resistance has not delayed the world-wide program seriously. But each year brings new reports of such resistance in hitherto unaffected areas. Obviously basic research is required to solve this annoying problem.

**Drug Resistance**

In over three centuries of widespread use no evidence of acquired parasite resistance to quinine has ever been demonstrated. Moreover, as regards the newer synthetic remedies, no acquired resistance has been demonstrated against plasmoquine, in use since 1925, quinacrine (Atabrine) in use since 1930, chloroquine (Aralen) in use since 1934, amodiaquine (Camoquine) in use since 1946, and primaquine, used since 1950.

But significant acquired resistance by plasmodia to chlorguanide (Paludrine), in use since 1945, and to pyrimethamine (Daraprim), used since 1951, has been reported from several areas. This acquired resistance is inheritable and quite stable, and it persists through repeated mosquito passages. The resistance has been manifested chiefly by schizonts but has also been observed in pre-erythrocytic forms and in gametocytes. Cross resistance between chlorguanide and pyrimethamine has also been demonstrated. While a genetic origin of this drug resistance is suggested, little is known about the actual mechanism of its development.

Chlorguanide promised great usefulness because of its low toxicity, low cost, high effectiveness as a prophylactic against falciparum malaria, and its sporontocidal action resulting in a marked inhibitory effect on malaria transmission by mosquitoes. So the appearance of resistance has posed a problem.

The other drug, pyrimethamine, is remarkable in its action (1) to effect complete suppression of quartan and suppressive cure of vivax and falc-
parum malaria in extremely small doses; and (2) to inhibit sporogony and thus to prevent malaria transmission (Covell et al., 1955). The drug is tasteless and inexpensive, and has very low toxicity. So it is another drug of great promise that has become a resistance problem.

Resistance of Malaria in Central Africa

Malaria in Africa between the Tropics of Cancer and Capricorn has an extremely stable and relatively high endemicity based on several factors. For instance, the chief vector, A. gambiae, has a high man-biting frequency; Macdonald (1957) has estimated that the chance of this mosquito feeding on man during its lifetime is 136 times greater than the same chance in reference to A. culicifacies in Madras. Anopheles gambiae also has a relatively high expectation of life of 13 days as contrasted to 3.8 days of culicifacies. Furthermore, average temperatures in Central Africa are favorable to rapid completion of the development of the plasmodium in its mosquito host. The second of the principal vectors in Central Africa is funestus, not much inferior to gambiae in its vectorial powers.

Moreover, there are administrative difficulties due to the underdeveloped governmental services, communications, and especially public health departments. Yet the very high endemicity and the stability of malaria require greater and more sustained efficiency in eradication procedures than are usually needed elsewhere. Certain other difficulties, although not unique in Africa, are quite troublesome. For example, (1) the resistance of gambiae to Dieldrin in areas of West Africa; (2) the unfavorable reaction between wall surface and insecticide that curtails the effect of the toxicant, a phenomenon exhibited by many mud walls in Central Africa; and (3) outdoor feeding by gambiae.

On the other hand, a possible advantage in Central Africa is the preponderance of falciparum malaria over vivax. We possess against falciparum the drug chloroquine, which produces a radical cure and which can be administered to masses of individuals with a minimum of medical supervision. However, we need more suitable formulations for mass use of this drug.

So, Central Africa presents problems for solution. Several studies are going forward and preliminary reports of results in Northern Nigeria are good. But obviously much more study must go into the problem of malaria eradication in Central Africa.

Conclusions

World malaria incidence has fallen by tens of millions in the past few years under the impact of modern residual insecticides applied on a nation-wide scale in many countries, with the leadership, technical, and
financial aid of WHO, PASO, UNICEF, ICA, and progressive national health departments. Advances have been so great that world-wide malaria eradication seems a practical goal although we still have a long road to travel. As previously stated, there were probably 200 million cases of malaria throughout the world in 1957 with two million malaria deaths. There is need for much more international monetary and professional assistance, for more trained malariologists, and particularly for more malaria research.

Undoubtedly, the difficulties of world-wide malaria eradication are enormous, but so are the potential resources of money and technological skills that can be put to the task if there is the will to do so. We face a golden moment that intelligently utilized will lead us to a tremendous international public health victory.

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