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No. 27

**CHEMOTHERAPY OF MALARIA**  
REVISED SECOND EDITION

# CHEMOTHERAPY OF MALARIA

REVISED SECOND EDITION

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**CORRIGENDUM**

Page 5, lines 5-6:

*Delete* recent observations with the weekly administration of 200 mg of proguanil ...

*Insert* recent observations with the daily administration of 200 mg of proguanil ...



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## PREFACE

At its fourth session, held in Kampala, Uganda, in December 1950, the WHO Expert Committee on Malaria recommended that information on the properties of antimalarial drugs should be summarized for the benefit of the medical profession. On its advice a drafting committee was appointed to undertake this task, consisting of Sir Gordon Covell (Chairman), Dr G. Robert Coatney, Dr John W. Field and Lieutenant-Colonel Jaswant Singh. The members of the drafting committee prepared a text which was reviewed in consultation with a number of experts in this field and published in a WHO monograph entitled *Chemotherapy of malaria* (1955).

Since the publication of this monograph, scientific literature on this subject has increased in both quality and quantity. WHO itself has published reports of scientific groups on malaria chemotherapy and the resistance of plasmodia to antimalarial drugs in its Technical Reports Series. However, the fresh information is widely dispersed through the literature and needs to be brought together for all those in any way involved in the control of malaria. It should be noted, too, that the considerable scientific progress of the past 20 years relates more to knowledge of the effects of existing drugs than to the development of new ones. Research involving the screening and testing of more than 250 000 compounds has shown that only 4 or 5 have a chemotherapeutic index sufficient to justify clinical and field trials. Observations on these compounds have been included in the present monograph.

Chemotherapy has been of great importance since the control of malaria was first attempted. However, the development of residual insecticides somewhat overshadowed the role of antimalarial drugs, particularly in the late 1950s and 1960s. With the dramatic resurgence of malaria in many countries and the increased resistance of vectors to insecticides, antimalarial drugs are regaining their importance, despite the resistance of some strains of *Plasmodium falciparum* to 4-aminoquinolines, particularly in South-East Asia and South America, and to pyrimethamine and proguanil in Africa. This resistance is an additional reason for bringing together in a monograph information on all the available drugs, their use (either alone or in combination), their dosages and regimens for different purposes (whether for prophylaxis, suppression or radical cure), and their toxicity or adverse effects. Such an up-to-date monograph should enable medical practitioners to make the most appropriate selection of antimalarial drugs, either for general use or for the treatment of individual cases.

At a time when governments are considering the development of a primary health care system as a basic function in the achievement of the goal of health for all by the year 2000, this monograph should represent a significant contribution by WHO.<sup>1</sup> It should be of particular importance to African countries south of the Sahara where no organized malaria control programmes can be undertaken on a large scale and where antimalarial drugs are in practice the only effective method of preventing the mortality and reducing the morbidity caused by the disease. Indeed, such drugs, if readily available to the rural population of Africa, would greatly reduce the number of deaths caused by the disease, which is estimated at approximately one million per annum in the child population under five years of age.

I should like to take this opportunity to express my gratitude to the editor and the authors, who have devoted so much of their time to the preparation of this monograph.

H. Mahler, M.D.  
Director-General

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<sup>1</sup>WHO/UNICEF (1978) *Primary health care. Report of the International Conference on Primary Health Care, Alma Ata, USSR, 16-20 September 1978*. Geneva, World Health Organization.

## REVISED SECOND EDITION, 1986

### DEVELOPMENTS IN MALARIA CHEMOTHERAPY, 1981-86

Since the publication of the second edition of this book in 1981, there have been a number of developments in malaria chemotherapy, and these were reviewed by a Scientific Group on the Chemotherapy of Malaria in Geneva in September 1983. The report of this Group<sup>1</sup> emphasizes the detrimental impact of drug resistance of *Plasmodium falciparum* and its further spread, especially in Africa south of the Sahara. It covers, in detail, the results obtained with mefloquine and the combination of mefloquine, sulfadoxine, and pyrimethamine. Both mefloquine alone and the combination have recently been registered and the latter will soon be available for the treatment of multiresistant malaria. The Scientific Group was concerned about maintaining the efficacy of antimalarial drugs and made recommendations for their operational use. As the development of resistance to antimalarial compounds cannot be avoided for ever, there will continue to be a need for new drugs. Phenanthrenemethanols and pyridinemethanols are candidate compounds at an advanced stage of development and hold considerable promise. Artemisinin (qinghaosu) and some of its derivatives may become useful drugs for the emergency treatment of severe falciparum malaria. There are yet other compounds that merit preclinical and clinical development. However, these investigations and the search for new candidate drugs and innovative principles in malaria chemotherapy will largely depend on the intensity of future research.

The chemotherapy of malaria has in recent years assumed a major role in primary health care and in complying with the basic objectives of preventing mortality and curbing morbidity and suffering from malaria. Antimalarial drugs make it possible to pursue these objectives in areas where other antimalarial measures cannot be applied for technical, operational, or financial reasons. It is therefore important to rationalize the use of antimalarial drugs in an effort to maintain their efficacy.

The following sections summarize the developments in malaria chemotherapy that have occurred since the publication of the second edition of

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<sup>1</sup> WHO Technical Report Series, No. 711, 1984 (*Advances in malaria chemotherapy: report of a WHO Scientific Group*).

*Chemotherapy of malaria.* Some of these developments have necessitated a certain number of changes in the main chapters of the book.

