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SCIENTIFIC EXPLORATION AND ACHIEVEMENT IN THE FIELD OF MALARIA*

Martin D. Young
Gorgas Memorial Laboratory, Panama, R. P.

ABSTRACT: Many of the major events in the evolution of malaria knowledge are related. The progress toward eradicating malaria, one of the world's worst diseases, is encouraging, but it has been hindered by prematurely reducing the research effort before some of the important problems were solved. Furthermore, some new problems have appeared. However, the accomplishments give hope for eventual success and suggest a design for the conquest of certain other parasitic diseases.

The tale of man's struggle with his worst disease, malaria, is one of many facets. It mirrors the growth of scientific methods and knowledge. Now in the current and perhaps final chapters of the story it reflects a scientific sophistication which in itself is a new aspect in the knowledge of human disease. Members of this Society have had an important part in the discovery, assembling, and dissemination of this knowledge.

The story involves the rise and fall of nations, the birth and death of cities, prisons and insane asylums, men, monkeys, and birds, wars and peaceful international cooperation, and many other complex manifestations of human and animal societies.

Malaria has been recognized as a serious disease throughout recorded history. Most civilizations in temperate and warm climates have been greatly influenced by the disease. The history of malaria in North America probably can serve as an example of the impact of malaria upon a nation. Before the colonization of America, it appears that this continent was free of malaria. Later it gained a footing and began to exert a profound and malignant influence, especially in the southern states.

Malaria was probably introduced by the settlers in the early part of the 17th century. By 1684, it had become a serious disease on the Atlantic seaboard. From there it spread over most of the continent as far north as Canada and as far west as the Pacific Coast. The Civil War intensified the incidence of malaria especially in the New England states. Malaria began to decline later in the 19th century, but was still of major importance, especially in the southeastern part of the country, until the 1940's.

The etiological agent of malaria naturally was unknown before the invention of the microscope and remained so for a long time afterward. The recognition of the relationship between the disease and water, in which (we now know) the mosquito vector breeds, gave rise to a popular theory that malaria was due to water vapors.

In 1880 a French army surgeon, Laveran, studying the pigmented spherical and crescent-shaped bodies found in red blood cells of malarious patients, saw flagella produced. He concluded that these forms were parasites which caused malaria. A few years later Golgi observed schizogony of the parasites and related the paroxysms to the maturation of the asexual cycle.

The gametocytes, which persist into the chronic nonsymptomatic disease phase, were thought by some to be the cause of relapses. In 1897 MacCallum, studying *Haemoproteus*, a parasite related to the human plasmodium, in the blood of a crow, saw the male gameto-

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cytes produce flagella which then fertilized a female parasite. He later saw this same process with falciparum malaria in blood from a patient. It was then clear that gametocytes were part of a sexual cycle and probably not the cause of relapse.

Ross, a surgeon in the Indian Medical Service, on 20 August 1897 in Secunderabad saw a pigmented cyst on the gut wall of an *Anopheles* mosquito which had fed on a malarious patient. Noting that the cysts were larger in mosquitoes dissected the following day, he concluded that these were malaria parasites developing in the mosquito. Soon after this discovery the researches were interrupted because Ross was transferred to a place where little human malaria existed. In February 1898 he was sent to Calcutta where he resumed work using *Culex* mosquitoes which he fed on malarious sparrows. He saw the development of the sporozoites and subsequently their location in the salivary glands. He fed infected mosquitoes on other birds and transmitted the infection, thus proving that malaria is transmitted by mosquitoes. Shortly thereafter the Italians demonstrated the same thing for human malaria. Although the cause and method of transmission were then known, it took another 50 years to arrive at an efficient method of control.

