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Historical Review

THE malaria parasite is a well organized, highly adapted end-product of thousands of years of biological evolution which would mark it as successful, regardless of the criteria. Species of the genus *Plasmodium* are currently found in every group of strictly terrestrial vertebrates and adaptive capacities have been particularly well demonstrated in birds and primates where the level of speciation is high. When one considers the complexity of the life cycle, including the necessity for adjustment to two decidedly different host environments, the precise combination of temperature and humidity required, plus vector and vertebrate host habits necessary to assure continued transmission of the parasite, its survival in nature alone, is amazing. Recent history has confirmed the hardiness of these parasites. Man's concentrated attacks on the parasites and their vectors have met with only limited success and a great deal of frustration. Even areas freed of human malaria remain in a precarious position because the parasites keep up an unrelenting pressure on their borders, maintaining a constant threat of reinvasion with the production of epidemics such as occurred in Ceylon in 1968.

The chronicle of human malaria begins in pre-history and continues for thousands of years through a tortuous path of sickness and death. The full antiquity of the man-malaria parasite association remains obscure, but Hippocrates, "The Father of Medicine" and the first malariologist, described the various malaria fevers of man 400 years before the birth of Christ. Progress in understanding the disease was slow, but about 30 A.D., Celsus described two types of tertian fevers; 150 years later, Galen recognized the appearance of these fevers with the summer season and a jaundice in

infected people. For approximately the next 1500 years, man did little about malaria but suffer and die from it. Then, in the middle of the 17th century, the bitter extract from the bark of a New World tree was found to have remarkable powers against these intermittent fevers so common in the Mediterranean area. The romance surrounding the discovery of quinine has served to obscure the real story, and today, there are a number of versions from which to choose. It now seems doubtful that the Countess of Chinchon was ever treated for malaria with Peruvian bark, but her name was used as the genus name for the Cinchona tree, by way of a spelling error, by Linnaeus. Cinchona bark first appeared in European medical literature in Heyden's *Discours et Aris sur les flus de ventre Doloureux* published in Antwerp in 1643. The efficacy of the extract was known by that time and it is probable that it had been used in Lima and possibly Spain, earlier. Its value was soon recognized and thus began a long period of intrigue and frustration associated with efforts to secure sufficient quantities of the extract to treat the increasing number of malaria infections in the world.

The 18th century saw three advances which can, in the light of our present knowledge, be recognized as important. Lancisi noted the presence of black pigment in human brains and spleens, but did not associate these changes with malaria, and in 1717 suggested a relationship between marsh insects and the occurrence of malaria. In 1775, Torti recognized that quinine was not therapeutic for all fevers, thus effectively separating the malarial fevers from human febrile illnesses of other etiologies. It can be seen that the status of knowledge of malaria at the beginning of the 19th century was at a very low level. Meanwhile, the problem was becoming more acute due to European

explorations and settlements in the tropics of Asia. In addition, the malaras introduced into the New World in the 16th and 17th centuries had found fertile ground, and, by the early 1800's, severely challenged man's ability to survive in parts of the American tropics and subtropics.

The 19th century proved to be a momentous one in the field of malaria. Initially, information continued to be fragmented and uncoordinated. In 1820, two French chemists, Pelletier and Caventou, isolated the active anti-malaria component from quinine powder. Boyle (1831) while working in Africa gave credence to the swamp theory of malarial etiology. The probable relationship between malaria and swamps was so firmly established that it had given the two most frequently used names to the disease *mal'aria*, later shortened to one word *malaria*, and *paludisme*. The black pigment, first noted by Lancisi, was specifically associated with malaria by Schutz (1848) when he observed it in the internal organs of patients who had died of malaria. Meckel in 1847, without recognizing its true importance, probably saw malaria parasites for the first time when he described black pigment in protoplasmic masses in the blood of a patient with fever; it was not until 1879, however, that Afanasiev proposed that these bodies might be the agents of the disease.