### **Drug Resistance of *P. falciparum***

Chloroquine resistance of *P. falciparum* in eastern Asia and Oceania has shown further consolidation and a significant westward spread. All of Indonesia and practically all areas of India with *P. falciparum* are now affected by chloroquine resistance, which has also been reported from one focus in northern Pakistan. In South America, the situation has largely remained unchanged as far as the geographical distribution of chloroquine-resistant *P. falciparum* is concerned, but there has been a general consolidation in the degree of resistance.

Major and alarming changes have occurred in Africa, south of the Sahara and in islands off the eastern coast. Chloroquine-resistant *P. falciparum* has now been reported from 14 African countries, namely Angola, Burundi, Central African Republic, Comoros, Gabon, Kenya, Madagascar, Malawi, Namibia, Sudan, Uganda, United Republic of Tanzania, Zaire, and Zambia. While chloroquine is still clinically quite useful for the treatment of falciparum malaria in most semi-immune persons, a significant number of RII and even RIII responses have been observed in young children, especially in Malawi, United Republic of Tanzania, and Zambia.

Resistance to the first-line alternative combination, sulfadoxine-pyrimethamine, has also spread and consolidated itself in certain hard-core areas of chloroquine resistance in South America and eastern Asia, such as Brazil, Colombia, Democratic Kampuchea, Thailand, and Viet Nam. In parts of Thailand, for instance, the efficacy of sulfadoxine-pyrimethamine is compromised to a degree that precludes its routine use for the initiation of treatment of falciparum malaria. Resistance of *P. falciparum* to sulfadoxine-pyrimethamine has also been reported from East African countries such as Kenya, United Republic of Tanzania, and Zambia.

### **Assessment of Drug Response of *P. falciparum***

While a post-treatment observation period of 28 days generally—though not always—suffices to exclude RI responses in the *in vivo* test for chloroquine, a much longer period of 63 days is required for ascertaining S responses to mefloquine. This is because of the long half-life of mefloquine (usually 20–30 days in adults).

The *in vitro* macrotest for mefloquine sensitivity of *P. falciparum* has been phased out and replaced by the microtest, which is now also available for testing sensitivity to amodiaquine and quinine, as well as to chloroquine and mefloquine. A microtest procedure for assessing sensitivity to sulfadoxine-pyrimethamine is currently being developed.

## Drug Prophylaxis of Malaria

Detailed recommendations for the drug prophylaxis of malaria in non-immune visitors to malarious areas, non-immune and semi-immune residents of malarious areas, and specific risk groups are given in the report of the Scientific Group on the Chemotherapy of Malaria.<sup>2</sup> Pyrimethamine alone can no longer be recommended for prophylaxis; recent observations with the weekly administration of 200 mg of proguanil in East Africa<sup>3</sup> indicate that this drug has retained a remarkable prophylactic potential against *falciparum* malaria.

The forthcoming introduction of mefloquine, alone and in combination with sulfadoxine and pyrimethamine, is expected to modify prophylaxis recommendations in areas with multiresistant *P. falciparum*, where, so far, a common practice has been to administer a combination of a 4-aminoquinoline (amodiaquine or chloroquine) and sulfadoxine-pyrimethamine.

### Operational Use of Antimalarial Drugs

The operational use of antimalarial drugs was extensively reviewed by the Scientific Group on the Chemotherapy of Malaria in 1983.<sup>2</sup> In view of the considerable selection pressure exerted by mass drug administration (especially if it is repetitive) and the associated risk of promoting and accelerating the occurrence and spread of drug resistance, such mass administration and prophylaxis are no longer recommended. Instead, the use of curative dose regimens is recommended for the treatment of clinical malaria cases, wherever possible on the basis of microscopic diagnosis. The primary health care concept lends itself to such a procedure, which becomes practically mandatory in areas of multiple resistance, when relatively expensive alternative drugs need to be employed. Pregnant women comprise the only group among semi-immune residents of malarious areas for which drug prophylaxis is recommended (from the fourth month of pregnancy to 6 weeks after delivery).

Presumptive treatment (i.e., treatment given to a presumptive malaria case at the time when a blood sample is taken for examination, aimed at relieving symptoms and preventing transmission) should be used only when the delay between blood sampling and administration of curative treatment can be kept below 7 days.

The above considerations preclude the further use of potentially subcurative, low doses of drugs in areas with a relatively high, general immunity, e.g., in tropical Africa. Curative doses are to be used instead, being all the more necessary when the presence of clinical malaria indicates insufficient immunity in the individual patient.

<sup>2</sup> WHO Technical Report Series, No. 711, 1984.

<sup>3</sup> McLARTY, D. G. ET AL. *Lancet*, 2: 656-658 (1984).

## Radical Treatment of Vivax and Ovale Malaria

Hypnozoitocidal (antirelapse) treatment of vivax and ovale malaria in adults is usually based on a fortnight's treatment with daily doses of 15 mg of primaquine (base), following the administration of blood schizontocidal therapy with a 4-aminoquinoline. This may cause significant methaemoglobinemia and haemolysis in subjects deficient in glucose-6-phosphate dehydrogenase (G6PD), who are more effectively treated with *weekly* doses of 45 mg of primaquine for 8 weeks. This regimen is better tolerated than the daily administration of a smaller dose; it can be given without prior G6PD screening and is of advantage in areas where G6PD deficiency occurs frequently.

