PERSPECTIVES IN MEDICINE: MALARIA

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INTRODUCTION

Malaria is a disease of man caused by the malaria parasites of man and transmitted from man to man by the bite of infective anopheline mosquitoes. The disease manifests itself, among other signs and symptoms, with the occurrence of intermittent fever.

To envisage the malaria situation in the world in general, and in the Malay Peninsula in particular, a hundred years ago with the vague empirical beliefs held then on various aspects of the disease, and to trace through the years of development and acceptance of progressive scientific views, is a subject of absorbing interest.

Fig. 1 Professor A. A. Sandosham MD DSc JSM PJK. Professor of Parasitology, Singapore 1950 - 1960. Author of *Malariology with special reference to Malaya* 1959. Senior Malaria Research Officer 1961 - 1963. Director of Institute for Medical Research 1964 - 1965.

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The occurrence of malaria is traceable to the remotest antiquity as judged by the references to the seasonal occurrence of intermittent fevers in ancient Egypt, India and China. Hippocrates, the Greek physician in the fifth century before Christ studied the clinical picture of malaria, recognising the different types of periodic fever. Little progress was made concerning the disease until 1640 when cinchona was introduced into Europe from Peru. It was specific for malaria and enabled the physicians to separate it from other fevers with which it had been confused.

Colonisation of the Tropics

A hundred years ago, the Europeans commenced the colonisation of the tropical region and opened up the countries for agriculture, commerce and industry. Throughout the history of tropical enterprises, the opening up of a country by felling jungle and planting, building roads and railways etc., was always followed by violent outbreaks of malaria (Fig. 2). This exerted a profound influence upon the colonialists as well as the indigenous people, affecting their health, vitality and retarding their physical development, social, intellectual and political progress.

Need to resolve problems locally

The problems of malaria vary from place to place and it is necessary to define and resolve the problems in each territory. The blind acceptance of conclusions arrived elsewhere and the adoption of measures

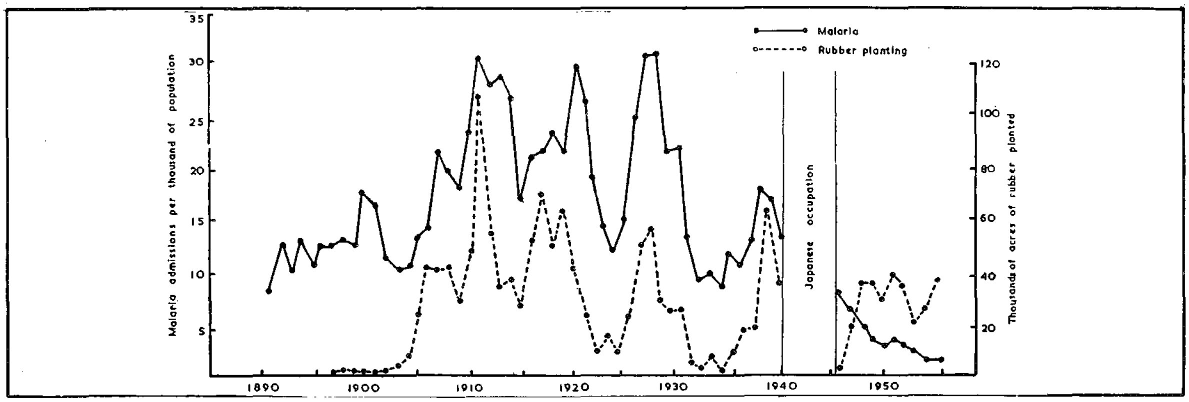

Fig. 2 Rubber planting and malaria(Courtesy: Malariology).

found satisfactory to deal with malaria in other countries, do not always meet with success locally. Malayan workers investigated their problems locally; these will be dealt with later under appropriate sections.

THE MALARIA PARASITES

The close association between swamps and marshes with malaria had long been noted. It was thought to be due to miasma or foul air (hence the Italian term *Mal aria*) or its close association with swamps (hence the French name *paludisme*) used to describe the disease.

Discovery of Malaria parasites

Since the days of Pasteur and other workers, it became evident that microscopic organisms invaded the human body and caused the illnesses of man. Malaria pigment was recognised in the tissues of the body in malaria cases. However, it was not till 1880 that a French army surgeon in Algeria, Dr Alphonse Laveran (Fig 3), first noted and described malaria parasites in the red blood cells of a patient. He examined fresh blood (liquid and unstained) and noted exflagellating forms from crescents which had rounded themselves. His discovery was either ignored, explained away or rejected as simply beyond belief for four years. Scientists were on a look-out for a bacterium of some sort.

Subsequently, other workers described in detail and named the malaria parasites of man as:

Fig. 3 Dr Alphonse Laveron MD, the discoverer of the malaria parasite(Courtesy: University of Malaya).

Plasmodium malariae **Laveran, 1881**; *Plasmodium vivax* **Grassi and Feletti, 1890**: *Plasmodium falciparum* **Welch, 1897**; *Plasmodium ovale* **Stephens, 1922.**

To this list must be added the parasites of non-human primates which have been implicated, though rarely, as natural infections of man namely: *Plasmodium cynomolgi bastianellii* **Garnham, 1959**; *Plasmodium knowlesi knowlesi* **Sinton and Mulligan, 1932**; *Plasmodium simium* **Fonseca, 1951.**

Of the above three species, Eyles *et al,* found human infections of *Plasmodium cynomolgi* from a monkey source (*Macaca fascicularis*) which had been taken to the United States from the east coast of the Malay peninsula. Chin *et al.*, reported a case of an American surveyor who had acquired *Plasmodium knowlesi knowlesi* infection while working at night in the jungles of Pahang, a state in the Malay Peninsula. Yap *et al.*, reported another case of a Malaysian with naturally acquired *P.k. knowlesi* infection.

