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The Secretary of the Expert Committee on Malaria
has the honour to communicate hereunder
the following note:

THE ROLE OF DRUGS IN THE PREVENTION OF MALARIA*

by

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(Items 2 and 2.1 of the Provisional Agenda)

I. THE LIFE CYCLE OF THE PARASITE AND THE RANGE OF PREVENTIVE THERAPY**

The sporozoites are apparently resistant to all known drugs, but their successors, the pre-erythrocytic liver schizonts, may be destroyed by some of the synthetic compounds. Complete destruction of the organism at this stage, before infection reaches the red blood corpuscles, is known as causal prophylaxis. Causal prophylaxis is possible in all forms of human malaria but is seldom practical except in falciparum infection.

The mature liver schizonts burst and liberate merozoites which invade the blood stream to begin a series of schizogonic cycles in the red blood corpuscles. Again the complete destruction of the organism is possible. Eradication by treatment at this later stage is called radical cure, or suppressive cure if due to continued suppression. With modern drugs radical cure is usually possible in all forms of human malaria; suppressive cure is likely only in falciparum infection. When the schizogonic cycle in the blood is interrupted but not eradicated the effect is known as suppression; the

* The material for this account is largely drawn from a contribution to the forthcoming WHO Brochure on modern anti-malaria drugs.

** This discussion is restricted to therapy which aims specifically to prevent malaria. Early and efficient treatment for acute attacks in a malarious population also has a significant preventive effect.

parasites remain though in numbers too small to cause symptoms. Efficient suppression is possible in all forms of human malaria. Continued for a month or more after the last date of infection suppression in falciparum malaria often leads to suppressive cure.

There remains the preventive effect attained by elimination of the gametocytes. Destruction of the gametocytes, or damage inhibiting their development in mosquitos, arrests the transmission of infection to a fresh human host. This effect is known as direct gametocytocidal prophylaxis. Transmission may also be arrested or reduced by drugs which have an indirect effect on the gametocyte reservoir. Gametocytes arise as an offshoot of the schizogonic cycle in the blood, and drugs which eliminate this cycle arrest the further production of gametocytes. This effect is called indirect gametocytocidal prophylaxis. Suppression and suppressive cure have this indirect gametocytocidal effect.

II. THE ANTI-MALARIA DRUGS OF TODAY

For the chemoprophylaxis of malaria today drugs may be classified broadly into four chemical groups, with differences in anti-malaria activity which are summarized in Table 1.

TABLE 1. CLINICAL ACTIVITY AND CHEMICAL STRUCTURE OF THE COMMON ANTI-MALARIA DRUGS

Chemical group	Main members of the group	Preventive activity in malaria
(1) 4-amino-quinolines and related compounds	Quinine Mepacrine Chloroquine Amodiaquine	Essentially schizontocides. No action on exo-erythrocytic parasites, or on the gametocytes of <u>P. falciparum</u> . Excepting quinine all are powerful suppressives, often producing suppressive cure. Low toxicity. Do not induce drug resistance.
(2) 8-amino-quinolines	Pamaquin Pentaquine Isopentaquine Primaquine	Poor schizontocides, but active against gametocytes and exo-erythrocytic parasites. Used mainly for direct gametocytocidal prophylaxis and for radical cure in vivax infection. Moderately toxic. Do not induce significant drug resistance.

Chemical group	Main members of the group	Preventive activity in malaria
(3) Biguanide	Proguanil	Schizontocide and gametocytocide. Active also against the pre-erythrocytic forms of <u>P.falciparum</u> . Main uses - causal prophylaxis in falciparum infection, suppression in all forms of malaria, and gametocytocidal prophylaxis. Non-toxic. Liable to induce drug resistance.
(4) Pyrimidine	Pyrimethamine	Actively similar to that of proguanil, but unlike proguanil has some action on the exo-erythrocytic forms of <u>P.vivax</u> . Main uses - causal prophylaxis in falciparum malaria and suppression in all forms of malaria. Toxicity probably low. Liable to induce resistance.

III. THE PERSONAL PROBLEM OF MALARIA PREVENTION BY DRUGS

The suppression of symptoms is perhaps the most useful clinical benefit conferred by regular and prolonged administration of small doses of anti-malaria drugs, but it is not the only benefit. Some infections are cured, and with particular drugs some are eradicated before they reach the blood. The term "suppression" is hence too restricted in its meaning, and clinically unrealistic, and in this brief account we shall use the broader term "clinical protection" to include suppression, suppressive cure, and radical prevention. The "clinical protection" which may fairly be expected of modern drugs is summarized as follows:

- (a) suppression in all forms of malaria;
- (b) causal prophylaxis or suppressive cure in falciparum infections;
- (c) suppressive cure in some vivax infections (pyrimethamine only).