## Treatment of Severe and Complicated Malaria

Recent studies on the management of cerebral malaria have indicated that corticosteroids are contraindicated in the treatment of this condition.<sup>4</sup> Similarly, the use of heparin is unhelpful and may be positively dangerous.<sup>5</sup>

An initial loading dose of quinine of 20 mg/kg of body weight in patients suffering from cerebral malaria and known to be previously untreated permits the establishment of high plasma levels (15–20 mg of quinine/litre) in the acute phase. The efficacy of this treatment outweighs the risks of toxicity, and patients given such a loading dose have a higher chance of survival than those treated in the conventional way.<sup>6</sup> It has been found that the pharmacokinetics of quinine are altered significantly by malaria infection, clearance and apparent volume of distribution being lower during the acute phase of falciparum malaria. Thus a reduction in the quinine dose after clinical improvement (as suggested in the 1981 edition of this book) is inappropriate and it is recommended that quinine be given in 3 daily doses of 10 mg/kg of body weight each for 7–10 days (see Table 7, page 123).

The parenteral administration of quinine (intramuscular or intravenous) in children is strictly contraindicated for toxicological reasons.

Studies by White et al.<sup>7</sup> indicated that quinidine is more effective than quinine. Other, as yet unpublished, observations have confirmed this finding. Where quinine is not available, quinidine may therefore be an acceptable alternative for emergency treatment of severe and complicated malaria. This drug is commonly found in the cardiology department of hospitals. However, particular care should be taken to monitor any cardiotoxic effects of quinidine.

<sup>4</sup> WARRELL, D. A. ET AL. *New England journal of medicine*, **306**: 313–319 (1982).

<sup>5</sup> PUNYAGUPTA, S. ET AL. *American journal of tropical medicine and hygiene*, **23**: 551–559 (1974).

<sup>6</sup> WHITE, N. J. ET AL. *American journal of medicine*, **73**: 564–572 (1982).

<sup>7</sup> WHITE, N. J. ET AL. *Lancet*, **2**: 1069–1071 (1981).

## Mefloquine

Following detailed preclinical studies as well as extensive clinical and field trials,<sup>8</sup> both mefloquine and its combination with sulfadoxine and pyrimethamine have been registered in Switzerland. Registration of the combination is pending in several countries where multidrug-resistant *P. falciparum* is a problem.

In experimental models, the combination of sulfadoxine and pyrimethamine with mefloquine proved to delay the emergence of resistance against the latter. Therefore, it is not envisaged to employ or even market mefloquine alone (registered under the name of Lariam) in countries where *P. falciparum* is transmitted. Likewise, it is envisaged that the use of the combination of mefloquine, sulfadoxine, and pyrimethamine (to become available under the trade name of Fansimef) will be largely restricted to the curative treatment of falciparum malaria.

Fansimef tablets contain 250 mg of mefloquine (base), 500 mg of sulfadoxine, and 25 mg of pyrimethamine. A curative dose for adults of normal weight (50–70 kg) consists of 3 tablets of Fansimef administered in a single dose. For adults and children above 5 years of age, the dose should be adjusted on the basis of 12.5 mg of mefloquine (base) per kg of body weight. The medicament is generally well tolerated, but patients treated with Fansimef should be advised to stay in bed for at least 3 days, and preferably 7 days.

Fansimef has not yet been cleared for administration to pregnant women or to children below the age of 5 years, as appropriate clinical observations have not yet been completed.

The Scientific Group on the Chemotherapy of Malaria, recognizing the urgent need to protect mefloquine and ensure its deployment, strongly recommended:

(a) that governments should legislate for strict control of the importation, distribution, and utilization of mefloquine alone or in drug combinations;

(b) that the use of mefloquine by communities in endemic areas should be restricted to the treatment of acute malaria attacks that are likely to be due to multiple drug-resistant *P. falciparum* in specific groups;

(c) that, when available, drug combinations known to delay the development of drug resistance should be used for prophylaxis and treatment instead of mefloquine;

(d) that mefloquine should *not* be distributed for use as a single prophylactic drug by residents in endemic areas.

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<sup>8</sup> WHO Technical Report Series, No. 711, 1984.



## CHAPTER 1

# GENERAL

### Introduction

The present monograph attempts to retain as much as possible of the outline of the previous edition, but at the same time aims at incorporating most of the substantial changes that the chemotherapy of malaria has undergone during the past two decades, and especially those owed to the appearance of resistance of plasmodia to our most reliable antimalarial drugs.

The task of the authors has been facilitated by the issue by WHO of a number of documents that have periodically reviewed the problems created in the field either by operational difficulties in malaria eradication or by technical obstacles.

The present second edition of the monograph aims primarily at helping the medical profession and public health officers in tropical developing countries where malaria is still prevalent. It is also hoped that it will serve as a handy reference book for medical practitioners in many parts of the world where cases of imported malaria are increasingly common. It should be of value to undergraduate or postgraduate students and provide guidance for those medical auxiliaries who qualify for more advanced training in health care programmes. The ready availability of up-to-date information on the prevention and treatment of malaria should make it easier to offer sound advice to travellers to tropical countries.

### Historical Outline

From time immemorial malaria has been one of the most prevalent of human diseases, affecting particularly the populations of tropical regions but also in the past those of temperate climates. It is also one of the oldest infections mentioned in early writings in Egypt, India and China. Its clinical symptoms were fully described by Hippocrates 400 years before the Christian era.

Attempts at treatment by the roots, leaves and flowers of many plants were of little, if any, value, although the powdered roots of Ch'ang shan (*Dichroa febrifuga*), used in China for at least 2000 years, have an undoubted medicinal effect, owing to the presence of an alkaloid, febrifugine, isolated and analysed only recently. Qing hao (*Artemisia annua*), also used for a similar period in

China, has been shown to be a schizontocide of very low toxicity (see page 101). However, the first potent remedy against malaria was discovered only in the seventeenth century following the contact of Europe with the New World.

