THE CHEMOTHERAPY OF MALARIA

By PROFESSOR F. MURGATROYD, M.D., F.R.C.P., D.T.M.*

Wellcome Professor of Clinical Tropical Medicine, University of London, and Director, Department of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine; Physician, Hospital for Tropical Diseases, London

The chemotherapy of malaria is complicated by the fact that no anti-malarial drug so far discovered is therapeutically effective against all stages of human malaria. Not only do malarial parasites differ in their reactions to drugs at different stages in their complicated life cycles, but different species of parasites at comparable stages of development show different responses, and finally, strains within a given species may show significant differences in susceptibility to treatment. Furthermore, the treatment of patients in whom immunity may be disregarded is not necessarily that most suitable for the partially immune and indigenous patients of a malarious region.

These matters must be kept in mind if treatment is to be intelligently applied, and as a basis some understanding of modern views regarding the development of malaria in man is necessary.

Malarial Cycle in Man

There are four human species of malarial parasite, namely, *Plasmodium falciparum*, which produces the severe and dangerous malignant tertian malaria, *P. vivax*, the parasite of benign tertian malaria, *P. malariae*, producing quartan malaria, and *P. ovale*, with which is associated tertian fever resembling that of vivax malaria. These parasites follow the same general pattern of development, but *P. falciparum* shows certain differences which have an important bearing on treatment.

Infective forms of the malaria parasite, known as *sporozoites*, are injected into man with the saliva of the biting infective female anopheline mosquito, and these circulate for a short time, less than an hour, in the blood. They then disappear from the circulation, and the blood then remains non-infective for some seven to nine days, during which time, the incubation period of the disease, the patient remains free from significant symptoms. In this period the parasites undergo development and multiplication in the parenchyma cells of the liver and, as this multiplication precedes the invasion of the red blood corpuscles, this stage of development is known as the *pre-erythrocytic* phase. This pre-erythrocytic schizogony finally produces ovoid plasmodial bodies which reach 40 to 60 μ in diameter and come to contain, by nuclear division, some 10,000 to 30,000 small nuclei.

Segmentation and rupture of these mature pre-erythrocytic schizonts on the seventh to the ninth day liberate numerous small parasites known as *merozoites*, the majority of which are destroyed by phagocytes while the survivors invade the red blood corpuscles of the circulation to initiate the normal erythrocytic cycle of malaria with which is associated the characteristic signs and symptoms of the disease.

Having entered the red blood corpuscle, the merozoite develops a vacuole and forms the typical malarial 'ring'; the parasite is now known as a *trophozoite* and steadily grows. The trophozoite becomes amoeboid, develops granules of pigment from metabolism of haemoglobin, and its nucleus divides repeatedly, giving rise to an *erythrocytic schizont*. Segmentation of the parasite and rupture of the erythrocyte liberates a number of merozoites which immediately invade further red blood corpuscles. This asexual erythrocytic cycle is then repeated serially, and with it is associated the characteristic periodic fever of malaria. With *P. falciparum*, *P. vivax* and *P. ovale* the cycle takes about 48 hours and with *P. malariae* about 72 hours, so that the first three parasites produce a tertian type of fever and the last a quartan fever.

After a time certain erythrocytic parasites enlarge without nuclear division and form gametocytes, which are differentiated into male and female parasites; they appear in irregular waves in the blood and survive for about a week. Gametocytes as such cause no symptoms in man, and are solely concerned with carrying on the development of the parasite after ingestion by suitable anopheline mosquitoes, the other forms of the parasite merely dying after being taken up by the mosquito.