The above discoveries did not explain all of the life cycle. For example, after an infected mosquito bites a person, it requires about 10 days or more for the fever to start. Schaudinn claimed in 1903 that he saw the sporozoites from the mosquito enter red blood cells. The incubation period was credited to the time required for the direct multiplication of these erythrocytic parasites to numbers sufficient to cause symptoms and to be demonstrable. The influence of his reputation resulted in this scientific misinformation being accepted for the next 30 years. Undoubtedly this theory interfered with the development of knowledge on this point.

Specific treatment of malaria began with the use of the bark of the cinchona tree. This therapy was introduced into Europe about 1640, to become widely used. For nearly 300 years the powdered bark, and later the alkaloids of cinchona, of which quinine was the most useful, was the usual treatment for malaria and even in some areas today it is still being used.

However, quinine was not universally accepted for a long time. Many other remedies were used for malaria. Among these were beverages made of sassafras roots, of cherry bark, or from horse dung. One country physician treated himself with salt and pepper. Many illiterate people carried amulets about their persons to prevent or to break the onslaught of malaria and other fevers. Most intelligent persons made use of more potent remedies. In the southern states, a common treatment of fevers in the early days was to "puke, purge, and bleed." Ipecac was given to induce vomiting. The patient was then purged. Then he was bled, from one to two cups of blood being drawn. This procedure might be repeated in a day or two if the fevers did not abate. We know now that instead of losing blood, the malarious patient might need the opposite. The heroic treatment prescribed for malaria unquestionably contributed to the emaciation of the sufferer, but stubborn diseases were thought to require drastic remedies.

It is needless to say that a good deal of whiskey was drunk to stimulate the flagging spirits of the victims of malaria. Indeed, it was belived that whiskey would prevent malaria, and for that reason it was issued to sailors in the Confederate Navy at an early hour every morning.

It has been said that the introduction of cinchona bark into medicine was as important as the whole concept of infectious disease (Russell, West et al., 1963). Prior to its discovery, all forms of treatment for all diseases were directed to purging, to sweating, or to causing increased urination in the hope of expelling evil humors. Cinchona induced none of these eliminations but it cured, at least temporarily, attacks of paroxysmal fever.

Cinchona bark came into wide use. Chapman, in 1821, listed the following ailments as being treated with this medicine: fevers, rheumatism, smallpox, measles, erysipelas, scarlatina, hemorrhage, dysentery, epilepsy, chorea, tetanus, pertussis, asthma, some cases of tuberculosis, scrofula, rickets, dropsy, scurvy, leucorrhea, and gangrene. It, however, was not

a cure-all. It was said that it generally failed against cancer.

Some early workers had noticed that methylene blue would stain the malaria parasites. The dye was tried against malaria infections in humans and found to have only a slight effect. When the Germans lost their source of quinine during World War I, they began a search for synthetic drugs. By modifying methylene blue, drugs were found which were more active against malaria in canaries. Finally, in 1924, pamaquine (Plasmochin), an 8-aminoquinoline, was produced. This drug was effective against gametocytes but was toxic, especially to dark-skinned races. In the hopes of decreasing the toxicity, the Germans introduced further modifications which in 1932 resulted in the production of mepacrine (Atabrine), a 9-aminoacridine. By this time, 12,000 compounds had been tested.

A great impetus in the search for drugs came at the beginning of World War II when the quinine supply of the Allies was lost to the enemy. This was one of the most fortunate accidents that ever occurred in the field of malaria since the intensive programs which resulted, after testing some 16,000 compounds, revealed several drugs of greater value than quinine. Camoquin, which is a 4-aminoquinoline, was developed in America as was the independent synthesis of chloroquine; the latter is a synonym of Resochin, which the Germans previously had developed but had not properly evaluated (Coatney, 1963). These are excellent schizonticides, quickly clearing the parasites from the blood stream and causing the disappearance of fever. The British also developed a good drug in 1944, proguanil, a biguanide which had the advantages of the above and in addition was quite cheap.