The scene was now set for the dramatic events which crowded into the last 20 years of the 19th century. In 1880, Laveran, working in North Africa, described exflagellation of the *Plasmodium falciparum* male gametocyte in the blood of a malarious patient. The reception of Laveran's discovery was less than enthusiastic. Most of the scientific world was convinced of the bacterial etiology of malaria. Meanwhile, according to Garnham (1966), Danilewsky (1884) was able to observe parasites of malaria in the blood of wild birds, and, in the same year, Laveran's influential countryman, Pasteur, became convinced of the soundness of the former's observations. The true nature of the organisms seen by Laveran was finally made clear by MacCallum in 1897 who, while in Canada, observed fertilization in bird malaria and later, at the Johns Hopkins Hospital in

Baltimore, in *P. falciparum* in man. In 1891, Romanowsky developed a stain which allowed for differential identification of blood parasites, including malaria.

The animal nature of the malaria parasite had fairly wide acceptance by the last decade of the 19th century. It is during this period that some of the most dramatic and far-reaching work in the field of malaria was to take place. The possible association of insects and the transmission of malaria had been discussed in various parts of the world for a long time. As early as 1848, Nott published a paper in the U.S.A. which contrasted yellow fever and remittent fever and proposed that mosquito involvement was the best explanation for the occurrence and distribution of both kinds of fever. In 1856, Burton noted that some African tribes believed that mosquitoes were responsible for certain fevers. The development of filarial larvae in mosquitoes was demonstrated by Manson in 1883, and in 1893, Smith and Kilborne reported the transmission of Texas cattle fever by ticks.

Information on the probable association of insects and certain disease syndromes had no doubt begun to accumulate on both sides of the Atlantic before Ronald Ross's epoch making work on mosquitoes and malaria in India; communications were poor, however, and there was little opportunity to correlate the various observations arising from such divergent points as Russia (Danilewsky) and the U.S.A. (Nott). Patrick Manson, who encouraged, stimulated, and advised Ross, was committed to the idea that insects were involved in disease transmission.

Ross's early results, reported by Manson in 1896, included the observation of exflagellation by *P. falciparum* gametocytes in the stomach of a mosquito. Manson (loc. cit.) therefore concluded that the mosquito's stomach provided an appropriate medium for the development of the malaria parasite outside the vertebrate host. In the same year, according to Russell (1955), Theobald Smith came to the conclusion that mosquitoes were vectors of malaria. The following year, Ross reported the presence of pigmented bodies in spotted winged mosquitoes after the insects had fed on patients with malaria.

At that point, Ross was forced to interrupt his investigations on human malaria, but was soon (1898) able to observe the sporogonic cycle of a bird malaria (*P. relictum*) in the mosquito, and, to transmit the parasite to healthy sparrows.

It is at this time that the famous, acrimonious and long-lived conflict began between the British and Italian malariologists over priority in the transmission of malaria by mosquitoes. Bignami, in 1898, successfully infected a volunteer with *P. falciparum* by the bites of mosquitoes collected from a malarious area. There is no serious challenge to the validity of either Ross's or Bignami's work. The acrimony arose over who was the first to demonstrate the role of the mosquito in malaria. It would seem that Bignami's was the first report but both Ross and Manson insist that the ideas for the Italian investigations came from unpublished reports of Ross's work. Confirmation of the mosquito role in the transmission of malaria came in 1900 when Manson arranged for three people from the London School of Tropical Medicine to spend the summer near Ostia in the Roman Campagna. Their days were spent in various excursions in the vicinity, but each night was passed in a screened hut. The three did not come down with the disease, although transmission of malaria continued at its usual high rate in the surrounding area. Final proof came when mosquitoes previously fed on a malaria patient in Rome were allowed to bite healthy volunteers in London. The London participants in these experiments, including Manson's son, came down with typical vivax malaria two weeks after exposure. The complete cycle of *P. falciparum* was observed by Grassi, Bignami, and Bastianelli in 1899 and in the same year, Bastianelli and Bignami accomplished the same feat with *P. vivax*. The Italian studies on the sporogonic cycle of malaria were summarized in what was to become a classical monograph by Grassi in 1900.