The drugs used to achieve these effects and the doses suggested are summarized in Table 2.

TABLE 2. DRUGS AND DOSAGE SUGGESTED FOR CONTINUOUS CLINICAL PROTECTION

Drug	Dosage in milligrammes (and tablets)						
	Interval	Over 16 years	11-16 years	7-10 years	4-6 years	1-3 years	Under 1 year
Proguanil ¹	daily	100(1 tab)	100(1)	75*	50*	50*	25*
Chloroquine base ²	weekly	300(2 tabs)	225(1½)	150(1)	100(2/3)	75(½)	37(¼)
Amodiaquine base	weekly	400(2 tabs)	300(1½)	200(1)	133(2/3)	100(½)	-
Mepacrine ³	daily	100(1 tab)	75*	50*	25*	-	-
Pyrimethamine base ¹	weekly	25(1 tab)	25(1)	18(¾)	12(½)	6(¼)	-
Quinine salt ⁴	daily	500-600 (8-10 grains)	300-500 (5-8 grains)	200-250 (3-4 grains)	130-200 (2-3 grains)	130(2 grains)	65(1 grain)

* Tablets of 25 mg proguanil or mepacrine are prepared by some manufacturers.

¹ Contra-indicated in areas where the prevailing malaria is known to be resistant to either of these drugs.

² See note in text.

³ Beginning 10 days before exposure to infection.

⁴ Recommended only when other drugs are not available.

Chloroquine and amodiaquine - These 4-amino-quinolines are powerful suppressives; they will achieve suppressive cure in falciparum infection, they have a low toxicity, and they do not induce drug resistance. They will seldom eradicate vivax or malariae infection, and they have no action on the pre-erythrocytic forms or gametocytes of P.falciparum. A dose of 300 mg base once a week will usually be adequate even for non-immunes; but under particular conditions the larger dose of 100 mg base daily recommended in the Fifth Report of the WHO Expert Committee on Malaria may be necessary.

Proguanil - This drug has a wide effective range and very low toxicity. It is a causal prophylactic against falciparum infection, a good suppressive, and an active gametocytocide in all forms of malaria. A tendency to induce resistance is its main limitation: against resistant strains there is a general loss of activity throughout its plasmodicidal range.

Mepacrine - This compound resembles chloroquine in its clinical range but it is somewhat less active and not entirely free from toxic side-effects. Though a thoroughly reliable drug for clinical protection it can now be recommended only when the more effective 4-amino-quinolines are not available.

Pyrimethamine - Dose for dose, this compound is the most powerful suppressive known, but this does not mean that it is the best. It simply means that suppression is achieved at a dosage which for the same effect is lower than that of other drugs. The activity of pyrimethamine is similar to that of proguanil, but, unlike proguanil, it will sometimes achieve suppressive cure in vivax infection. Like proguanil, it is liable to induce resistance in parasites exposed to sub-lethal doses.

Quinine - Though a useful drug for clinical protection in malaria, and a drug highly regarded in some countries by persons of conservative habit, quinine is less efficient than the synthetic compounds mentioned above and can be recommended only when these compounds are not available.

Eradication of falciparum infection

Drugs given at a dosage appropriate for the prevention of infection may eradicate P.falciparum either at the pre-erythrocytic stage (causal prophylaxis) or at the erythrocytic stage (suppressive cure); and if suppressive cure is attained before symptoms appear the results from a clinical standpoint are the same - the eradication of infection with complete protection from clinical manifestations.

The drugs available for the eradication of falciparum infection are proguanil, chloroquine, amodiaquine, mepacrine, and pyrimethamine. Proguanil and pyrimethamine eradicate infection at a pre-erythrocytic stage: chloroquine, amodiaquine and mepacrine achieve the same end-result at the later erythrocytic stage. Pamaquin and other 8-amino-quinolines are causal prophylactics but the toxicity of these drugs is such that this activity

confers no clinical advantage unless the dates of the infecting bites are roughly known and preventive therapy can be timed accordingly.

TABLE 3. DOSAGE OF VARIOUS DRUGS FOR THE PREVENTION OF FALCIPARUM INFECTION

Drug	Dosage
Proguanil	100 mg daily beginning on the first day of exposure and ending one week after the last day.
Chloroquine ¹	300 mg base weekly beginning on the first day of exposure, and ending one month after the last day.
Amodiaquine	400 mg base weekly - do -
Mepacrine	100 mg daily beginning 10 days before exposure and ending one month after the last day.
Pyrimethamine ²	25 mg base weekly beginning on the first day of exposure and ending one week after the last day.