Pamaquine, the 8-aminoquinoline, had been shown in 1930 to be effective in reducing relapse rates as well as interfering with mosquito transmission. A further experimental development of this group of chemicals gave three effective compounds, one of which, primaquine, has proven very useful. Fifteen mg daily for 14 days radically cures most infections so that no relapses occur.

Hitchings, and co-workers, in 1948 found that 2,4-diaminopyrimidines were competitive antagonists of folic and folinic acids in the growth of a bacterium, *Lactobacillus casei*. They reasoned that this action might prevent the multiplication of cells of malaria and upon experimental trial this proved to be true for pyrimethamine, a member of this series (Hitchings, 1952). Thus a new drug, pyrimethamine (Daraprim), which was effective in the minute amount of a single dose of 25 mg, was added to the list of antimalarial drugs.

Although Schaudinn had said that the sporozoites entered the erythrocyte directly and that multiplication therein resulted in paroxysms some days later, doubts began gradually to mount about this theory. For one thing, the blood was not infective during much of this incubation period. In the early thirties, scientists working with canaries found that the sporozoites initiate a cycle in reticuloendothelial cells and blood-forming tissues after which forms are produced which invade red cells. In 1948 it was demonstrated with monkey malaria and shortly thereafter with human malaria that a tissue phase differing from the avian type exists in mammalian malaria wherein the parasites develop in the parenchymatous cells of the liver. These fixed tissue forms offer the first reasonable explanation for the noninfectivity of the blood during the incubation period and, as they are not destroyed by schizonticidal drugs, for relapses.

In Vienna a psychiatrist, Wagner von Jauregg, noted that his neurosyphilitic patients with induced fevers showed more improvement and lived longer than others without such fevers. After many investigations with various methods of inducing fever, in 1917 he initiated the use of malaria for the treatment of central nervous system syphilis (Bruetsch, 1940). The use of induced malaria to treat neurosyphilis was one of the first specific methods for the treatment of mental diseases. This method spread to many countries of the world. It is difficult to estimate how many patients have received therapeutic malaria but it must be in the hundreds of thousands.

This method of inducing malaria in patients allowed for its study under controlled conditions. Consequently, research centers were established in several countries to utilize this arrangement, such as at the Berceni Hospital, Bucharest, Romania; The Malaria Laboratory, Horton Hospital, Epsom, England; the Rocke-

feller Station at Tallahassee, Florida; and the National Institute of Health Laboratory at Columbia, South Carolina. Much has been learned about the biology, epidemiology, host–parasite relationships, and treatment of malaria as a result of these studies.

The methods developed in inducing malaria for the therapy of neurosyphilitic patients led to the use of malaria in prisoner volunteers who were employed in the final and definitive testing of the new antimalarial candidate drugs. Thousands of volunteers, in state and federal prisons during wartime, performed for their country and for human welfare a service of perhaps far more value than they would have contributed had they not been in prison.

Long before it was known that mosquitoes were malaria vectors, people had tried to protect themselves against insects by various methods. Oil had been used to prevent mosquitoes from breeding. The value of drainage had been recognized. Bed nets and, later, wire screens were used to prevent mosquitoes from biting. Dr. Gorrie, a physician in Apalachicola, Florida, at one time suggested that Washington, D. C., be enclosed in a giant screen to keep out mosquitoes. Dr. Gorrie also had other ideas. In his hospital he had many fever cases, probably yellow fever. In order to cool his patients, he invented an ice-making machine, the original of which is in the Smithsonian Institution.

After it was found that mosquitoes transmitted malaria, control measures involved eliminating breeding waters or poisoning the water with arsenic or kerosene, protecting people with screens, etc., and killing adult mosquitoes with contact poisons such as the pyrethrums. Unless vigorously pursued, these methods were only moderately successful. The costs of control were high and recurred annually. In 1935 there were estimated to be 6 to 7 millions of cases of malaria in the United States, resulting in over 4,000 deaths. The cost of illness was estimated to be $57 million and the economic loss to be $500 million (Williams, 1938).