Meanwhile, the same group of Italian workers had been busy with other facets of the rapidly developing fund of knowledge about malaria. Credit for the genus name *Plasmodium* goes to Marchiafava and Celli (1885) and the initial differential descriptions of *P. vivax* and *P.*

malariae were made by Grassi and Feletti in 1890. However, the situation was not as clear-cut as would be indicated by this short statement. Chaos was the order of the day in the taxonomy of the malaria parasites for many years. Numerous generic names were proposed, including *Haemamoeba*, *Oscillaria*, *Laverania*, and *Haemomonas*. Confusion continued well into the 20th century over whether all of the parasites belonged to one species or to several. In the confusion, it is difficult to know exactly which parasite was under observation by some of the early authors. There is little doubt that Laveran saw and described parasites of what was to become *P. malariae* in 1881, and that he first used the species name "malariae." It is also clear that Laveran first saw the gametocytes of *P. falciparum*, but he firmly believed that all of the parasites belonged to one species. In 1890, Grassi and Feletti described and illustrated two parasites that were to become *P. vivax* and *P. malariae*. Seven years later, Welch (1897) proposed the name *Haematozoon falciparum* for the parasite with the crescent-shaped gametocytes which Laveran had seen some 17 years earlier. The end result of this taxonomic chaos is now well known. The genus name *Plasmodium* of Marchiafava and Celli was maintained for all species. The species name of the parasite described by Grassi and Feletti as *Haemamoeba vivax* was eventually accepted to designate the benign tertian parasite of man, *Plasmodium vivax*. Welch's specific name gained wide acceptance for the malignant tertian parasite and *Plasmodium falciparum* became a permanent part of the malaria literature. With *P. malariae*, the situation is even more confused. In 1890, Grassi and Feletti gave malariae as the specific name for the quartan parasite and on the basis of priority, that name and date is valid.

The 20th century part of the malaria story began in what might be termed organized confusion. The last two decades of the 19th century had produced more information than could readily be assimilated, but a firm basis for the epidemiologic investigations, which were to dominate work in the early part of the 20th century, had been established. Three different human parasites were recognized (though not universally accepted) both clinically and

morphologically, and the role of the anopheline mosquito in the transmission of the parasite had been established.

The stage was now set for the development of new concepts of control based on biological aspects of mosquito transmission and the erection of some type of barrier between man and the insect vector of the disease. In 1900, Gorgas began his momentous work on the control of malaria and yellow fever in Havana and following his success there, he transferred his activities, in 1907, to the Panama Canal Zone where he achieved equal, if not greater, results in reducing the incidence of two deadly diseases-malaria and yellow fever. There is little doubt that Gorgas, LePrince, and Carter must, in a large measure, be given credit for the ultimate completion of the Panama Canal. During the same period, Watson began his classical work of draining the salt marshes, which made parts of the west coast of Malaya habitable. During the next two decades evolved the well known concepts of ditching and draining which achieved such notable results in malaria control in the southern United States and in Italy. In 1939, the Malaria Service of Northeast Brazil was organized to combat the populations of *Anopheles gambiae* which had been introduced from Africa. This effort at species eradication was enormously successful and the mosquito is still absent from the area. The control of malaria took a giant step forward in the late 1930's and early 1940's with the development of residual insecticides and synthetic antimalarials. However, the history of these developments is outside the scope of this work.

The capacity of a malaria fever to frequently improve the condition of people suffering from general paralysis of the insane by Wagner-Jauregg (1922) may be one of the most important discoveries in the history of malaria in that it allowed for the systematic study of the disease under controlled conditions. It was in such mental hospitals as those in Milledgeville, Georgia and Columbia, South Carolina in the U.S.A.; Horton Hospital in England; and in Bucharest and Socola, Roumania that studies on induced malarias revealed much of our information on pathology, biology, drug responses, and relapse mechanisms. It would be

difficult to overestimate the contribution that thousands of patients, in many such institutions, have made to our understanding of malaria.

