Essential Malariology

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To Joan
and in memory of
Dr Emilio Pampana

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Leonard Jan Bruce-Chwatt

Foreword

Malariology – science and practice, has progressed importantly since last described in an authoritative text. Life histories of plasmodia and anophelines are better known, interactions with man more clearly understood, phenomena of immunity give more promise of helpful vaccines, wide spectra of drugs and insecticides have been explored, physical, chemical and biological control methods have been improved, and a most important concept of malaria eradication has had considerable success.

In 1955 the World Health Organization began a malaria eradication campaign that was strongly supported by the Pan American Health Organization, the United Nations Children's Fund, the US Public Health Service, the US Agency for International Development and its predecessors, and by many national health departments. Directly and indirectly this program resulted in the eradication of malaria from the United States, most of Europe, much of the Middle East, important areas in the Caribbean and South America. Two of the most malarious islands in the world, Taiwan and Mauritius, were completely freed from malaria. In India malaria incidence was reduced from millions of cases to an estimated 50 000 cases in 1961. In Sri Lanka (Ceylon) success seemed at hand.

But today malaria is tragically resurgent in Asia and in certain areas elsewhere. Estimates of malaria cases in India in 1977 were as high as 30 million! Malaria also returned to high incidence in Sri Lanka. Numerous failures to eradicate have occurred also in Central and South America. In fact, it seems reasonable to estimate that malaria incidence in the world today is as high as it was half a century ago.

Reasons for the present situation include increased costs of insecticides and labour, inability to obtain, or prohibition to use, DDT, and resistance of plasmodia or anophelines in localised areas to chemical weapons. Most importantly, adequate training of malariologists has been rare, and there has been a crippling decline in the attention devoted to malaria control by international, national, and philanthropic agencies. Other health problems have seemed more urgent or more interesting.

Very likely the demonstration of malaria's power of damaging human health and slowing down socio-economic advance will soon stimulate a revival of interest in malaria control.

In my opinion few men are so well prepared to write *Essential*

Malariology as is Prof. Bruce-Chwatt, whom I first met in 1950 in Lagos, where he was an energetic malariologist. During his brilliant career he has practiced this speciality in laboratory and field and at the director's desk, dealing with local and national areas and later with some international problems.

The author was for many years in the service of the Federal Government of Nigeria and of the World Health Organization. He then became Director of the Ross Institute and Professor of Tropical Hygiene at the London School of Tropical Medicine.

I welcome this concise and authoritative book, especially at a time when malaria is increasingly prevalent and neglected.

North Edgecomb, Maine, USA
July 1978

Paul F. Russell, MD, MPH
Formerly, Member Field Staff,
Rockefeller Foundation;
Chief Malariologist,
Allied Military Government, Italy;
Malaria Consultant to
Surgeon General, US Army and
to the World Health Organization.

Introduction

No one who has followed over the past five years the annual reports of the World Health Organization on the situation of malaria, can doubt that the former rapid progress of the eradication of this disease has now come to a halt and that the resurgence of the infection causes much concern. The number of confirmed cases of malaria reported to the WHO increased from 3.2 million in 1972 to 7.5 million in 1977, but this is only a small proportion of the total number of cases. Malaria continues to be a major problem of tropical developing countries and the recent years have seen the return of it to areas freed from the disease in the 1960s.

The causes of this setback to a unique international health endeavour have often been analysed and commented upon. Certainly technical factors such as resistance of insect vectors to insecticides played a major role in these reverses of fortune. Not less and probably more important were other, often imponderable factors. Inadequacy of planning, administrative shortcomings, financial stringency, shortage of personnel, poor training were equally responsible for the recent shift of strategy from malaria eradication to malaria control in countries not equipped for the undertaking of a complex and difficult programme of eradication.

One of the first steps needed for a realistic approach to the problem of malaria is to admit that we have not developed the technological means to control this disease in all circumstances. We have reduced the malaria morbidity and mortality over large areas of the world at the periphery of the natural geographical distribution of the disease but the core of endemic and epidemic malaria in the tropics remains.

The close relationship between disease and socio-economic advance of developing tropical countries has been abundantly proved. It is now clear that the successful implementation of malaria eradication requires a certain minimum level of basic health services. In countries where malaria is a serious impediment to general advance there is now a new drive for reduction of the burden of the disease to pave the way for speeding up the pace of socio-economic development, which may in the long run contribute to a future eradication of malaria.