Improvements in staining

In 1891 Romanowsky introduced oxidation products of methylene-blue (such as methylene-azure) to eosin (an acid stain) and methylene blue (basic stain), in stains which resulted in differential staining of the varying cellular elements, for example the chromatin of the malaria parasite staining a deep red (Romanowsky effect). Modified Romanowsky stains like Leishmans and Giemsa work best when there is no acid or alkaline bias thrown against their action by changes in the reaction of the diluent. Within recent years, there has been a tendency to use buffer solutions as diluents. The reaction of buffer solutions remains stable even when exposed to the action of small amounts of acid or alkali; in other words they act as a buffer against abrupt changes in pH. Field and Sandosham (1964) have pointed out that the aqueous stains show a definite superiority over methanolic stains. The introduction of the Romanowsky stains has enabled workers to recognise malaria parasites easily and describe them more accurately.

Electron-microscopic studies

The electron microscopic study of malaria parasites has revealed that the ultra-structure of the different species is generally similar except in the erythrocytic stages which is related to the intake and digestion of food by the parasite from the host cell.

The recently developed techniques for the continuous cultivation in the laboratory of the asexual erythrocytic satges of *P. falciparum* brings the day for vaccine production against this species

Fig. 4 Dr Hamilton Wright MD, Organiser and first Director of IMR, Kuala Lumpur 1900 - 1903. Author of *The Malaria Fevers of British Malaya 1901*(Courtesy: IMR).

nearer. *In vitro* cultivation has opened up the opportunity for carrying out experimental chemotherapy to assess the sensitivity of parasites to drugs. The ability to produce large quantities of erythrocytic-stage parasites will enable them to be used as antigens in immunological investigations and serodiagnosis.

The strains of malaria parasites

Within each species of malaria parasites, there may be different strains, antigenetically different. The strains may exhibit varying degrees of susceptibility to drugs and infectivity to vectors. There may also be differences in the incubation period, perpatent period, latency period, frequency of relapses, numbers of merozoites in mature schizonts, etc. Three strains of *P.vivax* were recently isolated in Malaya (Field *et al.*, 1965)

Work in Malaya

In Malaya, the work of Wright (1901) (Fig. 4) had established the presence in the country of *P. vivax*, *P. falciparum* and *P. malariae.* It is doubtful if *P. ovale* is endemic in this country although ovale-like parasites have occasionally been seen, which could have been variants of *P. vivax.* The 'spotty' distributions of *P. malariae* all over the world and its special association with the aboriginal inhabitants of a country rather than with its immigrant population has been noted in the Malay Peninsula. It was probably more prevalent in the early days of Malayan history than at the present time. Figures quoted by Wright (1901), Darling and others (1915-1917) give a percentage incidence of about 20 whereas the present-day percentage incidence is between zero and seven. It may however be the dominant species in isolated places. In a recent survey of some rural valleys in Negeri Sembilan, it was found that out of 1000 people examined, 181 were infected and 115 of these people were infected with quartan parasites. Without any control the quartan infection dropped in a few years to 9 out of 69 per 1000 examined. Green (1931) examined 165 Sakais (an aboriginal tribe) and found *P. falciparum, P. vivax,* and *P. malariae* and mixed infections, distributed in the proportion of 3:1:3:1. Thomas and Dissenaike (1977) detected fluorescent antibodies in 89% of the Malayan aborigines with *P. falciparum* antigen and 62% with *P. brasilianum* (for *P. malariae*) antigens.

Malaria parasites of non-human primates

The importance of the study of parasites of non-human primates was evident from the discovery of pre-erythrocytic stages in the liver of monkeys infected with *Plasmodium cynomolgi bastianellii* by Shortt and Garnham in 1948.

Eyles *et al.*, (1960) showed that *Plasmodium cynomolgi bastianellii* of a macaque could be transmitted to man by mosquito bites. Rodhain had shown that *Plasmodium malariae* occurs in African chimpanzees and that man is readily susceptible to this strain and *vice versa.* However, the likelihood of man becoming infected in nature with *Plasmodium malariae* from the ape source is small; but there are places where monkeys live in close association with man, both infected with closely related malaria parasites, hence the greater chances of being bitten by the same anophelines. In such places malaria may prove to be a zoonosis and monkeys could be a reservoir of infection as in yellow fever. The study of this problem was considered important and a team from USA composed of Eyles, Warren, Bennett, Dunn and Quinn worked in collaboration with the staff of the Institute for Medical Research in Kuala Lumpur comprising of Sandosham, Yap, Wharton and Cheong over a three-year period. They described several new species of malaria parasites, the various hosts they were found in and their distribution in Malaya. In addition to the findings of Eyles *et al.*, (1960) of the transference of *Plasmodium cynomolgi bastianellii* from a monkey to a man by a mosquito bite, there are two records in Malaya of the natural infection of *Plasmodium knowlesi knowlesi* in man by Chin *et al.*, (1965) and Yap *et al.*,(1971).

The experimental infection of the rhesus monkey by *Plasmodium cynomolgi* has occupied an important place in the testing of new antimalarial drugs. Young's finding that human malaria parasites can be transmitted to *Aotus trivirgatus*, a Columbian nocturnal monkey is a new area for chemotherapy tests. The animal hosts of human malaria constitute a ready source of obtaining large numbers of the different stages in the life history of malaria parasites as antigens for immunological studies and the possible preparation of vaccines.

The malaria parasites of non-human primates have been summarised in *Malariology with special reference to Malaya* by Sandosham and Thomas (1983) and Sandosham (1967) lists records of malaria parasites which have been identified in non-human hosts in Malaya.

Life history of Malaria

The transmission of malaria from man to man remained a mystery for a long time. There had been various speculations, however they lacked proof. References to the probability of mosquitoes playing a role had been made from time to time. However in 1883, King in an article entitled *Insects and disease mosquitoes and Malaria* advanced nineteen arguments in support of the thesis that mosquitoes conveyed the disease. Manson's (Fig. 5) Goulstonian lectures of 1894, based on his previous discovery of the mosquito-transmission of the human filarial infection, were the starting point of the scientific investigations of this problem.

Fig. 5 Sir Patrick Manson FRS. He showed that mosquitoes transmitted filariases to man and encouraged Sir Ronald Ross to work on transmission of malaria by mosquitoes(Courtesy: J.D.Gillet).