¹ For non-immunes in some areas 100 mg base daily may be necessary (Fifth Report, WHO Expert Committee on Malaria)

² Reported to afford complete protection against a West African strain of P.falciparum (Covell et al. 1953). Pyrimethamine and proguanil alike are contra-indicated when the prevailing strains of P.falciparum are resistant to either drug.

Complete prevention against falciparum infection, the most dangerous of the malarial infections, by the eradication of the parasites has a special value for persons passing through or temporarily resident in malarious countries. The collateral benefits are those conferred by "clinical protection", indeed the drugs used and the doses given are the same; the difference lies solely in the duration and timing of protective therapy.

Eradication of vivax and malariae infection

The prospects of eradicating vivax infection by drugs given at preventive dosage are not good. The most active drugs are the 8-amino-quinolines, and pyrimethamine. Given at the time of the infecting mosquito bites or early in the incubation period primaquine and pamaquin will eradicate infection at its

source in the liver parenchyma; but the times of infecting bites are seldom known and both drugs are too toxic for prolonged administration. Pyrimethamine will not destroy vivax infection at its source, but continued administration at the minute dosage of 25 mg base once a week for two months after infection has been shown to achieve suppressive cure in some cases (Coatney et al., 1953), and present evidence suggests that, imperfect though it may be, pyrimethamine is the best drug we have for this particular purpose.

Quartan infections behave much like vivax infections, and by analogy it is assumed that preventive therapy is subject to the same possibilities and limitations.

Toxicity of drugs

Any drug which has to be taken over long periods must be free from serious side-effects. At the dosage appropriate for prophylaxis, proguanil is non-toxic; pyrimethamine, given continuously in doses of the order of 25 mg daily, has a reversible depressive effect on the bone marrow, but the dose recommended for prophylaxis is so extremely small that the risk of toxic effects is remote; chloroquine and amodiaquine carry no known risk of any consequence; mepacrine stains the skin and conjunctivae, and sometimes causes a lichenoid dermatitis, while psychoses occurring during suppressive administration have been reported. All in all, the risks of harmful side-effects from collective prophylaxis based on these drugs are small, particularly when they are assessed in the light of the benefits the drugs confer. With mepacrine only are these effects ever likely to discourage wide-scale use.

IV. THE COMMUNITY PROBLEM

Malaria in a community is a social expression of the biological relationship between malaria parasites, their human hosts, and the mosquitos which bring them together. Eliminate the mosquitos or break their contact with man and malaria will disappear. The most effective and permanent forms of malaria control take advantage of this fact. Eliminate the parasites or interrupt their life cycle at points which are vulnerable to drugs and malaria will likewise disappear. This is the aim of collective drug prophylaxis.

Drug control is impermanent, but it is quick to take effect and under particular conditions it may be almost complete.

Principles

So long as clinical protection against malaria is restricted to a few interested and zealous individuals, the collateral effect on the malaria of the community to which they belong will be incidental and probably small. But when personal prophylaxis is spread so widely as to become collective prophylaxis a new series of effects, cumulative and highly significant for the community, comes into play - the reduction or elimination of the seed bed from which mosquitos become infected. Personal drug prophylaxis depends essentially on the interruption of the asexual cycles of the parasite; collective drug prophylaxis brings into play an additional effect on gametogony and sporogony, with an interruption in the transmission of infection to mosquitos. The factors which operate when a good schizontocide is continuously administered to a whole population at suppressive dosage are simply analysed below, chloroquine and proguanil being taken as examples.

Suppressive chloroquine

<u>Effect on asexual blood cycle</u>	<u>Collateral effect on gametocyte reservoir</u>
(a) Suppression or suppressive cure of falciparum infection.	None at first; with cessation of attacks no further production.
(b) Suppression of vivax and malarial infection.	Existing gametocytes destroyed: with cessation of attacks no further production.

Suppressive proguanil

<u>Effect on asexual cycles in blood and tissues</u>	<u>Collateral effect on gametocyte reservoir</u>
(a) Causal prophylaxis in falciparum infection.	No production.
(b) Suppression or suppressive cure of existing falciparum infection.	Gametocytes inhibited; with cessation of attacks no further production.
(c) Suppression of vivax and malariae infection.	- do -

Amodiaquine and mepacrine resemble chloroquine in their effects; pyrimethamine in most respects resembles proguanil. These drugs given efficiently to every member of a closed community might be expected on theoretical grounds to arrest transmission completely, but practical difficulties limit their effect. Communities are seldom isolated from outside sources of infection, and the administration of any drug with unflinching regularity to every member of a community is an exacting task. The collateral effects of collective drug prophylaxis will hence be related to the epidemiological situation, and to the proportion of members in the community under regular drug administration.