Although many historians maintain that malaria was introduced into the Americas only after the discovery of the New World by Columbus, there is some evidence that the disease was known to the local populations long before then. Whether the curative virtue of the bark of the "fever trees" growing on the mountainous slopes of the Peruvian Andes was known to the local inhabitants before the Spanish conquest remains uncertain and controversial. The story of the Countess of Chinchón, wife of the Viceroy of Peru, having been cured in 1630 of tertian fever by an administration of an infusion of the bark has been often told in the past. This romantic episode has now been disproved by modern historians, but the latinized and misspelled name of *Cinchona*, given in 1749 by Linnaeus to the "fever tree," became part of our scientific heritage.

The exact date of the introduction of the new remedy into Europe is not known, but it is likely that it was brought to Rome in 1632 by Spanish priests. It became widely used a few years later, thanks to the interest of Cardinal Juan de Lugo, who used it himself for treatment of his fever and then stimulated the distribution of the new drug to missionaries in distant lands. In 1663 Sebastiano Badi (or Bado) in Italy described the medicinal uses of Peruvian bark in various fevers and the powdered preparation became widely used in southern Europe. The connexion of the new drug with the Roman Catholic Church slowed down its use in Protestant England, but when it cured King Charles II's tertian ague it gained greater acceptance and Thomas Sydenham popularized its use. However, religious prejudice against "Jesuits' bark" and the occasional death of patients treated with small amounts of it or with mixtures of other ingredients purporting to be bark created a current of opinion hostile to it. Another factor in its unpopularity was that it was used indiscriminately for the treatment of any febrile disease.

The spectacular cure in 1682 of the French heir to the throne by the English pyretologist Robert Tabor enhanced the popularity of the new remedy all over Europe and beyond. It was soon introduced into India by the British and the Dutch. In 1692 the missionary fathers cured the Chinese Emperor K'ang Hsi of a malignant fever using powdered bark brought from India.

Its therapeutic value was gradually recognized, and by 1677 it was included in the London Pharmacopoeia as *Cortex peruanus*. Although Francesco Torti in Italy insisted in 1712 that cinchona bark was specific only for intermittent fevers, the new remedy suffered from a period of unpopularity owing to erroneous prescribing by many physicians. This lasted until 1765, when James Lind in Calcutta showed that to obtain the best results the drug must be given in full doses. His conclusion that "In the proper administration of the bark the cure of ague may be said to entirely consist" paved the way for wider use of cinchona powder, which eventually became a sovereign fever

remedy. In some countries its success was still doubtful until Maillot, a French physician in Algeria, started using it in large doses with good results.

For 200 years the crude bark was used for the preparation of powders and infusions. Many chemists attempted to isolate the active principle of the drug; it seems that, at the beginning of the nineteenth century, Antonio Gomez in Portugal and Th.I. Gize of Kharkov in Russia obtained a crystalline substance from an alcoholic extract of the bark. But the final isolation of two basic alkaloids of cinchona—quinine and cinchonine—was not accomplished till 1820, by the French chemists Pierre Pelletier and Joseph Caventou. Following the isolation of two other alkaloids of cinchona (quinidine and cinchonidine), factories for the manufacture of various salts of quinine were established in many parts of the world.

The demand for the new drug was so great (especially during the Civil War in the United States of America) that the production of quinine was insufficient to satisfy all the requirements. The exploitation of the native forests of cinchona in Peru was carried out in a most improvident manner. Attempts to develop cinchona plantations in other parts of the world were made by the French in 1743, when de Condamine was sent to Ecuador and Peru, but they ended in failure. The Dutch started the first cinchona cultivation in Java in 1854, thanks to Justus Hasskarl, a botanist who collected the seeds in Bolivia and Peru. In 1872 the British geographer, Clements Markham, established successful plantations in Ceylon and the Nilgiri Hills in India, but his seedlings, as also those of Hasskarl, had a low yield in quinine. Another collector, Charles Ledger, obtained seeds of Bolivian plants of high quality with great difficulty and sold them to the Dutch. From these seeds of *Cinchona ledgeriana* came the best-yielding trees and within 50 years the Dutch plantations of Java were producing 97 % of the world's supply of quinine and had a virtual monopoly, producing in the 1930s about 10 million kg of bark a year.

During the Second World War, in 1943–44, an attempt to increase the production of cinchona bark in South and Central America from seeds transported by air from the Philippines was made by the Americans, but by then the synthetic antimalarials had made their appearance and the demand for quinine was less urgent.

### *Synthetic antimalarial drugs*

The development of synthetic antimalarial drugs forms one of the most interesting chapters in the history of chemotherapy. To understand its successive stages mention must be made of two events that took place concurrently at the end of the nineteenth century. In 1880 Laveran discovered malaria parasites in the blood of man. His discovery stimulated a search for similar organisms in animals and 10 years later Danilevsky found a variety of parasites in the blood of birds. The Russian worker's discovery was published at the same time as Guttman & Ehrlich's observation that methylene blue

had some beneficial effect on a patient suffering from malaria. Thirty years later these two seemingly unconnected findings were linked together.

The search for synthetic antimalarial drugs stimulated by Perkin's early unsuccessful attempts at producing artificial quinine was pioneered by German chemists. This search would have been impossible without some method of testing the action of new compounds on animal models. Avian malaria provided such a method and in 1926 Roehl modified and standardized the technique used previously by French workers, the brothers Sergent. Roehl's method, using *Plasmodium relictum* in canaries, is the first routine screening test that compared the activities of new compounds in relation to quinine. Other tests using different malaria parasites of birds were introduced at a later stage.

Various attempts at synthesizing quinine were made soon after the isolation of the active principles of cinchona, but all of them failed. Already during the First World War the Germans, finding themselves cut off from the main world supply of quinine in India and Java, had begun to consider the possibility of producing alternative compounds with antimalarial action. The observation made by Ehrlich of the effect of methylene blue was the starting-point of the new venture. Roehl's test provided a method of assessment of the effectiveness of the various compounds synthesized by the chemists.

