MALARIA

Volume 1

Epidemology, Chemotherapy, Morphology, and Metabolism

Edited by

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Preface

The last major effort to review our knowledge of malaria was by Mark F. Boyd whose "Malariology" published by W. B. Saunders of Philadelphia in 1949 is still a valuable resource. The exquisite volume "Malaria Parasites and other Haemosporida" by P. C. C. Garnham published by Blackwell Scientific Publication of Oxford in 1966 is also a valuable review of malariology but in the author's words "is about malaria parasites and not malaria."

This three-volume treatise is appearing in a period of rising activity in malaria research. In the 1950s and 1960s and even into the 1970s funds for this research were scarce and only the hardiest of individuals remained in the field. At present malaria research is again receiving the attention it deserves. The mistaken belief common in the 1950s and 1960s that malaria would soon be eradicated by vector control and chemotherapy and that research was therefore rather pointless has been abandoned in the face of a widespread resurgence of this disease.

A variety of national and international agencies are now funding malaria research. Many individuals attracted by the possibility of funding are turning their efforts to malaria research. Biochemists, immunologists, biophysicists, and molecular biologists among others are entering the field. Many of these individuals, skilled in their specialities, know little or nothing about malaria. It is perhaps to such individuals particularly that this broad review of malariology will be of most value. Even those of us who have worked in some aspects of malaria research for some time may find the reviews of the state of the art in areas other than our own speciality of interest. Those of us actively working in a particular area may find few new facts in the reviews of the areas of our own speciality. I have, however, encouraged the authors to write critical reviews and to relate the facts reported in the literature to each other. Interpretation and speculation are discouraged by the reviewers of most scientific journals in the United States. A book such as this is thus naturally a convenient vehicle for individuals to present their thoughts as well as the facts.

The authors of the reviews of malaria research included in these volumes met in May 1979 in Mexico City with individuals doing research on the closely related disease babesiosis. Babesiosis has an effect on the development of animal husbandry somewhat similar to the effect of malaria on human societies. At this conference current research on malaria and babesiosis was reported and the similarities and differences between malaria and babesiosis were discussed. As an outgrowth of this conference a volume on babesiosis was developed, which will complement these volumes on malaria.

I extend my thanks to the co-organizers of the conference, Dr. Miodrag Ristic of the College of Veterinary Medicine of the University of Illinois with whom I edited the volume on babesiosis, and Dr. Carlos Arellano-Sota of the Instituto Nacional de Investigaciones Pecuarias in Mexico City. I particularly wish to thank the sponsors of the conference for their encouragement and help. Their support made the conference possible and made the preparation of these volumes on research in malaria and babesiosis a more pleasant task.

I particularly wish to thank John Pino, Director of Agricultural Sciences of the Rockefeller Foundation without whose early support the conference and the babesiosis volume would have been impossible. I also wish to thank Kenneth Warren, Director of Medical Sciences of the Rockefeller Foundation, Edgar A. Smith, Health Services Administrator, James Erickson, Malaria Research Officer of the United States Agency for International Development of the Department of State for their support of the conference.

In addition to the Rockefeller Foundation and the United States Agency for International Development several other organizations contributed to the support of the conference and the development of these volumes. These were The Pan American Health Organization, Parke-Davis Corporations, Merck Sharp & Dohme, Anchor Laboratories, Sandoz Ltd., Pfizer Corporation, and the Wellcome Trust.

Last but by no means least I wish to thank all the authors of the reviews that make up these volumes and Academic Press for their unfailing support.

Julius P. Kreier

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Walther H. Wernsdorfer

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I. HISTORICAL REVIEW

Malaria is the accepted name denoting the disease or condition of infection in man caused by parasites belonging to the genus *Plasmodium*. Although the name malaria, which is derived from the Italian word for bad air, is not directly related to the cause of infection, it is the term commonly used, since the scientifically more appropriate term—plasmodioses—has never come into wide use.

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The term malaria was originally restricted to plasmodial infections in man, but it now includes all infections caused by organisms belonging to the family Plasmodiidae which, therefore, are commonly referred to as malaria parasites.

Human malaria is probably as old as mankind and, until very recent times, many examples of the disease influenced the course of history. The earliest indications of human disease suggestive of malaria come from ancient Egypt and are found in the Edwin Smith Surgical Papyrus, 1600 B.C. (Breasted, 1930), which describes measures to be taken against the entry of disease-laden, fever-provoking vapors into houses. The Papyrus Ebers, 1550 B.C., refers to the association of rigors, fever, and splenomegaly (Garnham, 1966). Inscriptions on the walls of the Temple of Dendera in Upper Egypt contain the word AAT, denoting an intermittent fever which recurred annually at the same season (Deaderick, 1909) and was associated with the Nile River floods (Halawani and Shawarby, 1957).