Methods, Drugs and Dosage

The continuous administration of a good schizontocidal drug to a whole population, with dosage intervals related to the potency and persistence of the drug in the body, seems to be the most efficient method of collective drug prophylaxis. Initial "mass" or "blanket" treatment at a dosage appropriate for acute attacks is sometimes recommended but seldom necessary. Other methods of administration - intermittent "mass" or "blanket" treatment at intervals of weeks or months, and selective treatment for parasite carriers - have usually been less successful. Collective drug prophylaxis based on pamaquin has been largely abandoned, though the possibilities in this direction of the more active and less toxic 8-amino-quinoline, primaquine, have yet to be defined.

For the community, as for the individual, the most suitable drugs are proguanil, chloroquine, amodiaquine, mepacrine, pyrimethamine and quinine (Table 4).

TABLE 4. DRUGS AND DOSAGE SUGGESTED FOR COLLECTIVE PROPHYLAXIS

Drug	Communities with little immunity; armies in the field, etc.	Communities in endemic areas
Proguanil ¹ or	100 mg daily	200 mg twice a week, or 300 mg once a week
Chloroquine ² or	300 mg base once a week	300 mg base once in 1-2 weeks
Amodiaquine, or	400 mg base once a week	400 mg base once in 1-2 weeks

Drug	Communities with little immunity; armies in the field, etc.	Communities in endemic areas
Mepacrine, or Pyrimethamine ¹ or Quinine ³	100 mg daily 25 mg base once a week 650 mg (10 grains) daily	200 mg twice a week, or 300 mg once a week 25 mg base once a week 300 mg (5 grains) daily

The doses for children are summarized in Table 2.

¹ Contra-indicated when the prevailing malaria is known to be resistant to one or other of these drugs.

² For non-immunes in some areas 100 mg base daily may be necessary (Fifth Report, WHO Expert Committee on Malaria)

³ Recommended only when other drugs are not available.

Drug control of epidemics

Severe epidemic malaria demands quick action; many people are sick, some are dying, and by drugs alone can the immediate situation be met. Collective drug prophylaxis, starting with a loading dose, has here one of its clearest indications. The drugs and doses recommended are summarized in Table 5.

TABLE 5. DRUGS AND DOSAGE OF VARIOUS DRUGS FOR THE EMERGENCY CONTROL OF EPIDEMIC MALARIA

Immediate Single dose (adult)	Follow-up continuous dosage (adult)
Chloroquine 600 mg base, or Amodiaquine 600 mg base, or Mepacrine 600 mg	Proguanil* 100 mg daily, or Pyrimethamine* 25 mg base weekly, or Chloroquine 300 mg base weekly, or Amodiaquine 400 mg base weekly, or Mepacrine 100 mg daily.

* Contra-indicated where the prevailing malaria is known to be resistant to one or other of these drugs.

Persons with fever at the time of examination are not adequately treated with a single dose of mepacrine; further treatment with 300 mg daily for two days is desirable. The persons distributing the drugs should ensure that the full dose is swallowed and washed down with a drink of water. This precaution, a wise one at all times in collective drug prophylaxis, has a special importance during epidemics.

When the malaria is under clinical control a reduction in the dose of proguanil or mepacrine to 200 mg twice a week, or 300 mg once a week may be considered. Drug administration should continue for at least one month - long enough for the suppressive cure of most falciparum infections. The likelihood of recrudescence vivax and malariae infections some weeks after stopping the drugs should not be forgotten.

The emergency distribution of drugs should not replace or delay other and more lasting forms of control. House spraying with residual insecticides should begin at once, and steps taken to ascertain the cause of the epidemic. Whether drugs should or should not play any part in the future control policy must depend on the prevailing conditions and available resources.

Drugs in malaria control projects

There is little evidence that malaria can be controlled completely and permanently by drugs. Major control projects involving large static populations must hence be based on attempts to control the vector. Even so, drugs may still play a useful role under particular circumstances. The present position in Malaya where a tradition of malaria control goes back for nearly half a century may perhaps be taken for illustration. There will often be a parallel in other countries.*

Control in towns - In densely populated urban areas the well-known anti-larval measures, subsoil drainage, permanent land drainage, ditching, and spraying breeding places with larvicides, have given excellent results over many years. These measures banish vector mosquitos and give a higher degree of protection under Malayan conditions than can be expected from any other method. In these circumstances, drugs have no place in preventive practice.