Ross (Fig. 6), at the suggestion of Manson and after many months of patient research, made an important discovery in 1897. He noted early stages of the development of the malaria parasites of man in the wall of the midgut of the dapple-winged mosquito. Sadly, he was transferred to a place where he could not continue with his life-history studies of human malaria. He worked on bird malaria and in 1898 worked out the complete life-history in sparrows. In the same year, Italian workers described the cycle in human malaria which they found to be identical with Ross's work with bird malaria and of which work they were conversant with. In 1900, Manson and his colleagues confirmed that malaria was transmitted by *Anopheles* mosquitoes. By protecting volunteers from being bitten by anopheline mosquitoes in a malarious area in Italy, they showed that infection could be prevented. At the same time infected mosquitoes could be brought from Italy to a non-malarious place in England and infect volunteers who were bitten by them.

It was long assumed on Schaudin's authority that the sporozoites injected into the blood stream of man entered the red blood cells directly. Raffaele in 1934 discovered that avian parasites developed in internal organs of infected canaries. Fairley working with human volunteers showed that the malaria parasites disappeared from the peripheral circulation within about half an hour of injecting sporozoites; malaria parasites reappeared only after five to eight days, depending on the species of *Plasmodium*. Garnham (1974) in Kenya showed *P. kochi* of monkeys developing in the liver. He joined Shortt in London and in 1948 they discovered in the liver of a rhesus monkey the pre-erythrocytic forms of *P. cynomolgi* (closely allied to *P. vivax* of man) of a macaque. In the following year Shortt *et al.*, described pre-erythrocytic stages in the parenchyma cells of the liver of *P. falciparum* in man.

Subsequently, these liver forms were shown to be present in all human malaria parasites. These tissue-forms developed into mature schizonts which liberated merozoites that entered the red blood cells and multiplied (schizogony). The completion of the primary exo-erythrocytic schizogony may be followed by the secondary forms as the result of re-entry of merozoites in the liver cells. These were regarded as being responsible for late relapses in malaria, although the latest theory is that certain sporozites remain in a dormant state (hypnozoites) for varying periods and cause relapses.

The distribution of Malaria

The geographic distribution of malaria is dependent on a wide range of climatic factors which affect the occurrence and density of vector species of anophelines and the development of the various species of malaria parasites on the insect host. Of the various factors involved, temperature seems to be the most important since the boundaries of malaria distribution, corresponding roughly to those of the mean summer isotherms of 60°F (15.5°C) which at their greatest divergence approximate to 60°N and 40°S latitude. Within this limit malaria occurs at altitudes ranging up to (1524 m) (5,000 ft) to (2,745.m) (9000 ft) above sea level; as latitude increases, the maximum altitude at which malaria is indigenous decreases.

Wilson points out that there is a close relation between the mean wet bulb temperature and the incidence of malaria in Malaya. It probably affects malaria by its influence on the mosquito since it has been found that insects have a body temperature

Fig. 6 **Sir Ronald Ross FRS. He discovered that mosquitoes transmit malaria(Courtesy: J.D.Gillet).**

corresponding to that registered by the wet bulb thermometer.

Broadly speaking, the highest incidence of malaria would have been the equatorial regions, declining as we proceed away from the Equator to the tropical, sub-tropical and temperate zones.

The prevalence of Malaria

The annual incidence of malaria in the world was estimated in the 1950s 'to be about 250 million cases with 2.5 million people dying of the disease each year. In 1980, twenty-five years after the initiation of the World Health Organisation (WHO) programme for the global eradication of malaria, it was estimated that 848 million people were living in areas where eradication or control programmes were in progress and that 343 million (the majority in Africa) were in endemic areas which were not protected by any specific anti-malaria measures. It was also estimated that every year, the disease causes the death of one million children under the age of 12 years.

Conditions in the Malay Peninsula during the closing years of the nineteenth century can be pictured from Carey ' s observations quoted by Watson (1921) (Fig. 7) on New Amherst Estate in the Federated Malay States, where malaria broke out in epidemic proportions among a non-immune community reported to work in a potentially malarious area. " Between the years 1892 and 1898 there were an average of fifty Tamil women on check-roll each year. Yet in the whole period no living child was born. Several women because pregnant, but only in one case did the child become quick, and even in this case the woman eventually had a miscarriage. The estate was so riddled with malaria that the coolies were all miserably anaemic and lacking in strength and the estate had eventually to be abandoned. ''The town of Jugra was abandoned at one time while orders were actually sent by telegraph by the High Commissioner to close down Port Klang within two months of its being opened, because of malaria.

Fig. 7 **Sir Malcolm Watson MD. A pioneer malariologist of Malaya (1901 - 1927) who successfully introduced anti-larval control measures directed specifically against the vectors (species sanitation) (Courtesy: Journal of Tropical Medicine and Hygiene).**

THE TRANSMISSION OF MALARIA

Distribution of *Anopheles*

There are about 400 species of anopheline mosquitoes in the world and of these, only about 60 are important vectors of malaria under natural conditions. Owing to the limitation of zoo-geographic distribution, only a small number of these are encountered in any particular region. Malaysia is one of the sub-regions of the Oriental Region but the border line separating it from its neighbours is not sharply defined and species characteristic of the adjoining sub-regions tend to extend into its zone.

Even within the confines of the Malay Peninsula, a number of species exhibit a discontinuous distribution, which may be due in some cases to climatic differences and in others to the development of new species or sub-species by geographic isolation, resulting from land changes in recent geologic times. Another feature of geographic distribution of Anophelines worthy of note and which is probably related to climate, is that members of the sub-genus *Anopheles* are distinctly more numerous in the Malaysian part of the Oriental Region, with its uniform climate supporting evergreen tropical rain forests. About 60 species and sub-species of *Anopheles* are currently recognised as being present in the Malay Peninsula.

Vectors of malaria vary from place to place; a vector in one area need not necessarily act as a vector in another area. The inherent susceptibility of an Anopheline mosquito for the full development of a malaria parasite varies according to the species of *Plasmodium* and its strain, whether or not it bites man repeatedly in sufficient numbers, whether it lives long enough to permit the development of the malaria parasite to form sporozoites which find their way to the salivary glands.