Another important event that tends to be forgotten was the use, dating from 1918, of malaria therapy for the treatment of neurosyphilis. This led to rapid advances in knowledge of plasmodial infections themselves and of various methods of treatment. The contribution of malariotherapy centres in Britain, France, Italy, Romania, the USSR and the USA has been invaluable.

With Ehrlich's previous observations in mind, Schulemann and his colleagues, Schönhofer and Wingler, first directed their attention in the 1920s to thiazine derivatives related to methylene blue. One of the compounds with a basic dialkylaminoalkylamino side chain was found to be active against avian malaria parasites. Combination of the basic group with a 6-methoxyquinoline, which is the quinoline nucleus of the cinchona alkaloids, led to the first synthetic antimalarial compound of the 8-aminoquinoline series, named Plasmochin (pamaquine). The chemical structure of pamaquine was published only in 1928, but by then a number of British, French and Russian workers had some knowledge of the relationship between the chemical structure of these compounds and their antimalarial action. In the 1930s the French synthesized several homologues of pamaquine and one of them, known as Fournau 710 or Rhodoquine, became widely known.

Soon after the discovery of pamaquine it became obvious that, while it was highly active against avian plasmodia, it was not so in human malaria; it had a limited action on the asexual forms of *P. falciparum* and toxicity that was by no means negligible. The search for better quinine substitutes continued.

In 1932 Kikuth announced the discovery by Mauss & Mietzsch of a series of compounds synthesized by attaching the basic side chain (evolved for pamaquine) to other heterocyclic compounds. The quinoline ring was

replaced by acridine—a yellow dye, and one of the compounds of the series, originally called Atebrin, proved to have considerable activity on the asexual forms of *P. falciparum*. About 12 000 different compounds were tested in the course of this work in Germany alone, but a number of related compounds were also prepared in the USSR.

The introduction of Atebrin, now called mepacrine (quinacrine in the USA), was delayed for a number of years because of uncertainty about the toxic effect of long-term administration. Trials carried out in Algeria, Italy, Malaya, Romania and the USSR under the aegis of the League of Nations confirmed the high suppressive value of mepacrine, but provided no decisive proof of its safety.

In the meantime Sinton & Bird in India discovered that pamaquine could greatly reduce the relapse rate of vivax malaria. This was of fundamental importance for further studies of the 8-aminoquinolines.

The Second World War cut off the Allies from the main sources of quinine in Indonesia, which was occupied by the Japanese Army. This created a serious military problem for the Allies, as their forces were engaged in campaigns in some of the most malarious areas of the world. Consequently research on synthetic antimalarials received very high priority in Europe and in the USA. In order to preserve the supplies of quinine a usable mixture of all the active alkaloids of cinchona, known as Totaquina, was recommended by the Malaria Commission of the League of Nations for wider use. Intensive studies of the absorption, distribution and excretion of mepacrine carried out in Britain and the USA indicated its value for the treatment of acute malaria. However, the importance of this drug as a suppressive, when taken for prolonged periods, became obvious only in 1943–1944 as a result of brilliant field studies by Fairley and his team. These tests, carried out on nearly 1000 Australian army volunteers, proved that a daily dose of 100 mg of the drug could be continued for months and even years without serious ill-effects. Huge quantities of the new compound were produced in the United Kingdom and the USA. Mepacrine was soon introduced for routine use in all the malarious theatres of war and enabled the Allied forces in south-east Asia and the south-west Pacific to maintain their fighting condition. There is no exaggeration in saying that this probably changed the course of modern history.

The discovery of mepacrine by the Germans had not stopped their attempts to find other and perhaps better antimalarials. During their studies the German scientists found that changes in the basic side chain attached in position 4 of the quinoline nucleus produce a series of compounds with good antimalarial properties. Two of these compounds of the 4-aminoquinoline series, named Sontochin and Resochin, were synthesized by Andersag as early as 1934, but a few tests did not show that they were superior to mepacrine. Just before the Second World War both compounds were retested by the Germans on cases of human malaria and Sontochin was given preference over Resochin because of its lesser toxicity. In 1941 samples of

these compounds were obtained by the French, who investigated them in Tunisia and confirmed their high activity.

This information was transmitted to the USA, where an extensive programme of chemotherapeutic research had already been launched in 1941. This programme depended on close cooperation between the armed services, scientific institutions, university laboratories and pharmaceutical firms. The chemotherapeutic studies involved the preliminary screening of over 17 000 compounds against several species of avian malaria, the evaluation of the toxicological and pharmacological characteristics of selected compounds in laboratory animals and the final assessment in cases of human malaria, often in volunteers.

In the course of this collective and remarkably coordinated study several derivatives of 4-aminoquinolines were found to be superior to any other drugs.<sup>1</sup> Two of these—chloroquine and amodiaquine—underwent extensive clinical studies in 1944 and the former (corresponding to Resochin) was found to be an outstanding antimalarial compound, faster in therapeutic action than mepacrine or Sontochin and less toxic. Amodiaquine was almost equally effective. The two remained the best therapeutic and suppressive drugs for over 25 years.

In the course of this research programme a number of compounds of the 8-aminoquinoline series were also synthesized and screened. Three promising antimalarials (pentaquine, isopentaquine and primaquine) were found. They differed from pamaquine in the structure of the side chain and had the same, if not a better, effect on relapsing vivax malaria in human subjects. Of these three, primaquine had the lowest toxicity. It remains today the best among comparable compounds for the radical cure of relapsing infections. A closely related compound, named quinocide (chinocid), has been synthesized more recently by Russian scientists.