One should beware of the error of considering malaria control as a poor man's malaria eradication. On the contrary, malaria control, because of its very flexibility, its adaptation to variable epidemiological conditions, its dependence on social, administrative, and even political

conditions of the country or area concerned, presents new challenges and demands knowledgeable and determined leaders.

With the general recognition of the magnitude of our unfinished task came the understanding of pressing needs for further research into methods of malaria control and the return to the provision of adequate information on many essential aspects of parasitology, entomology, epidemiology, prevention, treatment and control of malaria. It is a fact that the older generation of malariologists has largely disappeared and the number of professional workers in tropical community health competent in the field of malaria control is woefully inadequate, while the need for them is steadily growing. In the context of factors related to the inadequacies of personnel and training, good leadership is an essential ingredient of success. Leadership is often an innate quality of an individual but it may be enhanced by judicious selection and proper training. The renewed concentration of both the national governments and international organisations on the provision of and assistance to training centres in malaria control is a good augury for the future.

The past progress of malaria eradication in advanced countries has engendered among many public health administrators, practising clinicians and the general public a false notion, that malaria is a vanishing, if not a vanished, disease. This undue optimism, largely based on the ignorance of the true situation, has often led to the neglect of recognising the infection brought into a non-endemic area of the temperate world by travellers arriving from the tropics. A number of tragic deaths due to missed diagnosis of malaria or to its wrong treatment have caused much concern among the medical profession. The need for more and easily available information on this subject has often been stressed.

The provision of concise and up-to-date description of clinical and public health aspects of human malaria is the purpose of this book. It attempts to present in a factual and readable form the principles and practice of prevention, diagnosis, treatment and control of malaria in individuals and in communities of both advanced and developing countries.

Its approach has been inspired by Dr Paul F. Russell's most successful primer, published a quarter a the century ago. Like Russell's *Malaria: Basic Principles briefly stated*, the present book does not intend to elaborate on all, often highly specialised and increasingly complex branches of applied science, which contribute to the sum total of the discipline of malariology. For this some of the older books, quoted in the references, are still unsurpassed, while much of the newer knowledge will be found in publications and other documents of the WHO, that form an admirable source and constant stream of authoritative information.

As a precept to this text which presents the essentials of the practical

approach to an ancient disease, that still defies our ability to eradicate it, but which nevertheless can be substantially reduced, one could do no better than by quoting the following words:

> 'Malaria control is as simple as prescribing two tablets of chloroquine a week, and it is as complex as the distribution of residual DDT on the walls of 3 million houses in Brazil in one single year. It is as easy as releasing an aerosol spray and it is as technically difficult as the anti-anopheline engineering operations of the Tennessee Valley Authority. The old sayings: "Haste makes waste", and "Look before you leap" as well as "Nothing ventured nothing gained" all have basic implications as regards to malaria control schemes, but the greatest single danger lies in fetishes sometimes cherished by all sanitarians, who should keep their minds as cleanly functional as their spraying equipment. . . .
>
> 'One should cling tenaciously to sound general principles while departing freely from conventional methods in order to meet local needs. Obviously in view of the complex epidemiology of malaria and the multiple lines to its control those applying funds in this field have a special responsibility to comprehend the significance of what is being done and to determine if it can be done more effectively and cheaply' (Russell, 1952).

It is apposite and perhaps significant that the need for the present book arose at the time when we are about to commemorate in November 1980 the centenary of the discovery of the malaria parasite by Alphonse Laveran. The readers of *Essential Malariology* will be able to judge how much has been achieved since that date, but they may also realise what remains to be done to free the world from malaria.

Wellcome Museum of Medical Science
London NW 1

'Some of them will saye, seynge that I graunte that I have gathered this booke of so manye writers, that I offer unto you an heape of other mennis labours . . . To whom I aunswere, that if the honeye that the bees gather out of so manye floure of herbes, shrubbes, and trees, that are growing in other mennis medowes, feldes and closes maye justelye be called the bees' honeye . . . so maye I call it that I have learned and gathered of manye good autoures . . . my booke'.

William Turner
A New Herbal *(1551)*

Contents

Chapter 1

Historical Outline

It is assumed that the evolutionary history of mammalian plasmodia started with the adaptation of Coccidia of the intestinal epithelium to some tissues of the internal organs and then to the invasion of free cells in the blood. The next step was the possibility of transmission of the parasites from one animal to another by bloodsucking Arthropod vectors. The great antiquity of malarial infection is confirmed by the fact that about 100 parasite species similar to those of man are found in a wide range of vertebrates from reptiles or birds to higher apes. None of the parasites, except for those found in some monkeys, can be transmitted to man. This high host specificity indicates a long association between the human species and the four particular species of plasmodia that infect man.