It seems that with *P. vivax* and probably also with *P. malariae* and *P. ovale*, some of the pre-erythrocytic parasites persist in an *exo-erythrocytic phase* forming a reservoir of parasites from which circulating erythrocytes may from time to time become re-infected when immunity is waning, and perhaps long after the initial attack, thus giving rise to the relapses which are so characteristic of these infections. With *P. falciparum* it seems that the exo-erythrocytic phase does not continue long beyond the pre-erythrocytic period. Consequently, a recrudescence of fever with *P. falciparum* is probably due to persisting infection of the red blood corpuscles and follows the primary attack at a short interval. These facts have important bearings on the nature and duration of treatment that are required, and on the

* As this goes to press, we learn with the greatest regret of the sudden death of Professor Murgatroyd on December 16th.

long-term prognosis in the various types of infection.

General Chemotherapeutic Considerations

From what has been said, it is clear that there are several different stages at which a drug may act upon the malarial parasite. For example, a drug which could be taken continuously without toxic effects and which would maintain in the blood a concentration lethal to sporozoites, would kill these parasites on their introduction by the mosquito, and such a drug would therefore act as a true causal prophylactic agent. Unfortunately, there is no such compound which is sufficiently non-toxic to man that it can be so used in practice. Furthermore, there is no drug in practical use which alone can with certainty be relied upon to destroy all pre-erythrocytic parasites; proguanil in therapeutic doses destroys pre-erythrocytic parasites of certain strains of *P. falciparum* but does not appear to destroy all strains, and it is relatively inactive against pre-erythrocytic forms of the other species.

There are, however, several drugs which in therapeutic doses have a very powerful action against the erythrocytic trophozoites and schizonts of malaria, and as these stages of the parasites are responsible for the clinical manifestations of malaria, such drugs, commonly known as schizonticides, furnish most powerful weapons for the control of the acute stages of the disease. They do not, however, destroy exo-erythrocytic forms of vivax, quartan or ovale parasites, and consequently with any of these infections successful treatment of the acute attack does not necessarily mean that relapse may not occur.

Many of the schizonticidal drugs are sufficiently non-toxic to be taken continuously in doses which maintain a schizonticidal concentration in the blood and thereby suppress the initial development of the erythrocytic parasites from the pre-erythrocytic stages. This suppressive action is greatly used in practice to keep individuals who are exposed to the risk of malaria free from symptoms of the disease. It is obvious, however, that such drugs, acting only on the erythrocytic forms, will not prevent delayed primary attacks, arising from a persisting exo-erythrocytic reservoir of infection, from becoming manifest after the suppressive treatment is discontinued. This often happens in patients after their return from the tropics when they discontinue their anti-malarial drug. Such attacks of vivax, quartan and ovale malaria may occur months after leaving the tropics owing to the long persistence of the exo-erythrocytic reservoir in these infections.

Finally, certain drugs bring about the dis-

appearance of gametocytes or prevent their further development in the mosquito. Because gametocytes as such give rise to no symptoms in man, drugs acting on them are of no direct therapeutic interest, although they may be of some indirect value in limiting the spread of malarial infection.

Specific Drugs

Besides the standard anti-malarial drugs, many other compounds exert some anti-malarial activity but their potency is usually limited. On the other hand, a number of new and promising compounds are under trial, but these have not yet come into practical use. The drugs at present used in practice fall into five groups:—

1. Cinchona alkaloids. Of these quinine in various salts is most used, although other cinchona alkaloids have been employed; on the grounds of cheapness considerable use has been made of totaquina, a standardized mixture of total cinchona alkaloids containing not less than 70 per cent. of crystallizable alkaloids of which not less than 15 per cent. is quinine.

2. 9-amino-acridine compounds. The outstanding representative is mepacrine.

3. 4-amino-quinoline compounds. These include chloroquine, camoquin, and a number of related compounds.

4. Biguanide derivatives. Of these the practical example is proguanil.

5. 8-amino-quinoline compounds. These include pamaquin, pentaquine and isopentaquine.

The first four act as schizonticidal agents, destroying the asexual parasites in the erythrocytes. Through this action they can be used either to control acute malarial attacks or, if taken continuously, to suppress the development of parasites in the blood, thereby preventing the development of clinical symptoms. In addition, proguanil destroys pre-erythrocytic forms of certain strains of *P. falciparum* and also prevents gametocytes from developing fully in the mosquito.