During the years of World War II, a Swiss chemist, Paul Mueller, was one of many trying to find better insecticides. He was routinely screening compounds as contact poisons. One day he used an old compound of no known value, dichloro-diphenyl-trichlorethane, on some flies in a cage. The results were disappointing; the flies were not immediately knocked down. He put the cage away and several days later put flies in it for a few hours preparatory to another experiment. Fortunately, there was a lapse of time before he was ready to use the flies and when he came to use them they were all dead. This puzzled him and out of curiosity he put more flies in the cage. These, too, died later, although their companions elsewhere continued to live. In searching for an explanation of the deadly attributes of this particular cage he remembered that the apparently useless compound had been sprayed on that cage several days previously. Experiments then showed that this compound, now known as DDT, has the unusual quality of retaining insecticidal properties in the residuum. When sprayed upon a surface, the resulting crystals remain lethal for months to any insects coming in contact with them. This discovery, which won a Nobel prize for the scientist, changed the approach to malaria control and has resulted in prolonged life and improved health for millions of people.

As a result of the new insecticides and improved antimalarial drugs, in combination with other factors, the malaria picture began to change. The United States became free of malaria for the first time since 1670. Reports of large areas of other countries becoming free of malaria began to appear. Gradually the idea grew that malaria not only could be controlled but perhaps eradicated from entire areas and countries, and, the more optimistic said, from continents and perhaps the world. Governments became interested in eliminating this burden of sickness and expense from their people for the benefits of health and economic development in return. The World Health Organization, a part of the United Nations, after again documenting the status of malaria as the world's most serious disease, announced a plan of world eradication. Our own federal government, believing that the democratic way of life might be well exemplified by the benefits of good health and the economic development resulting therefrom, began to support malaria eradication programs as a part of its Point Four Programs whereby technical aid

and assistance in health, agriculture, etc., are furnished to underdeveloped countries. The program is well under way and, as will be mentioned later, progress is evident in most malarious areas of the world.

With the good results obtained from residual insecticides, there was a great burst of enthusiasm and optimism for the eradication of malaria. Standard plans were advocated. The general feeling among administrators was that enough knowledge was available and that research scientists were no longer needed in malaria. The answer to malaria was simple: Have technicians spray insecticides on the walls. In our own country, malaria research laboratories were closed, malaria research programs were changed into something else, established malariologists were actively encouraged to go into more vital fields. One prominent member of this society said before a scientific meeting that it was easier to get rid of malaria than it was to get rid of malariologists. The use of malaria research as a tool to produce knowledge applicable to a variety of fields was discounted, falling into the "deadwood" category. The short-range viewpoint of expediency, so often characteristic of the interest and support of tropical disease research, was in full force. The endeavors of those preparing and defending budgets often were directed toward new fields of research, especially those of greater significance or those which could excite greater interest in the mind of the public. But they forgot to evaluate the extent of our ignorance about malaria and underrated the versatility of the parasite and its vectors. This error of judgment was to become painfully clear only a few years later.

Much has been accomplished since the World Health Organization adopted malaria eradication as a goal. Millions have been spared the suffering and economic losses caused by malaria.

Out of 142 countries or political units recorded as originally having malarious areas, 103 (73%) are involved or have been involved in plans or programs for malaria eradication. Twenty-nine countries, 26 of which are in Africa, south of the Sahara, have not yet joined the global effort to eradicate malaria.

In population figures, as of 30 September 1963, of 1.5 million people inhabiting the originally malarious areas of the world (not including Mainland China, North Korea, and North Vietnam), 92% live in areas where malaria either has been eradicated or where there are programs and plans under way; only 8% of the world's people are still living in malaria-risk countries with no plans for eradication of the disease (17th World Health Assembly, Official Records of the World Health Organization No. 135. July 1964. Geneva). The largest area left out of this general improvement is in Africa, where there is a tough combination of virulent malaria, efficient mosquito vectors, poor housing and diet, and limited financial resources. There is hope that this unusually tough problem will be solved.