Experimental infections

Much work has been carried out in the Malay Peninsula since the turn of the century to elucidate these points. Attempts were made to establish the relative susceptibility of different anophelines under experimental conditions. The introduction of the artificial mating of anophelines has enabled the maintenance of colonies of these insects in the insectariums.

Eighteen species of five-day-old anophelines were bred in the laboratory, starved and given the same opportunity of taking blood from gametocyte carriers. Sixteen days after the blood meal those that took blood were dissected for evidence of oocysts or sporozoites or both. About 4000 dissections were made. The results showed that few, if any, Malayan species of *Anopheles* are incapable of becoming infected under suitable conditions by local strains of *Plasmodium falciparum* and *Plasmodium vivax.* There are limitations to laboratory infectivity experiments in determining the relative importance of anophelines under natural conditions because it was found that two inocuous species as determined by epidemiologic evidence like *A. vagus* and *A. kochi* were found to be readily infected. Other factors have to be taken into account.

Feeding preferences

An anopheline mosquito that showed a marked preference for human blood (anthropophilic) as compared with animal blood (zoophilic) might well prove to be an important vector of malaria. When attempts were made to test this by giving various Malayan anophelines opportunity to consume human blood, it was found that *A. maculatus*, the most important vector, showed the greatest avidity (more than 70% engorging themselves). *A. maculatus* is a non-vector in Kalimantan (Borneo) and indicates there is a geographic difference in the innate degree of attraction to man in this species.

A comparison of the relative abundance of different species of anophelines caught in human-bait traps placed near human habitations and at nearby cattle sheds may give some indication of their basic feeding preferences. When catches were made in this way on three estates it was found that *A. maculatus* headed the list for human-bait trap.

The source of a recent blood meal of an anopheline mosquito can be determined by carrying out precipitin tests. A large number of such tests has been carried out in the Malay Peninsula and *A. maculatus* and *A. umbrosus* head the list.

Length of life

The natural length of life of an anopheline mosquito is of importance as a transmitting agent of malaria because prior to the infective bite, the infecting blood meal must have been digested, the oocyte matured and ruptured, and the sporozoites ready in the salivary glands for injection. Information regarding longevity of each species under natural conditions is, however, difficult to obtain. Parasites and predators probably take a heavy toll of anopheline life. Some indication of the natural span can be obtained by observing the number of days that members of each species survive under laboratory conditions. The maximum age (in days) observed when one blood meal had been taken was 66 for *A. maculatus*, 63 for *A. barbirostris* and 59 for *A. umbrosus*, while those of the known non vectors were much lower.

Some indication may be obtained of the age of an anopheline mosquito by noting the degree of damage to the wing fringe and the extent to which the scales of the abdomen are denuded. The presence of attached water mites to the body and meconium (larval food) in the stomach are evidence of immaturity in mosquitoes. Dissection may show the presence of retained eggs in ovaries. The sporozoite rate, the proportion that have laid eggs and the appearance of tracheoles in ovaries may give some information on the longevity of anophelines.

Natural infections

An opinion as to the danger of an anopheline species may be formed by observing the degree of natural infection encountered in mosquitoes trapped in the wild. More than a hundred thousand dissections have been made in the Malay Peninsula; in attempting to interpret the findings, it must be remembered that often the human-bait was used and collections were made near labourers ' settlements. In some cases, infections could have been of malaria parasites of monkeys and other mammals.

Epidemiologic findings

The ralative importance of the species of *Anopheles* may be obtained by the combination of sporozoite rates and the numbers biting a person from which it is possible to estimate the number of infective bites. The incrimination of a species has often been the result of epidemiologic investigations; the occurrence of malaria only where a particular species was present or where it was the dominant species. With added information regarding feeding preferences, prevalence and the extent to which they are found infected in nature, the following list of Malayan vectors can be presented as:

Anopheles (Cellia) maculatus **Theobald, 1902**;
Anopheles (Anopheles) letifer **Sandosham, 1944**;
Anopheles (Cellia) sundaicus **Rodenwaldt, 1925**;
Anopheles (Anopheles) campestris **Reid, 1962**;
Anopheles (Anopheles) umbrosus **Theobald, 1903**;
Anopheles (Anopheles) nigerrimus **Giles, 1900**;
Anopheles (Cellia) dirus **Peyton and Harrison, 1979.**

To the above list may be added the following as potential vectors; *Anopheles (Cellia) minimus* **Theobald, 1901**; *Anopheles (Anopheles) whartoni* **Reid, 1963**; *Anopheles (Anopheles) donaldi* **Reid, 1962.**

A. aconitus, A. barbirostris, A. sinensis, and *A. philippinensis,* known vectors elsewhere, do not transmit malaria in the Malay Peninsula.

The distribution of vectors

The vectors differ in different ecological zones according to the nature of the terrain and vegetation. Thus, the country may be broadly divided into three main zones namely, the brackish water zone, the coastal plain, and the hills and mountains (Fig. 8). Within these categories may be found dichotomies based on whether or not the land has been cleared of jungle and cultivated: further subdivisions are also possible. However, there are no hard and fast lines between these zones. Even if the zones can be rigidly demarcated and the breeding of the vectors confined to a particular zone, these anophelines may extend their influence for a distance of a half a mile or more into neighbouring areas.

The Brackish Water Zone is a narrow strip along the coast extending for varying distances up the big rivers. In the untouched mangrove swamps, no vector species of anophelines breed and the area is free from malaria transmitted by brackish water breeders. When the mangrove is cleared and the tidal waters come in contact with the exposed collections of fresh water, *A. sundacus* breeds prolifically and becomes responsible for malaria transmission there.

The Coastal Plains, which extend from the tidal zone to the foothills vary considerably in extent in different parts of the Peninsula. The vector species of the untouched jungle swamps is *A. umbrosus.* When such a jungle swamp adjoins cleared areas under cultivation, *A. umbrosus* emerges from the jungle to bite man living within half a mile and transmits malaria. When the jungle is cleared for cultivation, *A. umbrosus* is replaced by *A. campestris* and *A. letifer.*

The hills and mountains intersected by numerous valleys form the backbone of the Peninsula. The virgin hill jungle is sparsely populated but the nomadic aboriginal tribes are infected, transmission being effected by members of the *A. leucosphyrus* species group and *A. umbrosus* species group. Whenever the cover of the jungle is removed from hilly areas, *A. maculatus* breeds readily and transmits malaria.