Prehistoric man in the Old World was subject to malaria. It is probable that the disease originated in Africa which is believed to be the cradle of the human race. Fossil mosquitos were found in geological strata 30 million years old and there is no doubt that they have spread the infection through the warmer regions of the globe, long before the dawn of history. Malaria followed in the wake of human migrations to the Mediterranean shores, to Mesopotamia, the Indian peninsula and South-East Asia. How malaria established itself in the New World is subject to speculation as no reliable historical or other data exist on this point. It is possible that *Plasmodium vivax* and *P. malariae* were brought from South-East Asia by early trans-Pacific voyages, while *P. falciparum* is of post-Columbian origin, through the African slaves brought by the Spanish colonisers of Central America.

References to seasonal and intermittent fevers exist in the ancient Assyrian, Chinese and Indian religious and medical texts but their true identity with malaria is uncertain. These afflictions, usually ascribed to the punishment of gods or vengeance by evil spirits – were met only by incantations or sacrificial offerings. Hippocrates, who lived in Greece in the fifth century BC, was the earliest physician to discard superstition for logical observation of the relation between the appearance of the disease and the seasons of the year or the places where his patients lived. He was also the first to describe in detail the clinical picture of malaria and some complications of the disease. Galen and other Greek and Roman physicians have also left various references to malaria in the second century AD. Non-medical writers alluded to fevers that affected those who lived in marshy areas. Malaria or 'Roman fever'

was common in the vicinity of Rome and cyclical epidemics of malaria continued in Greece, Italy, many parts of Europe and other continents through many centuries.

For nearly 1500 years no additional knowledge of the extent, cause or treatment of malaria was forthcoming. However, the awareness of the association of fevers with stagnant waters and swamps led to various methods of drainage practised by the Greeks and Romans already in the sixth century BC and continued, for the improvement of agricultural land and better health conditions, throughout the Middle Ages in Italy, France, Holland, England and elsewhere.

However, the main breakthrough in the long history of malaria was connected with the first real therapeutic advance. At the beginning of the seventeenth century came the discovery of the value of 'Peruvian bark' for treatment of fevers. The use of this remedy spread rapidly all over Europe and it soon became obvious that only certain fevers were easily cured by this drug. In the seventeenth century Morton and Sydenham in England and later Torti in Italy differentiated between the intermittent fevers and others that failed to respond to the drug, often known under the name of 'Jesuit's powder'.

These specific fevers known in England as 'agues' received in the eighteenth century the Italian name 'mal'aria', since it was then widely believed that their cause was related to the foul air common near marshy areas. The French term 'paludisme' indicating a close connection with swamps was introduced much later. In 1735 the tree producing the Peruvian bark was given, by Linnaeus, its scientific name of Cinchona but quinine, the active principle of it, was not isolated until 1820 by Pelletier and Caventou in France.

The most important events in the history of malaria took place towards the end of the nineteenth century, when the sciences of bacteriology and pathology were discovering the causes of infectious diseases, seeing the morbid changes in the organs and tissues and also perceived the role of insects in the transmission of some infections. It was in 1880 that Laveran, a French army surgeon in Algeria, first saw and described malaria parasites in the red blood cells of man. Soon after that Romanowsky in Russia developed a new method of staining the malaria parasites in blood films and this made further studies of plasmodia very much easier.

However, the way in which the disease was transmitted from man to man was still a mystery although a few early and inspired guesses pointed to the possible association between swamps, mosquitos and fevers.

Patrick Manson, a Scotsman who was practising medicine in China, showed in the 1880s that mosquitos were arthropod hosts of human filarial parasites found in the blood. Soon after that David Bruce demonstrated in Africa that tsetse flies can transmit the trypanosome,

a blood parasite of horses and cattle, from one animal to another. This provided a new clue for considering mosquitos as possible vectors of malaria. But the final elucidation of the actual mode of transmission was not forthcoming until 1897 when Ronald Ross in Secunderabad (India) found a developing form of the malaria parasite in the body of a mosquito, that had previously fed on a patient with the plasmodia in his blood. The whole complex picture of the cycle of development of malaria parasites in man and in the female Anopheles mosquito became clear as a result of further studies by the Italians Amico Bignami, Giuseppe Bastianelli and especially Battista Grassi in 1898–99. A striking confirmation of the fact that malaria is transmitted by Anopheles mosquitos was based on the combined field experiment carried out by Patrick Manson and his colleagues near Rome and in London in 1900. This proved that protection from the bites of Anopheles prevents the occurrence of the infection; another experiment showed that Anopheles obviously infected in Italy and brought to England were capable of transmitting the disease by their bite.