The picture, however, is not without certain troublesome spots. Twenty-two malaria vectors have shown resistance to insecticides. Ten of the vector species show or have shown resistance to dieldrin only, one to DDT only, and 11 to both groups of insecticides, but not always in the same area (WHO Exp. Cmt. Rpt. on Malaria. 11th Report, 1964). Fortunately, such resistance occurs in only a small part of the geographical range of each species.

The insecticides generally are sprayed on the house walls. As the mosquito rests on the walls after biting the sleeping victim, it contacts the poison and is killed. However, this wall method cannot be used always. In some areas the houses are without walls. The nomadic tribes often use tents or skin huts. Some people sleep in the open on the ground. Others live in dwellings inaccessible to spray teams, and large congregations, such as religious festivals, armies, etc., may not be in housing suitable for insecticides. To protect these, drugs may be used. In some disciplined groups, such as armies and labor camps, this has been done successfully. In other groups it is impractical or impossible to give drugs regularly by mouth. The incorporation of the drug in articles of food, such as table salt, is a recent innovation that has worked in certain areas and is being tried on a wider scale (17th World Health Assembly).

The use of drugs where insecticides cannot be employed, or as an adjunct and partner to insecticides, has proven useful in eradication programs. It reduces the supply of parasites to be transmitted and by reducing the

illness of the patients results in good will and public support of the program. Unfortunately, as with the mosquitoes, the malaria parasites are also developing resistance to some of the drugs. Significant drug resistance arose about 15 years ago with the large-scale use of proguanil (Paludrine). Shortly afterwards the same problem arose with pyrimethamine (Daraprim). These occurrences did not cause major concern because of the widespread use and confidence in the 4-aminoquinoline drugs, such as amodiaquine and chloroquine. However, in 1960 chloroquine and amodiaquine resistance was documented in *Plasmodium falciparum* from Colombia, South America (Young and Moore, 1961; Young, 1961). Later *P. falciparum* resistance to chloroquine was reported from southeast Asia (Young, Contacos, Stitcher, and Millar, 1963).

Resistance of *P. falciparum* parasites to the 4-aminoquinoline drugs has been reported so far from Colombia, Brazil, British Guiana, Thailand, Malaya, Cambodia, and Vietnam. The spectrum of resistance varies with the strain. Some strains are resistant to all of the synthetic schizonticidal drugs, in which case resort must be had to quinine.

The resistance of some anopheline mosquitoes to insecticides and the resistance of some strains of malaria parasites to drugs indicate the urgency of achieving the eradication goal before further resistance develops.

Contrary to some of the overly optimistic opinions of a few years ago, we now find that there are still many problems to be solved, some of which may hold the key to actual global eradication. Suddenly, the problems appear large and the supply of malariologists and facilities inadequate. Ironically, some of these are old problems which were being pursued in the past and the answers might now be nearer had the research work not been choked off. Some of the problems are new, however, such as resistance to antimalarial drugs.

The information needed covers a wide range of biology, host–parasite relationship, chemotherapy, etc. While it is hoped that eradication of malaria can be accomplished before all of the problems can be solved, it now seems logical to resume and to continue investigational work until malaria has actually been eradicated. The same logic might apply in the future to other diseases which might be the object of eradication. The moral is: eradicate the disease before liquidating the investigators.

In this general review of the association of man with his most serious disease, most of the exciting details of the day-by-day research and developmental experiences, of successes and disappointments, have necessarily been omitted. The accomplishment so far in malaria and the bright possibility that it can be eliminated from the world is a breathtaking prospect charged with far-reaching significance. It would mark the first successful elimination of a major disease, which at the same time happens to be the most serious one, from this planet. It would improve the health, happiness, well-being, and economic status of vast segments of the world's population. It gives hope and a design for further conquests of disease, especially those transmitted by arthropods or those which can be attacked by drugs.

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