CLINICAL ASPECTS OF MALARIA

Malaria is a chronic disease in which a series of classical febrile paroxysms occur, separated by apyrexial periods of varying lengths. In its classical form the febrile attack, which is related to the rupture of a sufficient number of mature schizonts, starts after an incubation period of varying lengths (usually eight to fourteen days in Malaysia) after the infective bite preceded by prodromal symptoms and a stage of shivering (rigor). The hot stage, accompanied by headache and nausea, is followed by profuse perspiration and fall of body temperature. The apyrexial interval varies according to the species of parasite being of 48 hours in tertian infections and 72 hours in quartan species.

In areas where the population is exposed to heavy repeated infections, the people develop tolerence to malaria in ten to fifteen years at the cost of a high death rate among the children. The adults may have afebrile parasitaemia or at most develop mild clinical symptoms. This form of immunity is also strain-specific, but owing to repeated infections

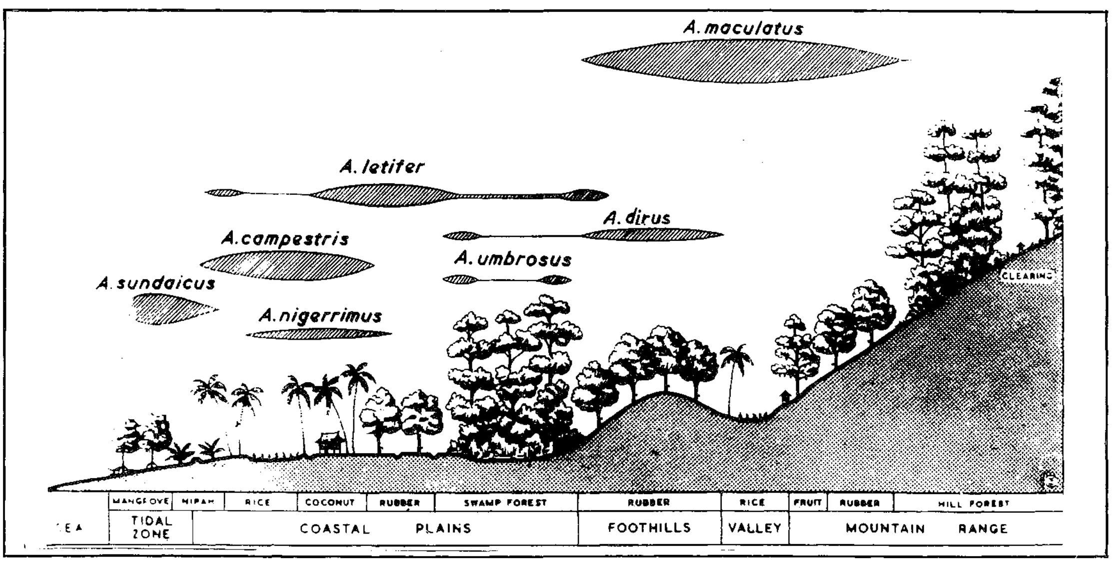

Fig. 8 Distribution and abundance of vectors(Courtesy: Malariology).

by all strains of malaria parasites prevalent locally, the immunity will be polyvalent.

Diagnosis of Malaria

This is dependent on the finding of the malaria parasites in the blood. The preparation and examination of thin blood films takes time and often clinicians want quick results in order to start treatment. The thick blood films are an advantage because of the concentration of parasites in a small field.

Unfortunately, the drying of the thick films and the staining take time and while satisfactory for survey work it is too time-consuming for clinical needs. Field (1941) (Fig 9) introduced a rapid method of staining thick blood films which revolutionised the diagnosis of malaria. Staining is possible as soon as the thick blood films cease to be obviously moist, i.e. usually within a few minutes of preparation and the films are ready for examination under the microscope in a matter of minutes instead of hours.

Splenic enlargement

The spleen plays a large part in the defence of the host against malaria and increases in size owing to the circulatory and congestive changes initially. Later the immunologically important lymphoid and reticuloendothelial cells undergo hyperplasia. The spleen enlarges with the febrile paroxysm becoming large enough to be palpable below the costal margin in a few days, particularly in children. Occasionally, the spleen becomes abnormally enlarged, extending well beyond the umbilicus to constitute the immunopathological entity known as tropical splenomegaly syndrome or big spleen disease. This condition has not been noticed in this country.

Malarial Cachexia

Persons repeatedly infected by malaria and neglected or imperfectly treated, tend to pass into a chronic condition known as Malarial Cachexia. The individual is extremely anaemic with earthy complexion and puffy face. Development is retarded,

Fig. 9 John W. Field CMG MD DSc (Courtesy: Yap Loy Fong).

and children are stunted, while adolescents frequently have undeveloped genitals and child-like appearance. Mental disturbances, fatigue and dislike of mental work are noticeable. Impotence and lack of sexual desire are common. This condition was not uncommon in pre-war years on very malarious estates but is relatively rare today.

Blackwater Fever

This occurs typically in people who have repeated and severe attacks of falciparum malaria imperfectly treated. The disease results from an acute haemolysis of the red blood cells, liberating the haemoglobin into the blood stream, in turn producing haemoglobinuria. This condition is relatively rare in this country but during the War, there was a considerable outbreak among non-immunes from Singapore sent to cultivate a very malarious place in Negeri Sembilan.

EPIDEMIOLOGY OF MALARIA

Even in a small place like the Malay Peninsula, the incidence of malaria, the anopheline vectors and other factors responsible for malaria vary considerably from place to place. A malariologist should therefore undertake to define the problem in a particular locality before a control programme could be formulated.

The epidemiologist is a medical detective who gathers information, analyses it and provides the explanation and guidance leading to the control, prevention and ultimately the eradication of the disease from the community.