An intensive research programme on synthetic antimalarials was also conducted during the Second World War in the United Kingdom. The British chemists started with the synthesis of a large series of derivatives of pyrimidine because of the known importance of pyrimidine compounds in cell metabolism. In the course of these studies Curd, Davey & Rose in 1945 obtained a compound of the chloroguanil series which they simplified by opening the pyrimidine ring to produce a biguanide. It was later found that this compound is metabolized in the body, producing a very active form of the drug. Thus proguanil (chlorguanide) was discovered to have an activity on avian malaria greater than that of quinine and with a good margin of safety in laboratory animals. This new drug was given exhaustive clinical trials by the Australian team of Hamilton Fairley at Cairns and proved to be an

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<sup>1</sup> The remarkable story of chloroquine from 1934 to 1946, about the involvement of a score of investigators in 6 countries and the initial discovery of the compound, its rejection, rediscovery and field evaluation and the final verdict, has been told by Coatney (1963). It illustrates the pitfalls in the search for and introduction of some chemotherapeutic compounds.

outstanding causal prophylactic agent in falciparum malaria and a satisfactory suppressive of vivax malaria.

Proguanil came into wider use at the end of the Second World War, by when most of the military problems related to a high malaria incidence in tropical areas had become less urgent because of the availability of mepacrine. Nevertheless, the value of the new causal prophylactic drug became firmly established for the prevention of malaria in persons working in the tropics. However, since its action was slow when given for the treatment of acute malaria, and since it seemed to induce drug resistance in some strains of plasmodia, the search for better compounds continued.

The discovery of proguanil, which started with the study of pyrimidines, stimulated further investigation of this group of compounds in the early 1950s. Several 2,4-diaminopyrimidines have the property of inhibiting the growth of lactic acid bacteria through competition with the folic (pteroylglutamic) and folinic acids necessary for their multiplication. The prediction that useful antimalarial compounds could be developed from that series was soon confirmed on bird plasmodia (*P. gallinaceum*), and even more so on the *Plasmodium berghei* of rodents discovered in 1948 by Vincke. The latter discovery was of great value, as it provided the scientists with an experimental animal model of unparalleled simplicity and convenience. The most active of the new compounds, pyrimethamine, developed in 1951 jointly by an American and British team (Falco & Hitchings) was found to be highly effective against human malaria.

The discovery of pyrimethamine was hailed as an important advance, since the new compound had activity similar to but far higher than that of proguanil. It persisted for a long time in the body and there was a remarkably wide margin of safety between the active and the toxic dosage. However, it was soon found that resistance to pyrimethamine appeared relatively rapidly, not only in experimental conditions but also in the field; and cross resistance between pyrimethamine and proguanil was also in evidence. Another closely related compound, trimethoprim, has more recently been shown to exhibit a varying degree of activity against strains of *P. falciparum* resistant to some of the older drugs.

The development of chlorproguanil, with an activity longer than that of its parent compound, was another step in the direction of expanding the range of available antimalarials. The improved reliability of screening methods, such as the testing of antimalarial drugs on *P. cynomolgi* and *P. knowlesi* in rhesus monkeys, perfected by Schmidt in the USA, represented another advance in chemotherapy.

In spite of some drawbacks of the new compounds, it seemed in the 1950s that the arsenal of antimalarial drugs was almost complete. Some workers believed that most of the problems related to the chemotherapy of malaria had been solved, and the generally successful large-scale use of a combination of chloroquine and primaquine in military forces returning home after having been exposed to malaria during the Korean war enhanced the conviction that,

while no single compound approached the ideal in all respects, the range of specific action of several available drugs was sufficient to deal with any malaria situation.

This may have been one of the reasons why, with the exception of a brief burst of enthusiasm generated by the possibility of the incorporation of chloroquine into common salt (the so-called Pinotti method) and the development of injectable repository compounds effective for a few months, chemotherapeutic research in malaria declined markedly in the late 1950s.

A new and menacing event in the history of the chemotherapy of malaria occurred in 1960 with the observation of resistance of *P. falciparum* to chloroquine, which came at a time when the eradication of malaria seemed to be showing good progress.

The concept of malaria eradication, which has been developing since the early 1950s, when residual insecticides were introduced in many fields of public health, was endorsed by WHO and given an integrated plan in 1956. At that time the increasing frequency of reports on the resistance of human plasmodia to proguanil and pyrimethamine caused some disappointment, but the importance of the phenomenon from the point of view of those concerned with malaria eradication seemed relatively small, firstly because during the period of change of strategy from malaria control to malaria eradication the role of drugs was not fully appreciated, and secondly because proguanil and pyrimethamine, particularly valuable for the prevention of infection and for their sporontocidal effect, are rather slow and uncertain therapeutic agents when used for the treatment of overt malaria.

On the basis of previous experimental work and field observations, it was believed that in human plasmodia the development of resistance to the 4-aminoquinolines was unlikely, to say the least. This complacency was shaken when the failure of chloroquine treatment to cure a *P. falciparum* infection originating in Colombia was reported in 1960 by the American workers Young and Moore. *P. falciparum* infections not responding to the usual curative doses of chloroquine were also described in Brazil and Venezuela. Reports on apparent chloroquine resistance soon came from Thailand, Peninsular Malaysia and other countries in south-east Asia, especially southern Viet Nam, where the number of cases occurring in the United States forces caused much concern. Acute *falciparum* malaria responded to quinine, even though this drug did not always produce a radical cure.