There is no doubt that the evolution of concepts of control and eradication have been the predominant feature story of malaria during the 20th century. However, significant strides have been made in its biology, parasitology, and therapy as well. One of the most important new developments was the discovery of the exoerythrocytic stages of the primate malarias. This story is reviewed in detail in Chapter 6. Actually, Grassi suggested as early as 1900 the possibility that the sporozoite did not develop directly into blood parasites. However, it was not until 1948 that Shortt and Garnham finally demonstrated the pre-erythrocytic stages of a primate malaria.

No discussion of the history of man's conflict with malaria would be complete without consideration of the plasmodia of other animals. The genus is extremely widespread in reptiles, birds, and mammals, and, in the light of this monograph, a brief review of the development of our knowledge of the malarias of non-human primates is in order. The evolution of an understanding of the plasmodia of non-human primates parallels, in many ways, and complements, the story of human malaria. The first plasmodium-like parasite (*P. kochi*) described from non-human primates was not a true malaria but a member of the genus *Hepatocystis* which was subsequently reported from a number of species of African monkeys (Kossel, 1899; Laveran, 1899). Most of the early observations on the blood protozoa of non-human primates were made on animals imported into Europe from Africa, Asia, and America. Laveran (1905) saw the parasite, later described by Halberstaedter and Prowazek (1907) as *Plasmodium pitheci*, in the blood of Javan orangutans housed in Berlin. In the same year, Halberstaedter and Prowazek examined blood of *Macaca irus* and *M. nemestrina* imported from Indonesia and Borneo and found another malaria parasite which they described as *P. inui*. In the same year, while Halberstaedter and Prowazek were working in Berlin, Mayer, working with Asian monkeys at the Hamburg Institute, described a parasite from the blood of a

Macaca irus, from Java, which he named *P. cynomolgi*. The following year, a cacajao (*Brachyurus calvus*) from Brazil was encountered in a circus in Hamburg and Gonder and von Berenberg-Gossler found a parasite in its blood which they named *P. brasilianum*. In 1932 and 1933, Sinton and Mulligan reviewed the confused situation with regard to the malaria parasites of monkeys, and, in a well reasoned two part paper, managed to bring some order out of the chaos. The African parasites fell into two obvious categories—one without schizogony in the blood which remained as *Plasmodium* (later to become *Hepatocystis*) *kochi*. The second parasite did have multiplication in the peripheral blood and the authors considered it to be more closely related to the *P. inui* of Asia; they therefore established *P. inui* var. *gonderi*. The Asian parasites also received careful attention. A parasite described but not named by Knowles and Das Gupta (1932) from a *M. irus* (= *fascicularis*) from Singapore was considered by Sinton and Mulligan (loc. cit.) and was given specific rank as *P. knowlesi*, on the basis of morphological characters and on the presence of a 24- rather than a 48-hour schizogonic cycle. The parasite of Mayer, *P. cynomolgi*, was believed to be a separate species also, but the investigators (Sinton and Mulligan, loc. cit.) considered the information available at that time to be too meager; they therefore established *P. inui* var. *cynomolgi*.

So well had Sinton and Mulligan done their work that the only change made later in their taxonomic arrangements was elevation of the two "varieties" of *P. inui* to specific rank. Rodhain and van den Berghe (1936) found the African parasite to be tertian in periodicity rather than quartan, as in *P. inui*, and gave *P. gonderi* specific rank. Mulligan (1935) established *P. cynomolgi* as a species separate from *P. inui* on the basis of morphology and its tertian periodicity.

The work of Sinton and Mulligan (loc. cit.) became the base on which the future taxonomy of the monkey malarias was to be developed. Workers in Malaya and India in the 1960's faced a much less complicated problem, and with reasonable confidence, described five new species of malaria in monkeys from these areas.