The first accurate clinical descriptions of malarial fevers were given by Hippocrates in 400 B.C. (Boyd, 1949), who mentioned the classic triad of chills, fever, and sweating and analyzed the characteristic periodicity of various forms of malaria and associated splenomegaly with the endemicity of malaria and its topographic aspects. Hippocrates recognized continued and "semitertian" fevers as the most dangerous, often fatal forms. These were probably infections caused by *Plasmodium falciparum*. He considered quartan fevers, obviously due to *P. malariae,* to be the longest lasting and least dangerous of these diseases.

Many Roman historians and writers mention fevers especially affecting populations living in the vicinity of marshes (Boyd, 1949). Celsus, in the first century A.D., gave rather precise descriptions of febrile diseases from which falciparum, vivax, and quartan malaria could be easily identified as separate entities. Galen, in the second century A.D., followed Celsus' classification. Western medicine adhered to his dicta regarding treatment of febrile diseases, including malaria, throughout the medieval era until the advent of cinchona bark.

It seems that malarial fevers were known also in ancient China and that Arab physicians, at the peak of Arab medicine during the eighth to the thirteenth century were commonly acquainted with intermittent fevers (Boyd, 1949).

Controversy still reigns regarding the occurrence of human malaria in the Americas prior to Columbus' discovery of the New World. Boyd (1949), Jarcho (1964) and Dunn (1965) came to the conclusion that human malaria was not present in the pre-Columbian era. Coatney *et al.* (1971) share this view and suggest that all forms of primate malaria now found in the New World are the outcome of post-Columbian introduction. There can be little doubt that *P. falciparum* arrived in the Americas with the Spanish and Portuguese invaders and African slaves. However, the discovery by Sulzer *et al.* (1975, 1978) of an isolated focus of hyperendemic *P. vivax* and *P. malariae,* and the conspicuous absence of *P. falciparum* in a primitive population in the Peruvian Amazon

jungle, may suggest the pre-Columbian antiquity of *P. vivax* and *P. malariae* in the New World.

The earliest attempts to prevent what appears to have been malaria are contained also in the Edwin Smith Surgical Papyrus (Breasted, 1930). The Papyrus Ebers mentions the use of an oil expressed from the *Balanites* tree as a mosquito repellent (Garnham, 1966). However, these measures apparently afforded little protection and, apart from following some precautions based on experience related to the *genius epidemicus,* for a long time there were no effective means for preventing malaria and not even organized attempts to analyze the correlation between specific bioclimatic and topographic factors and the epidemic and endemic occurrence of febrile diseases. This is the more astonishing, as epidemic fevers were recognized relatively early as an obstacle to land use and as a cause of defeat of many a northern army attempting the invasion of Mediterranean countries. Garnham (1966) rightly stated that the Crusaders, faltering and turning back from the borders of the Holy Land, were defeated more by malaria than by the Saracens.

The first impetus to the treatment of malaria came in the middle of the seventeenth century with the introduction of the bark of a Peruvian tree with which the Countess of Chinchón was successfully treated for her febrile condition. Paz Soldan (1938), though, states that it was the Count and not the Countess of Chinchón who first benefited from treatment with the bark. The bark was employed in local Indian medicine as a febrifuge, although its use was apparently quite limited (Jarcho, 1964), an observation which, according to Coatney *et al.* (1971) argues against the pre-Columbian presence of human malaria in the Americas. The bark of the Peruvian tree was brought to Europe about 1640 and was soon used generally throughout western Europe for the treatment of fevers.

The botanical description of the tree yielding the Peruvian bark became known only about 100 years after introduction of the bark into Europe. Linné, in memory of the Countess of Chinchón's recovery, named (but misspelled) the new genus of the bark-yielding tree *Cinchona*. Subsequently, the bark was generally called cinchona bark or merely cinchona. The response to the latter was used as a diagnostic tool by Torti (1712), to differentiate *ex juvantibus* between malarial and nonmalarial fevers.

The large variations in the therapeutic value of different batches of cinchona stimulated chemists to isolate the active principles. In 1820, Pelletier and Caventon succeeded in extracting two alkaloids which they named quinine and cinchonine (Scott, 1939) and of which quinine was found to exert the antimalarial effect. Subsequently the use of pure quinine rapidly replaced the administration of cinchona bark, and the pure drug was also increasingly employed for the prophylaxis against malaria. While the suppressive administration of quinine has been replaced by the use of modern synthetic antimalarials, the drug has retained its value as a life-saving medicament in severe cases of falciparum malaria.