The seriousness of the possibility of widespread resistance of *P. falciparum* to chloroquine—the most widely used drug in the chemotherapy of malaria and a powerful weapon in the service of malaria eradication—was fully recognized by WHO. Particular attention was then paid to careful appraisal of any reports on alleged drug resistance and to the determination of criteria for the recognition of this phenomenon.

The appearance of resistance in some malaria parasites to the 4-aminoquinolines and other available synthetic compounds revealed the relative poverty of the chemotherapeutic arsenal and the narrow margin of

safety in the treatment of disease caused by plasmodia resistant to the best of existing drugs. Steps were taken by WHO to assist research in this particular field which in the past decade has extended over three main areas:

- (a) the collection of data and assessment of the distribution, degree and other characteristics of drug resistance;
- (b) the study of the biological mechanisms involved; and
- (c) the search for new compounds that could be used as alternative therapeutic agents.

Many studies in various countries have been coordinated and sponsored by WHO, but the broadest and most comprehensive scientific effort was launched in 1963 in the United States of America by the US Army Research Program on Malaria. Two years later this gigantic programme was well in its stride and various compounds were being screened. It was set up when the USA faced the urgent task of protecting and treating its military forces in south-east Asia against the danger of falciparum malaria resistant to the 4-aminoquinolines and other compounds.

The availability of rodent and simian experimental models of malaria greatly facilitated the task of screening the new compounds produced by the chemists. Moreover, since 1965 it has been shown that the three main species of human malaria parasites can be transmitted to the South American owl monkey (*Aotus trivirgatus*), and this advance has substantially extended the scope of experimental studies.

At this point the sulfones and sulfonamides re-entered the modern history of the chemotherapy of malaria. Before the Second World War, when the use of sulfonamides revolutionized the treatment of bacterial infections, a number of reports had stated that these compounds have an effect on experimental malaria in animals and also on some infections in man. However, as the action of various sulfones and sulfonamides was slow and variable, this finding was of limited interest. Nevertheless, the results of investigation into the mode of action of sulfonamides drew attention to the chemical analogues of some metabolites as possible chemotherapeutic agents, and to the potentiating action of two compounds acting on different points of the biochemical cycle of growth of the malaria parasite. All this was revealed during the study of the biochemical action of proguanil and pyrimethamine in the 1950s. Following the discovery of resistance of *P. falciparum* to chloroquine, the synergistic action of sulfonamides or sulfones given together with pyrimethamine or proguanil aroused much interest and was of practical value, as shown by the Australians in south-east Asia.

The development of long-acting sulfonamides has increased interest in these compounds. Sulfamethoxypyridazine, sulfadimethoxine, sulfalene and sulfadoxine have been used (the latter two compounds most commonly), in association with pyrimethamine, for the treatment of falciparum malaria resistant to the 4-aminoquinolines.

Dapsone (diaminodiphenyl sulfone) with pyrimethamine or a diformyl derivative of the former were also introduced for the prophylaxis of malaria, but the value of these preparations has not yet been fully assessed. Other compounds or their combinations have been launched, some of them with rather indecent haste. Nevertheless, it is certain that a number of drugs of this series have already found their rightful place as antimalarials.

Some of these and related compounds have been extensively investigated. In the 1960s Thompson devoted much attention to the repository compound cycloguanil embonate, which was thought to be active for a long period after a single injection. Field studies showed that the protection afforded by this and other similar compounds was shorter than expected.

Various other compounds, such as diamidineureas, pyrocatechols, naphthoquinones, 6-aminoquinolines, tetrahydrofurans and quinazolines, have been screened for antiplasmodial activity. Some quinolines and their esters have shown a fair degree of effectiveness in experimental malaria in animals.

Recently several antibiotics have been used experimentally in monkeys and also in patients in south-east Asia, apparently with promising results. In fact, the early trials of antibiotics for malaria go back to the 1950s, when these drugs revolutionized the treatment of syphilis, yaws, relapsing fever, plague and rickettsial infections. Reassessment of these drugs showed that tetracyclines are of some value, but only when administered after a quinine regimen.

The drug screening programme carried out in the USA has been mentioned before. It seems that some of the most promising future drugs for the prevention and treatment of malaria will emerge from this far-seeing enterprise. The programme coordinated by the Walter Reed Army Institute of Research was designed to include the screening of available compounds from various sources and the synthesis of promising new compounds. During the past 12 years over 250 000 compounds have been screened in primary tests using mice infected with *P. berghei*. About 170 of the most active compounds were selected for advanced testing in monkeys infected with simian malaria. Pharmacological and toxicological studies were then carried out on selected compounds, and clinical and field tests on those which showed the greatest promise. By 1974, of the 26 new drugs or their combinations 11 had undergone full trials and of these several have demonstrated high activity against drug-resistant *P. falciparum*. It must be appreciated that the difficulty of trials on cases of human malaria is due to the amount and complexity of preclinical information now required and to the extreme care with which such trials are carried out.

As the result of this comprehensive research programme, 4 new chemical groups have emerged as potentially valuable new antimalarials: (1) 4-quinolinemethanols, (2) 9-phenanthrenemethanols, (3) 2,4-diaminoquinazolines, and (4) 2,4-diaminotriazines. Foremost among the new drugs was a

derivative of a 4-quinolinemethanol(WR 142490), which has now received the generic name of mefloquine.

Extended trials of this compound carried out on naturally infected populations produced good results and, although mefloquine is not yet available for general use, it and other valuable compounds (9-phenanthrene- and 4-pyridinemethanols) are a good augury for further advances in the chemotherapy of malaria generally and for the treatment of drug-resistant falciparum infections in particular.