The malarias of apes created a major problem in taxonomy. Much of the confusion arose because, for some time, their parasites were considered to be the same as their three morphological counterparts in man. *Plasmodium reichenowi* was given specific rank in 1922 by Sluiter, Swellengrebel, and Ihle. In 1939, Brumpt gave the *P. vivax* and *P. malariae* counterparts the specific names of *P. schwetzi* and *P. rodhaini*, respectively. Previous efforts had failed to establish these parasites in man, but Rodhain (1940) working with *P. malariae* transferred it, by blood inoculation, to the chimpanzee, and, in 1948, by the same route, transferred *P. rodhaini* from the chimpanzee to man. As a result of this work, some investigators have synonymized *P. rodhaini* with *P. malariae*. It is of interest in this connection that, as early as 1920, Mesnil and Roubaud had transferred *P. vivax* to the chimpanzee by blood inoculation but had not attached any significance to it. Recently, Contacos *et al* (1970) infected human volunteers with *P. schwetzi*, via mosquito bites, and pointed out the close similarity between the blood forms of *P. schwetzi* and of *P. ovale*. Coatney (1968) suggested that *P. schwetzi* might actually be *P. ovale*. The true relationship of these ape- and man-forms is still to be determined.

The taxonomic status of the malaria parasites of Asian apes is much less confused. Only one species, *P. pitheci*, has been found in orangutans. The situation with the gibbons is interesting in that taxonomic difficulties do not arise with the four distinct species known from these animals, but the systematic position of the apes themselves is so confused that it is sometimes difficult to clearly establish the type host for a given parasite.

The parallel histories of the malarias of human and non-human primates first became mixed when it was believed that the malaria parasites of the great apes of Africa were identical with those of man. Then in 1932 Knowles and Das Gupta reported the infection of a human volunteer, by the inoculation of blood stages of a parasite from the Malaysian monkey, *M. irus*. This parasite was later described as *P. knowlesi* by Sinton and Mulligan (1932). In 1934, Ionesco-Mihaiesti *et al*

successfully infected mental patients with a parasite which they believed to be *P. inui* but which was later identified as *P. knowlesi* (Garnham, 1966). Earlier, Clark and Dunn (1931) failed to infect man with the blood stages of *P. brasilianum* of the New World. The relationship between human and non-human primate malaras remained primarily of academic interest even though Mesnil and Roubaud (1920) had produced infection in the chimpanzee with *P. vivax* and Rodhain (1948) was able to induce infection in man with the *P. malariae*-like parasite of chimpanzees. All of these infections were blood induced and seemed to be of little natural significance. Then, in 1960, Eyles *et al* reported a natural infection of man with *P. cynomolgi*. True, it had occurred in the laboratory, but the transmission was accomplished by a mosquito. The fact that simian malaria was a true zoonosis was finally established by Chin *et al* (1965) with the report of a human infection with *P. knowlesi* acquired in the jungles of peninsular Malaysia. More recently, various workers have been successful in infecting owl monkeys (*Aotus trivirgatus*) with human malaras (Young *et al*, 1966; Porter and Young, 1966; Geiman and Meagher, 1967; Geiman and Siddiqui, 1969).

With the primate malaras, malariologists were provided with a tool for the controlled study of various aspects of malaria including drug responses, relapse mechanisms, immunity,

transmission studies, and pathogenesis. At the same time, unfortunately, Eyles's discovery (*loc. cit.*) raised the unwelcome specter of an animal reservoir for malaras infective to man. This situation underwent intensive study in Southeast Asia from 1961 to 1965 and the results form the substance of this monograph. The investigators concluded that the simian malaras of Asia might produce an occasional infection in man, but were not considered to be a serious public health problem. It was recognized, however, that such cases might threaten the eradication of malaria in the tropics where natural infections occur in monkeys and apes.

The 1970's find man's struggle against the malaria parasite still unfinished. The dream of eradication is no longer considered attainable within the foreseeable future in parts of Central America, South America, Africa, and Asia. The XXIInd World Health Assembly, meeting in Boston in 1969, called for a reevaluation of the concept of eradication with a reversion to classical approaches to control where necessary. Giant strides have been made against the disease, especially through the eradication programs, but we have probably reached the limit imposed by the techniques available and the last quarter of this century may need to be as innovative as was the first quarter, if we are to make real progress against the age-old scourge-malaria.

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(NS) = Not seen.