Compounds of the fifth group, the 8-amino-quinoline derivatives, are mainly used for their action against the exo-erythrocytic parasites. They are used in conjunction with one of the schizonticidal drugs in the treatment of attacks of vivax, quartan and ovale malaria. They appear to devitalize the exo-erythrocytic parasites, particularly if given along with quinine, and consequently they diminish the tendency of these infections to relapse. They also are capable of destroying sporozoites or pre-erythrocytic forms, but the dose required for this action is so close to the toxic dose that they cannot be used as practical causal prophylactic agents; they also destroy gametocytes.

Quinine 0.65 g. (10 gr.), preferably in solution,

for which a soluble salt or the addition of sufficient acid is required, given three times a day by mouth for about a week, will control an acute attack of malaria provided the drug is absorbed. If the patient is vomiting, if the circulation is so depressed that the absorption is slow, in the presence of cerebral malaria or some severe complication demanding very rapid control, it is necessary to administer the first one or two doses parenterally. For this purpose quinine dihydrochloride, 0.5 g., may be given slowly intravenously and, to prevent thrombosis, preferably in dilute solution; the drug may also be given intramuscularly but then sometimes produces pain and local necrosis.

For suppressive treatment a daily dose of 0.3-0.6 g. is often used, but it is not always effective and repeated low-grade falciparum infections may become established and so condition the individual for the development of blackwater fever, which is therefore common in areas where quinine is relied upon for malarial suppression.

Therapeutic doses may give rise to tinnitus and deafness; more rarely to vertigo, visual disturbances, nausea, headache, and very occasionally to urticarial rashes.

Quinine has a good therapeutic action against asexual erythrocytic parasites, although with some strains of malaria the disappearance of parasites and subsidence of fever do not always occur as rapidly as with a large dose of mepacrine or chloroquine. Quinine is without action on exo-erythrocytic parasites and therefore does not prevent relapses of vivax or quartan infections, and vivax malaria in some cases may relapse as early as one or two weeks after treatment. The drug has some action on the gametocytes of vivax and quartan infections, but none on those of falciparum infections.

Quinine is rapidly metabolized and excreted, plasma concentrations falling by 90 per cent. within 24 hours after ceasing administration of the drug. The drug appears to retard the growth, arrest development and produce degenerative

changes in the asexual parasites in the earlier stages of their cycle, possibly through interfering with their carbohydrate metabolism by inhibiting the oxidation of pyruvic acid, but the exact mechanism of action is obscure, as it is for all the anti-malarial drugs.

Mepacrine (atebrin, quinacrine, acriquine) is used, commonly as the hydrochloride, in doses of 0.2 g. three times daily by mouth for one or two days, followed by 0.1 g. three times daily by mouth for five to seven days, for the control of acute malarial attacks. Where parenteral injection is indicated the drug may be given intramuscularly; it may cause irritation and mepacrine methanesulphonate may be substituted. The drug may be given intravenously but the margin of safety by this route appears small; if so used, the drug should be given in very dilute solutions and slowly.

For suppressive treatment 0.1 g. mepacrine daily, taken by mouth, usually is very efficient but certain rare strains of *P. falciparum* may require 0.2 g. daily for their suppression. As it takes some time for the plasma concentration to reach a schizonticidal level with a dosage of 0.1 g. daily, suppressive treatment should commence with loading doses as advised for the treatment of acute attacks, or alternatively the normal suppressive regime should be started two weeks before the individual will be exposed to the risk of infection.

In therapeutic doses mepacrine does not usually cause serious side effects although it may stain the skin yellow, and occasionally produce a blue pigmentation seen especially over the nail beds, nose, palate, epiglottis and tracheal rings. Sometimes the drug produces gastro-intestinal symptoms, including nausea, vomiting and diarrhoea; more rarely mental excitation or toxic psychoses, visual disturbances and anaemia; while in a few persons mepacrine has been associated with skin lesions which may be excematoid, lichenoid and exfoliative.