The epidemiologists have carried out spleen and parasite rates from time to time and determined the endemicity of malaria in the different parts of the country at the time of enquiry. At the same time, anopheline surveys have been carried out to determine the local vectors, their prevalence and bionomics. The staff at the Institute for Medical Research, Kuala Lumpur have done much to elucidate the malaria problems in the country. These include Wright, Daniels, Stanton, Leicester, Strickland, Hacker, Pratt, Gater, Wharton, MacDonald, Cheong, Green, Field, Wilson, Edeson, Laing, Sandosham and Yap.

Of the Government and Estate Health officers, special mention must be made of Sir Malcolm Watson, a pioneer antimalaria worker in the country. By careful observations and experimentation, he was able to recognise the vectors of the tidal zone, the coastal plains, the inland plains, and the hills and apply specific control measures adapted to their habits. Other workers in this group include Travers, Wellington, Howard, Crawford, Barrowman, Wallace, and Waugh Scott.

As a preliminary to carrying out parasite and anopheline surveys, the investigators should acquaint themselves with the geography and the topography of the area, provide themselves with an adequate supply of up-to-date maps and carry out a geographic reconnaisance to determine the number of houses, their location, accessibility, type and the number of inhabitants. A knowledge of the customs and living conditions of the people is helpful. Information should be obtained of the metereologic conditions of the place.

Measurement of Malaria

The vital statistics of the place should be obtained as also the records of hospital admissions and attendances at out-door clinics and travelling dispensaries. Weekly returns of absentees from schools may also provide a clue to malaria incidence. Personal interviews of a number of individuals regarding their fever histories may be helpful.

The determination of the spleen rate is probably the most important single item which will help one to arrive at the intensity of malaria transmission in the district. The determination of the size of the enlarged spleen is useful. A parasite survey should aim at obtaining not only the parasite rate (the percentage of people with parasites in any age group) but also the parasite density (the average parasite count of the group).

Serodiagnostic techniques may prove useful in the epidemiologic assessment of malaria. It may help to supplement and complement the information obtained by determining the spleen and parasite rates. Having assembled all the relevant data, the epidemiologist should use his mature judgement to determine the amount and intensity of malaria.

Anopheline survey

This should be undertaken to determine the anopheline vectors in a particular locality and to study their prevalence and bionomics with a view to the application of this knowledge to their control.

The larval survey should be conducted systematically. The team should be adequately equipped with notebooks, pencils, map-tracings, dippers, spoons, pipettes, bottles with blank labels and some device for carrying them. The larvae should be transported in collecting bottles to the laboratory for identification and rearing as necessary. The larval and pupal pelts may be preserved and the hatched out adults identified.

The adult survey should reveal information on the occurrence, density, seasonal prevalence, longevity, feeding habits, susceptibility to infection and other aspects of the bionomics of the mosquitoes. Adult anophelines may be caught in houses, especially in the early mornings, on mosquito nets, or biting man (bare-leg catch). They may be caught in cattle sheds by automatic trapping methods, human-bait traps or window-trap huts. The mosquito is best caught by slowly placing over it with the mouth of a test tube. When the mosquito has flown into the tube, it is plugged with a piece of absorbent cotton wool dampened slightly to prevent the mosquito from dying. It is taken to a laboratory and identified. It may then be dissected or mounted as necessary. If engorged females are caught, the source of the blood meal may be identified by means of precipitin test. If an anopheline is dissected the midgut and salivary glands are examined for oocysts and sporozoites respectively.

Survey report

Having collected the data necessary for making an epidemiologic diagnosis of the malaria problem of a locality, a survey report should be prepared embodying in a summarised form all the available data together with tables, charts, sketches, maps and photographs.

The report should also give an analysis of the data assembled, emphasising the relevant facts and the investigator's conclusion on the malaria of the locality.

Finally, the report should include an opinion on the practicability of control and antimalaria measures or combination of measures best calculated to solve the local problem. If possible, it would be preferable to submit a detailed outline of the project by which these measures can be put into operation.

CONTROL OF MALARIA

General principles

According to Watson (1921), when Ross' discovery that mosquitoes transmitted malaria from man to man was first announced in 1898, it was treated with undisguised incredulity; when confirmed it was said to be intresting but valueless.

Malaya can claim to the honour of being one of the earliest countries in the world to have successfully applied the knowledge of the mode of transmission of malaria to its control. Attempting to control malaria by getting rid of mosquitoes seemed an impossible task as there are hundreds of these insects. Even when it was established that only anopheline mosquitoes carried malaria, the problem appeared collosal. No less that 400 species are recognised in the world today. Luckily, in any one locality only few of these are present owing to the limitation imposed by zoo-geographic distribution of anophelines. Even so, in a relatively small place like the Malay Peninsula, there are no less than 60 species of mosquitoes belonging to the genus *Anopheles.*

Luckily again, it was found that of the anopheline mosquitoes in any one country, only half a dozen or so were vectors of malaria and that not all of them were encountered in any one ecological zone. The recognition of these facts was due to the genius of anti-malaria workers like Sir Malcolm Watson and the painstaking researches of malariologists and entomologists. This knowledge led to much saving of energy, time and money by concentrating one's efforts against the vector species only (species-sanitation). The raising of the living standards of the people is in itself a valuable adjunct to antimalaria endeavours. Several countries of Europe and North America found that malaria receded with improved socio-economic conditions and without the application of any specific control measures against malaria, a situation referred to as 'Anophelism without malaria'.

Measures directed against aquatic stages

At the turn of the century, it was realised that it would be easier to attack the aquatic stages of the vectors than the adults on the wing. Even so, the control of malaria by antilarval measures was no simple matter. Watson (1921) says, " so far from the map of Malaya being evenly washed with the malaria taint, violent contrasts have been found in different parts and widely different, often diametrically opposed methods have been found necessary for its control. Some land, when covered with jungle, had been found to be malarial and some non-malarial; some land has become healthy when cleared of jungle, and some has become intensely malarial when so treated; drainage frees some land from malaria, but some remains malarial; some land is malarial whether drained or undrained, whether under jungle or cleared of jungle, some rice fields are malarial and some non-malarial; while in a single ravine, the various insect inhabitants may come and go in the wondrous fashion of a fairy tale ".

