Antimalarial Drugs I

Biological Background, Experimental Methods, and Drug Resistance

Editors:
W. Peters and W. H. G. Richards

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Preface

Of all the parasitic diseases that beset man in the warmer parts of the world, malaria is still the major cause of morbidity and mortality. In spite of intensive efforts to interrrupt its transmission malaria still threatens over 800 million people, more than one-fifth of the world's population. Malignant tertian malaria caused by *Plasmodium falciparum* probably kills a million every year. Vivax malaria temporarily incapacitates millions more. The search for antimalarial drugs, both natural and synthetic, has been and continues to be one of the most challenging and, at times, rewarding exercises ever undertaken by chemists and biologists. The magnitude of the effort is reflected by the fact that, in the last 15 years, well over 250000 compounds have been screened for antimalarial activity in just one programme, that carried out under the auspices of the Walter Reed Army Institute of Research, not to mention sporadic studies undertaken by other research workers and organisations.

While most people engaged in the search for new drugs agree that a rational approach based on knowledge of the intimate biochemical pathways of the target cells would be ideal as well as intellectually satisfying, most are reluctantly obliged to concede that, up to the present time, the chances of success following a more or less empirical search have been far greater. Spectacular advances in molecular biology and biochemistry in recent years, however, are rapidly changing this situation. New techniques for the study of the biology of malaria parasites and the host-parasite interface, and for the cultivation of both intraerythrocytic and tissue stages of *Plasmodium* have opened up new avenues, not only for such fundamental studies, but also for drug screening *in vitro* and the investigation of the modes of action of antimalarial drugs. We can anticipate, therefore, that future research on antimalarial chemotherapy will hinge more on an intimate knowledge of the basic biology of the target organism and less on 'random' screening.

It is remarkable that, over 100 years after the first discovery of the malaria parasites of man, yet one more stage of the cycle has been revealed, namely the tissue-dwelling 'hypnozoite' that we now believe is responsible for relapses of benign tertian vivax and ovale malaria. Much has been learned of the metabolic pathways used by the blood-dwelling stages of these and other species, but almost nothing of the metabolism of the tissue stages. New culture techniques, apart from their value for metabolic studies, are now being widely used for screening and these and other *in vitro* models, as well as animal models, are described in some detail. Drugs are, in a sense, simply an aid to Nature. Without an active immune response on the part of the host, it is unlikely that any antimalarial used today will cure a patient of his malaria. For this reason detailed reviews are given of the response of

the host to malarial infection, and the interaction between immunity and chemotherapy.

The course of antimalarial (as indeed any other) drug development spans the field from primary screening to advanced clinical trials in man. The different stages in this process are reviewed in order to provide guidelines for future investigators who would otherwise have to search widely scattered literature covering these activities.

The main stimulus for antimalarial drug development today (although by no means the only one) is the rapid rate of emergence of *P. falciparum* strains resistant to existing compounds. It is therefore essential to provide substantial background data on this problem and the last three chapters of Part 1 reflect this need.

Even while this volume was being conceived and prepared for publication an increasing flow of reports was being received by the World Health Organization and appearing in the medical press of patients with malignant tertian malaria who failed to respond to treatment with the best available drugs. The rapid geographical spread of such strains and the widening range of drugs to which the parasites are becoming resistant are such that the need for radically new types of antimalarial chemotherapy is becoming one of the most urgent requirements in what is, after all, becoming an ever shrinking world. Recognising this urgency, the Editorial Board of this series and Springer-Verlag have generously agreed to publish this volume *in toto,* in two parts, rather than trying to compress the material into their standard format.

In Part 2 of this volume, our contributions review in detail the range of drugs that are in current use, describe some novel approaches to their deployment and give an account of developments in different chemical series over the past decade.

We are deeply grateful to all our contributors and the staff of Springer-Verlag for their generous collaboration in this work.

WALLACE PETERS
WILLIAM H. G. RICHARDS

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