In the meantime, methods of detecting the presence of chloroquine-resistant strains of *P. falciparum* have been greatly advanced by the use of *in vitro* tests developed by Rieckmann. Their simplicity and convenience are a great advantage in assessing the geographical distribution and degree of resistance, which appears to affect populations everywhere, though at a slower pace than could be expected. Resistance of *P. falciparum* to 4-aminoquinolines has now been reported from east Africa, Bangladesh, Burma, China, India, Papua New Guinea, the Philippines, the Solomon Islands, and Vanuatu (formerly New Hebrides), in addition to the previously affected areas of northern South America and south-east Asia, though in most cases only part of the area seems to be marked by this phenomenon.

In spite of the distant promise of a malaria vaccine and some real advances in applied immunology, there can be no doubt that for the foreseeable future we shall depend on the now available and forthcoming chemotherapeutic methods for the prevention and treatment of malaria.

The malaria situation throughout the world (Fig. 1) causes increasing concern. The number of malaria cases in southern Asia and Middle America during the past few years shows a sharp increase; and the number of cases of malaria imported into the countries of the temperate zone has been rising every year, owing to the greater than ever mobility of human populations as well as the deteriorating malaria situation in many developing tropical areas. At the end of 1979 some 2350 million people were living in areas where the transmission of malaria has not ceased; at least one sixth of these people were still living in places where no organized antimalaria measures were being undertaken, especially in Africa south of the Sahara.

These figures show better than any other pointer that global eradication of malaria, however desirable, is an extremely difficult enterprise and that one of today's major tasks is not to lose the gains achieved during past decades.

The history of the chemotherapy of malaria over this century shows the value of close collaboration between fundamental research in academic or other institutions, applied work carried out by the pharmaceutical industry, and field work in which national and international health authorities are involved. Such collaboration offers the best hope for success in fighting one of the world's oldest, most debilitating and most prevalent tropical diseases.

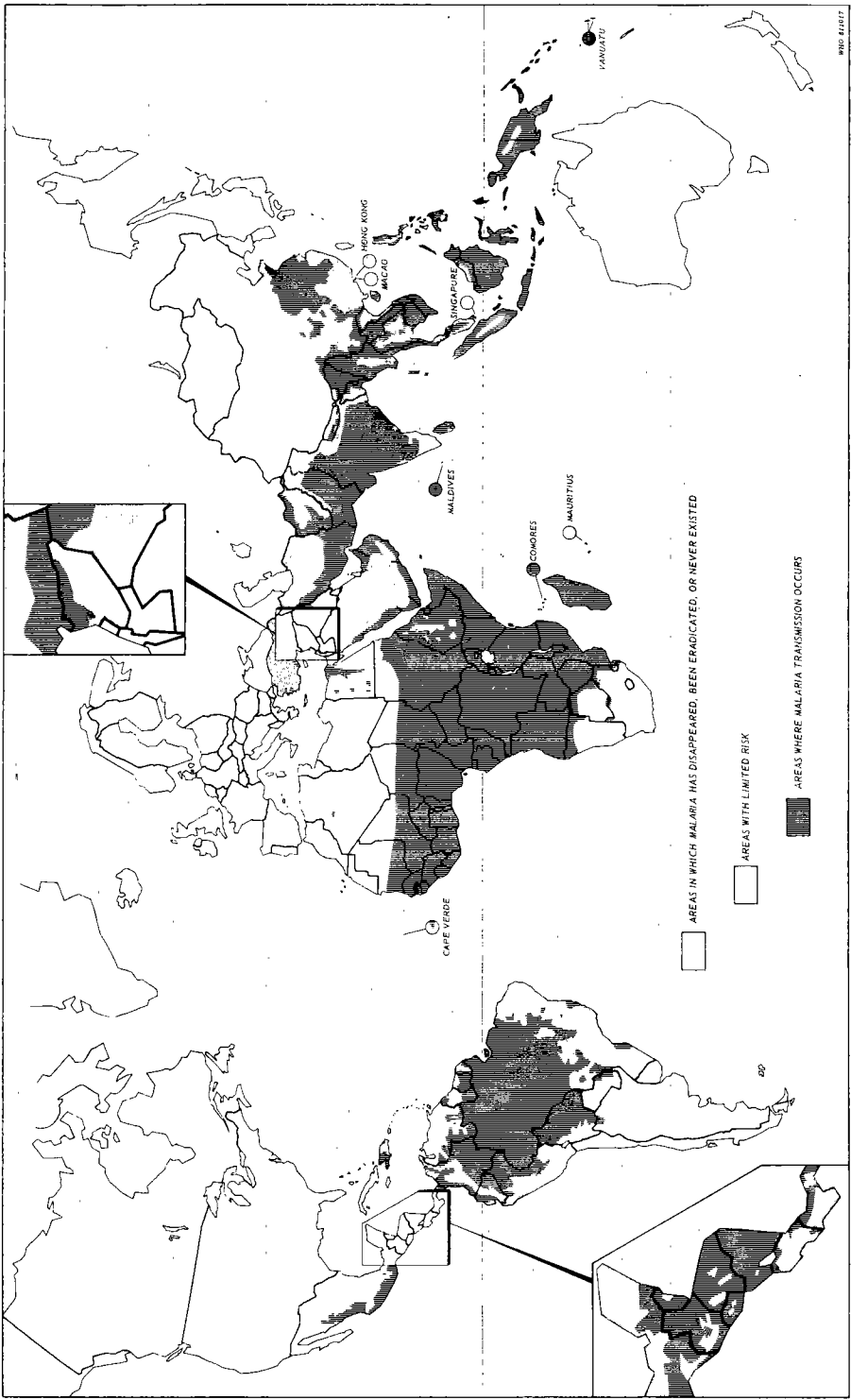


Fig. 1. Malaria situation in the world, 1980