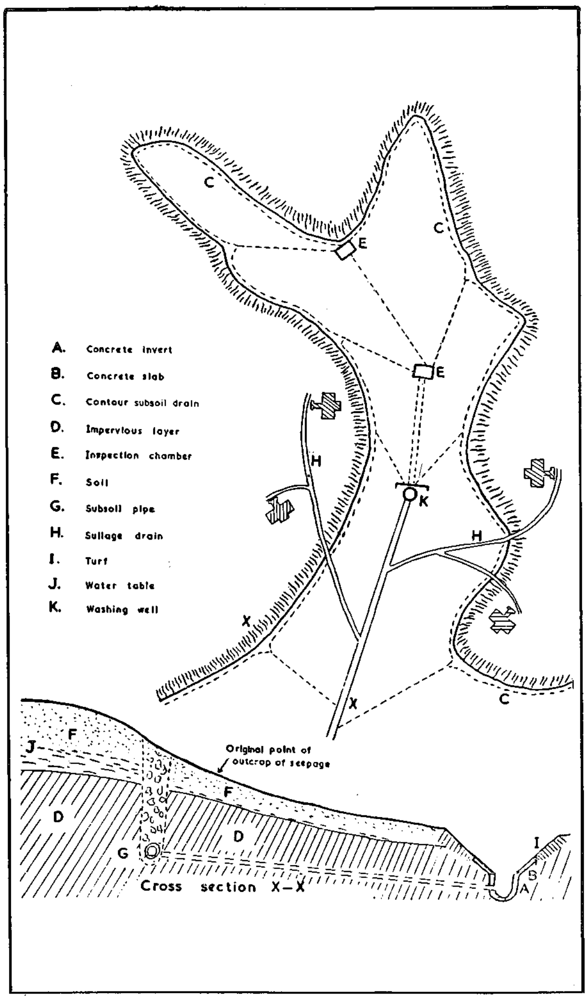

Fig. 10 Sub-soil drainage of ravine (Courtesy: Malariology).

It was realised that the multiplication of vectors may be prevented by removing all potential breeding places by filling or drainage (Fig. 10). Local researches had shown that collections of water may be rendered unattractive to vectors whose bionomics is known, by altering conditions of shade, movement of water, the degree of pollution or salinity, the amount and type of vegetation present, etc,. The aquatic stages can be destroyed by the use of the toxic substance such as petroleum-derivative oils, contact poisons like DDT and alimentary poisons like Paris Green, and by upsetting the ecologic balance of the breeding places through the introduction of natural enemies like fish, eliminating sources of food supply, etc.

Measures directed against the adult stage

Adult vectors may be killed by the use of insecticides and other toxic substances distributed in the air in the form of sprays, fumigants, smokes, fogs, etc. The residual insecticides may be sprayed on the walls of houses and other resting places periodically. The use of baited or light traps and the introduction of the natural enemies of mosquitoes may destroy a number of vectors. Adult mosquitoes may be prevented access to human beings by animal deviation, the destruction of daytime resting places of vectors near human habitations, rendering houses unattractive by creating repellant barriers of odoriferous plants and chemicals.

Measures dealing with humans

People may be protected from the bites of vectors by siting homes half a mile or more from their breeding places or screening the houses. The use of protective clothing, mosquito nets, repellants and insecticides like pyrethrum in atomised sprays are helpful.

The prompt and complete treatment with drugs of all infected persons will reduce the number of gametocyte carriers in a community or reduce the number of gametocytes undergoing development in the body of the vectors. It has been shown that the administration of suppressive doses of drugs will keep malaria parasites (including gametocytes) low in the peripheral circulation during that period thus preventing vectors from becoming infective.

A hundred years ago, we were aware of the value of the quinine in the treatment of malaria although there were instances of doctors resorting to blood-letting. The bark of the cinchona tree was brought to Europe from South America by the Spaniards about the year 1640 for the treatment of intermittent fever. Subsequently, one of the alkaloids with the therapeutic effect against malaria which was first isolated, namely quinine, held a dominant position until World War 1.

When the Germans found themselves cut off from their regular source of quinine which mainly came from Java, India and Sri Lanka, they synthesized pamoquin and mepacrine. Because of its toxicity, the former did not come into general use and the Germans synthesised chloroquine. During World War II, the British produced proguanil, and the USA and UK subsequently introduced pyrimethamine. Since then sulphones and sulphonamides have been added. Fansidar (a combination of sulphadoxine and pyrimethamine) and mephloquine are found effective against chloroquine-resistant falciparum malaria. Repository drugs with long-acting injectable prophylactic action are under field trial.

In 1921, Fletcher began inquiries in Malaya on the possibility of devising improved methods of treatment of malaria by quinine or other alkaloids of Cinchona. Green, Wallace, Field, and Niven made valuable contributions to chemotherapy and the prophylaxis of malaria in this country. Field and colleagues established the high suppressive value of atebrin in those living in areas of heavy transmission of malaria (Fig. 11).

Had this information been used by our troops from the early days of World War II, thousands of lives would have been saved. Since the last war, chemotherapeutic research with the newer drugs has been continued by Field, Wilson, Edeson, Laing, Ponnampalam, Andre, Lewis and Dondero in this country.

The main purpose of collective drug prophylaxis is to protect the population undergoing prophylactic treatment from the direct clinical manifestations of endemic malaria in order that its working capacity may be safeguarded. The plantation population, labour forces on temporary construction work and military forces have been successfully dealt with by this method. School children have been dealt with by teachers with little additional trouble.