In its action the drug resembles quinine, and if loading doses are given it controls acute attacks as rapidly as does quinine. Exo-erythrocytic parasites are not affected and consequently relapses of vivax or quartan malaria may occur,

but possibly owing to the slow elimination of the drug the parasites do not usually reappear until at least four to six weeks after treatment. The drug also resembles quinine in being inactive against gametocytes of *P. falciparum*.

Mepacrine accumulates, especially in the leucocytes, liver, spleen, heart and lungs, and is only slowly eliminated so that the plasma concentrations fall only about 50 per cent. per week after the drug is discontinued. The drug diminishes the amoeboid movement of the early asexual erythrocytic parasites, and produces abnormal forms with clumping and extrusion of the pigment; it possibly acts by interfering with some phosphorylation reaction necessary for the utilization of glucose by the parasite, or by inhibiting reactions involving riboflavin.

Chloroquine (aralen, resochin, nivaquine, SN 7618, 3377 RP) in the treatment of acute malaria is normally given as the diphosphate, by mouth, in an initial dose of 1 g. followed after six to eight hours by three doses each of 0.5 g. at 24-hour intervals. Where rapid action is required chloroquine hydrochloride, 0.5 g., may be given intramuscularly or very slowly intravenously.

7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline

For malarial suppression, 0.5 g. diphosphate by mouth once a week suffices, because degradation and excretion of the drug are very slow.

In therapeutic doses the drug is relatively free from side effects. Occasionally gastro-intestinal disturbances, pruritus, headache, and visual disturbances, such as blurring of vision or difficulty in accommodation, may occur; administration of the drug has also been associated with the occurrence of a toxic psychosis, but this appears extremely rare.

Chloroquine acts mainly against asexual erythrocytic parasites and it rapidly brings about the termination of a malarial attack. It does not eradicate exo-erythrocytic parasites; consequently vivax and quartan relapses may occur, although not usually until at least two to three months after treatment. Gametocytes of *P. falciparum* appear resistant to the drug.

The drug accumulates in the liver, spleen, kidney, lungs and leucocytes. Excretion of the compound is extremely slow and plasma concen-

trations drop only about 60 per cent. per week after the last dose. Because of the drug's slow excretion and powerful effect, relatively few doses are required for the control of an acute malarial attack and, in the case of falciparum infections, for radical cure; for the same reasons suppressive doses can be widely spaced, for example at weekly intervals.

Proguanil (paludrine, chlorguanide, M.4888) is used for the treatment of acute malaria, as the hydrochloride, in doses of 0.3-0.6 g. divided into two or three doses daily, by mouth, for ten days. For parenteral use acetate and lactate are more soluble and are recommended, but in severe falciparum infections where there is great urgency many physicians prefer quinine or mepacrine.

N₁-(p-chlorophenyl)-N₅-isopropyl biguanide

For malarial suppression, 0.1 g. proguanil per day may be used.

Proguanil is relatively non-toxic, very high dosage only sometimes producing gastro-intestinal symptoms, evidence of renal irritation, and increase in myelocytes or lymphocytes in the blood.

In its action on asexual erythrocytic parasites proguanil resembles the drugs previously mentioned but it does not eradicate the exo-erythrocytic phases, and relapses of vivax infection occur with about the same frequency and at the same time as after mepacrine. Proguanil has, however, an action on the pre-erythrocytic parasites of many strains of *P. falciparum*; it also renders gametocytes of these parasites incapable of completing their development in the mosquito. There appear to be certain African strains of *P. falciparum* which show some resistance to the action of proguanil, and overt infections have been reported where the drug has been relied upon as a suppressant. Similarly, when used for the treatment of acute attacks with such strains, the drug has failed to eradicate the infections, particularly primary infections; certain of these infections were radically cured when either quinine or mepacrine was given on the first day of the course of proguanil. Parasites also appear to become resistant to proguanil rather easily and in areas where proguanil is used, proguanil-resistant strains of parasites may arise.