During the twentieth century much research was devoted to malaria control. Larvicides in the form of oil or Paris green were introduced for preventing the breeding of mosquitos in various types of waters. Wider use of these and other methods of mosquito reduction demonstrated the practicability of controlling malaria and yellow fever in Cuba and the Panama Canal Zone, where two American campaigns brilliantly organised by General William Crawford Gorgas proved to be an outstanding success. This was followed in Malaya by Malcolm Watson who introduced the concept of 'naturalistic control' based on the knowledge of the breeding habits of species of Anopheles involved in the local transmission of the disease.

The ravages of malaria experienced during the First World War and the difficulties of securing cheap supplies of quinine stimulated a line of research in Germany aiming at the discovery of synthetic antimalarial drugs. This was brilliantly accomplished in 1924 by Schulemann's discovery of pamaquine. However, a much more valuable drug – atebrin (mepacrine) was prepared in 1930 by Kikuth, Mietzsch and Mauss. There can be no doubt that the availability of this compound played an immense role during the Second World War. Other valuable synthetic drugs developed by the Germans, the French, the Americans and the British followed in 1934 (chloroquine), 1945 (proguanil), 1946 (amodiaquine), 1950 (primaquine) and 1951 (pyrimethamine).

In the meantime another major discovery was to revolutionise the technique of malaria control by spraying insecticides against adult mosquitos. The possibility of the new method was foreshadowed in South Africa, where De Meillon's use of pyrethrum sprays greatly reduced the amount of malaria in rural areas.

At the beginning of the Second World War Paul Muller discovered in Switzerland the high insecticidal action of a synthetic compound, dichloro-diphenyl-trichloroethane, which was given the abbreviated name of DDT when samples of it were sent in 1942 to the United Kingdom. The value of this compound for control of flies and mosquitos was soon confirmed and in 1944 the first field tests were carried out in Italy. Other projects followed; in 1945 Venezuela and Guyana became the first countries where malaria control on a large scale was instituted.

Among other residual insecticides which were introduced soon after DDT, hexachlorocyclohexane (BHC or HCH) and dieldrin should be mentioned. Their general use for malaria control was less effective than first anticipated because of some unexpected difficulties related to the developing resistance of mosquitos.

The possibility of global extension of malaria control activities to bring about the final eradication of the disease was contemplated in the 1950s, when the results of the application of DDT in Venezuela, Italy, Greece, Guyana, Ceylon and the USA showed great promise.

In the meantime parasitological studies on the cycle of development of the malaria parasites continued although little progress had been made since 1900, when Grassi formulated the idea that there is a third, cryptic tissue phase following the inoculation of sporozoites by the bite of Anopheles. Raffaele in Italy was the first to demonstrate in 1934 the existence of this phase in bird malaria. This was soon followed by similar findings in other species of avian and monkey parasites. Then in 1948 the exo-erythrocytic stages first of monkey malaria (*P. cynomolgi*) then of human (*P. vivax*) malaria were discovered in the UK by Shortt and Garnham. This explained what happens to the parasite during the incubation period, how the relapses of malaria infection occur and gave new impetus to the chemotherapeutic research which was soon to develop new and powerful drugs.

The characteristics of DDT and other residual insecticides, namely their high potency against the mosquitos, low toxicity to man, ease of application in rural areas and relatively low cost, encouraged many health workers to press for malaria eradication. The examples of Greece and Italy, where in 1951 a temporary interruption of house spraying with DDT has not interfered with the elimination of the disease, confirmed the apparent practicability of malaria eradication, without necessarily eliminating the main Anopheles vector.

The concept of malaria eradication was adopted by the World Health Assembly in 1955 and two years later the World Health Organization launched the global campaign. Its results over the next fifteen years were excellent in Europe, North America, some parts of Asia, USSR, Australia and less good in tropical countries. The causes of this lack of progress are many and will be fully dealt with in the