Field and Edeson (1949) first established the development of resistance to proguanil of *P. falciparum* and later by Wilson *et al.,* (1953) of *Plasmodium vivax* in Malaya. Cross resistance appeared and it was established that *Plasmodium falciparum* resistant to proguanil became resistant to pyrimethamine also. Chloroquine had held a dominant place in malaria therapy for nearly two decades but Sandosham (1963) showed the existence of chloroquine resistance among the indigenous

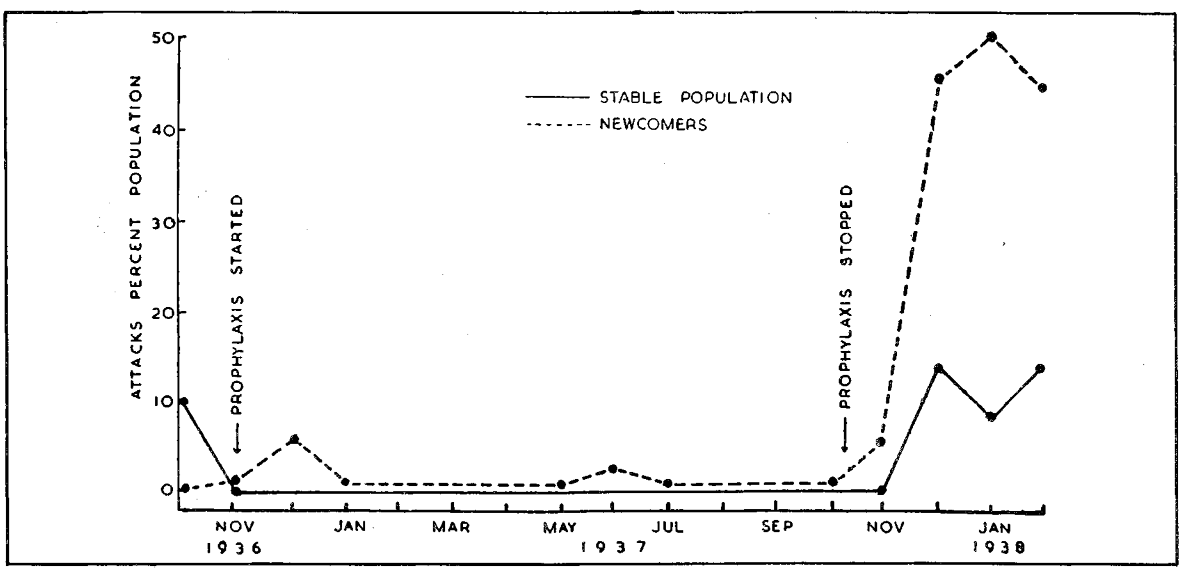

Fig. 11 Malaria in estate with atebrin prophylaxis (Courtesy: Malariology).

population in North Malaya. In some cases, they showed cross-resistance to amodiaquine and mepacrine. The presence of chloroquine-resistant falciparum malaria has also been noted in other parts of Malaya mostly consistent with late recrudescence RI type.

ERADICATION OF MALARIA

Although the concept of the complete eradication of malaria from the world had been accepted as feasible by the World Health Organisation as early as 1955, Malaya, unlike some of its neighbours, had not initiated a nationwide campaign until 1967. This delay may at first appear strange, considering that Malaya has been a pioneering country in malaria control. But for one thing, Malaya has been preoccupied with waging war with Communist terrorists and it was not till 1959 that the state of emergency was lifted. For another, some Malayan malariologists , for example Sandosham (1962) were not convinced that eradication campaigns successful in certain other countries would necessarily meet with success in Malaya.

It was the discovery by Paul Muller of Switzerland in 1939 of the insecticidal action of DDT and its use during the Second World War that revolutionised our views on malaria control. The residual insecticides proved to be the most reliable, feasible and economical method for the interruption of transmission. Greece was one of the countries where use of DDT had decreased the vector population and malaria had disappeared. War broke out in Korea in which the Americans were involved and the Greeks could not afford the increased cost of DDT and equipment. They decided to stop spraying certain places. The anopheline vectors returned in these areas in numbers and the authorities kept their fingers crossed expecting a return of malaria. It did not happen. What had happened was that the period of spraying had interrupted transmission and the disease itself being self-limiting (relapses usually last two or three years) had died out.

From this spectacular results of DDT spraying, grew the idea that a few years of intensive and thorough spraying of residual insectives on the walls of the inside of houses would eradicate the disease from a locality. The World Health Organisation thus started a worldwide programme and began coordinating activities and the provision of technical assistance.

Our neighbouring countries like Sri Lanka, Philippines and Pakistan had started their campaigns early but had their setbacks: Sri Lanka for instance had almost achieved eradication when there was a resurgence in 1954. Once again they were on the brink of total victory in 1962 but could not prevent malaria from returning in epidemic proportions (Harrison 1978).

In spite of this, Malaya officially launched its Malaria Eradication Programme in 1967 and in 1982, a third of the country was still in the attack phase, more than 11,500 cases having been recorded in that year. Instead of the estimated costs of $85 million to completely eradicate the disease, we have spent $120 million with no eradication in sight.

The World Health Organisation itself has realised that global eradication of malaria is not feasible and has advocated a 'flexible 'malaria control programme so that each country can develop its own long-term plan within its overall health plans and work towards its own goals according to its means.

THE FUTURE

There still remain many problems in malaria that require elucidation. the differentiation of the strains of the malaria parasites of man and the sorting out of the sibling species of *Anopheles* and the species complexes have to be carried out. A study of the genetic organisation and the manner in which the genetic factors are inherited are indicated. Enzyme electrophoresis and the biochemical characteristics of DNA may prove to be of value.

More electron microscopic studies of the inner structure of all stages of the malaria parasites is necessary. Newer drugs have to be synthesised and chemotherapeutic tests have to be carried out. Further tests have to be made before mephloquine can be safely put on the market because of its value for the treatment of falciparum malaria resistant to other drugs.

Work towards the development of a vaccine or vaccines against malaria should be extended. Trager 's continuous *in vitro* cultures of *P. falciparum* have to be continued as it may lead to the development of vaccine against this dangerous species. The value of 'Qing Ho Su ' a drug extracted in China from a medicinal herb has yet to be established. Immunological reagents and techniques have to be standardised to allow valid comparison of the results obtained by different workers in different areas and countries. Vaccines to form T. cell in macrophages are desirable. The programme to raise the living standards and the educational level of the people should be continued.

The bibliography of malaria is large and the following list of selected references concertrates on those of the very early workers and those related to Malaya.

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