Proguanil is fairly rapidly absorbed from the alimentary tract, and appears localized in the

erythrocytes, leucocytes, kidney and liver. Although it is fairly quickly degraded and disappears from the plasma after cessation of dosage, there is some evidence that a part of it may be converted into a plasmodicidal product. Asexual erythrocytic parasites exposed to proguanil develop until the early stage of their schizogony is reached; at this point development is arrested and the parasites then undergo degeneration. Although the drug appears to have no direct action on gametocytes, it nevertheless prevents their subsequent development in the mosquito. The mode of action of proguanil is unknown, but it has been suggested that it may interfere with the utilization of pteroylglutamic acid or with the porphyrin metabolism of the parasite, or inhibit the oxidation of glucose, pyruvate and lactate.

Pamaquin (plasmochin, praequine) is used, as naphthoate or monohydrochloride, in doses of 0.01 g. base two or three times daily by mouth for 10-14 days.

6-methoxy-8-(4-diethylamino-1-methylbutylamino)quinoline

Its action on asexual erythrocytic parasites is slight, and its usefulness depends upon the fact that it devitalizes exo-erythrocytic parasites which would otherwise give rise to relapses in vivax, quartan and ovale malaria; this effect seems to be enhanced by the concurrent administration of a schizonticidal drug, especially quinine. It is often said that the drug should not be given concurrently with mepacrine because in such circumstances the toxicity of both drugs appears to be increased, but in many cases the combination has been given without trouble. Pamaquin also destroys gametocytes, especially those of *P. falciparum*. It also has some action on sporozoites and pre-erythrocytic parasites, but the necessary concentration can only be attained by doses bordering upon the toxic and consequently the drug is of no practical use as a true causal prophylactic agent.

The drug tends to give rise to abdominal discomfort and it often produces methaemoglobinocythaemia, clinically manifest by cyanosis; occasionally its use is associated with intravascular haemolysis, which may be acute, or with granulocytopenia.

Pamaquin is found concentrated in the liver,

lungs and brain but is quickly metabolized. The plasma concentration is raised by the concurrent administration of quinine, mepacrine, or proguanil, especially by that of the two latter.

Pentaquine resembles pamaquin in its effects, but is perhaps a little less toxic and, as a phosphate, is used in twice the dosage recommended for pamaquin.

6-methoxy-8-(5-isopropylaminoamylamino)quinoline

Practical Treatment of Non-Immune Persons

Acute falciparum malaria. Of the four species of human malarial parasites, *P. falciparum* produces the most serious and dangerous illness, but fortunately, because of its response to drugs and the absence of any persisting exo-erythrocytic phase, it is the easiest infection to cure completely. The use of quinine is now declining because although it will control most infections, its ultimate action is inferior to that of some of the newer synthetic antimalarial drugs. Probably because of its incomplete action against falciparum infections its use appears to be associated with a relatively high incidence of blackwater fever. At the same time many prefer to use it initially in falciparum infections of grave urgency, but normally in acute attacks of falciparum malaria, non-immune persons should be treated by one of the schizonticidal drugs, chloroquine, mepacrine, or proguanil, in the doses indicated. The response is usually rapid. If the patient is not obviously under control within two or three days, the absorption of the drug or the diagnosis should be suspect.

Acute vivax, quartan and ovale malaria. Acute attacks of these infections can be controlled by any of the schizonticidal drugs such as quinine, mepacrine, chloroquine or proguanil given in the doses recommended, but these infections so treated may relapse, because of their persisting exo-erythrocytic parasites which are unaffected by these schizonticidal drugs alone. Consequently the schizonticidal drugs should be reinforced by the additional use of pamaquin or pentaquine. It has been stated that pamaquin is most effective when given with quinine, but if quinine is to be used the possibility of an accompanying although cryptic falciparum infection and the possible association of quinine with blackwater fever should be kept in mind. If a patient proposes to carry on

indefinitely with suppressive treatment immediately following the control of the acute attack, there may be no need to give the pamaquin or pentaquine, because any blood infection from any persisting exo-erythrocytic reservoir will be inhibited by the suppressive treatment before any symptoms can become manifest.

Suppressive treatment. As quinine appears inferior to the newer antimalarial drugs, it is gradually falling out of favour for suppression. It does not always adequately suppress falciparum infections or prevent low-grade infections, and consequently it allows patients to become conditioned for the development of blackwater fever. The drugs most commonly now used are mepacrine or proguanil daily, or chloroquine weekly. These drugs are most efficient and where they are regularly employed the malarial incidence shows a striking fall, and blackwater fever practically disappears. A certain number of failures of suppression are reported whatever drug is being used, and reference has already been made to the suggestion that certain African strains of *P. falciparum* are relatively resistant to proguanil. In individual cases, however, it is sometimes very difficult to be sure that the drug has been taken regularly.

Treatment of Partially Immune Persons

Acute attacks. Partially immune patients tend to suffer from only relatively mild and short attacks of fever, and these attacks are usually readily controlled by a very few doses of one of

the schizonticidal drugs. Furthermore, it is argued that it is impossible on economic and administrative grounds to treat large indigenous populations of malarious areas sufficiently to keep them free from infection, and that anything short of this tends to deprive them of the natural immunity and protection that they obtain from infection. Consequently, it is suggested that in partially immune persons all that is desirable is to give one of the schizonticidal drugs in the doses recommended above, but only for a period sufficient to control the acute manifestations of the attack. Such treatment may only require one or two doses, and at the most does not usually take more than two or three days. Where there is a well-marked seasonal incidence of malaria it may be desirable to treat each attack thoroughly, in the case of vivax or quartan infections using pamaquin or pentaquine together with a schizonticidal drug, but the most desirable regime to be adopted in any given circumstances can only be decided after careful consideration of all the factors, including the effects of the infections on the health and economic balance of the community, the part played by immunity in the protection of the population, and the cost of any proposed line of treatment.

Suppressive treatment. In partially immune populations relatively less frequent doses of suppressive drugs may be used, for example, mepacrine or proguanil once or twice a week, or small doses of chloroquine once a week, but again the exact regime that seems desirable depends upon a full consideration of all the factors involved.

NEW PRODUCT

'KEMADRIN'

A new product for the treatment of paralysis agitans (Parkinsonism) has undergone initial trials and is now available from Burroughs Wellcome & Co. Issued under the title 'Kemadrin' brand *di-1-cyclo* hexyl-1-phenyl-3-pyrrolidinopropan-1-ol hydrochloride, it causes a decrease of rigidity and leads to better muscle coordination. Patients are able to indulge in greater physical activity and reveal increased well-being and alertness. 'Kemadrin' causes less dryness of the mouth, less constipation, less retention of urine and less mydriasis than do the belladonna and stramonium alkaloids. Further trials are in progress. 'Kemadrin' is available as 5 mgm. compressed products in bottles of 25 and 100.

MANUFACTURERS NOTES

The Distillers Company (Biochemicals), Ltd., announces the availability of 'Distivit' B₁₂ injection solution of crystalline vitamin B₁₂ through the distribution facilities of Burroughs Wellcome & Co., Evans Medical Supplies, Ltd., and Imperial Chemical (Pharmaceuticals), Ltd. 'Distivit' B₁₂ is issued in ampoules of 1 ml. containing 20 micrograms; boxes of 5 x 1 ml. ampoules retailing at 4s. 3d. Literature is available upon request.

The Distillers Company (Biochemicals) Ltd., announces the availability, through their usual distributors, of Dihydrostreptomycin Sulphate DC(B)L in vials of 1 million units (equivalent to 1 gm. dihydrostreptomycin base) retailing at 5s. per vial.