* See Malaria Control by Modern Methods. Circular No. 7 (revised) Malaria Advisory Board, Federation of Malaya, July, 1954.

Villages, estates, mines - The choice here lies between larval control, house-spraying with insecticides, and drug suppression, and is guided by local circumstances. An extension of larval control from towns to nearby villages will often be an obvious course; and large estates with a central housing site often obtain excellent results from larval control alone. Elsewhere the choice rests broadly between house-spraying and drug suppression; and in general house-spraying is the method of choice, with drugs held as a standby should anything go wrong.

Rural areas - In the typical Malay "village", with houses scattered over miles of country, larval control is seldom practical, and drug suppression is difficult to organize and supervise. Here house-spraying with residual insecticides is the only practical method, though under Malayan conditions results are slow to appear. Drugs have an important place, however, for the immediate control of an urgent situation.

Mobile groups in malarious areas - Armies in the field, reconnaissance or survey parties, labour gangs on road or railway construction, can seldom be protected by measures directed against the mosquito, and it is in these and such like groups that drug protection is most clearly indicated. Indeed, no other method may be possible.

Individuals - Whatever may be the circumstances, and whatever the form of control, the individual will always be wise to protect himself with drugs should there be any significant degree of risk.

V. THE PROBLEM OF DOSAGE

A weekly dose of 300 mg mepacrine may give excellent malaria suppression in a community long exposed to malaria, but a daily dose of 100 mg is necessary for the adult person who has no immunity. A single dose of 50 mg proguanil may eradicate a falciparum infection at the pre-erythrocytic phase; yet a daily dose of 100 mg may fail to arrest a resistant infection at the same stage. These examples illustrate the fallacies which may underlie attempts to fix arbitrary levels of dosage, suitable for all malaria infections at all times. Confusion arises mainly from the immunity factor, from drug resistance, and from differences in geographical strains of the parasites.

The immunity factor

The response to drugs in malaria is usually, perhaps always, an expression of a dual effect. The action of the drug is reinforced by a contribution from the tissue defences. In non-immune subjects the contribution from the tissues may be small; in immunes the tissue defences alone suffice to break the schizogonic cycle of the parasite. Logically, the dose of a drug should then be related to the immune status of the subject. Immunity, however, is not always easy to assess; and the dosage usually recommended is that appropriate for the non-immune subject. Medical officers, with their special knowledge of the malaria with which they have to deal, are best able to decide whether and to what extent they may safely reduce the preventive dosage ordinarily recommended.

Strain of parasite

There is evidence that geographical strains of malaria parasites sometimes differ in their sensitivity to a particular drug. The Costa strain of P.falciparum seems to be less sensitive to quinine and mepacrine than the McClendon strain of the same species; a Dutch strain of P.vivax has been shown to be less sensitive to salvarsan than a Madagascar strain; other examples have been recorded. The differences are seldom marked, and they do not appear to be common, but at least they show that a drug dosage may not necessarily have universal validity, and they may sometimes explain why a drug regimen which gives good results in one part of the world may be disappointing in another.

Base or salt

Another source of confusion is the practice of expressing dosage sometimes as the salt, sometimes in terms of the content of active base. A proprietary brand of chloroquine is marketed as tablets of 250 mg with no mention of the amount of active base; another brand, sold as tablets of 200 mg has the base content printed in smaller type on the label. Both contain 150 mg of chloroquine base.¹ The amodiaquine (Camoquin) tablet of 200 mg on

¹ As is well known, there is another product where the base content only (0.10 g or 0.30 g) is indicated. (Editor's note)

the other hand, contains 200 mg of active base, and no other figure appears on the label. The dosage of pamaquin is even more confused: an 18 mg tablet of the naphthoate and a 10 mg tablet of the dihydrochloride alike contain 8 mg of active base, but the figures which receive prominence are 18 mg and 10 mg. For the older drugs like quinine we shall continue to think of dosage in terms of the salt, but for the newer drugs there is no good reason for the persistence of this confusing anomaly. The logical course is to give all dosage in terms of the active base; no other figure should appear on manufacturers' labels. Where this is not possible, the dosage in terms of salt having been established by custom, the base content should at least be stated.

Drug resistance

Dosage is normally based on the response to treatment of fully sensitive parasites. Should the parasites become resistant, the recommended dosage may be seriously at fault. Fallacy from this source is unlikely to arise with quinine, mepacrine, chloroquine, or amodiaquine. The only drugs giving rise to serious resistance are proguanil and pyrimethamine; both are almost useless against highly-resistant parasites, though mild resistance may be overcome by an increase in dosage. Resistance to these drugs involving the asexual parasites in the blood may invalidate the dosage recommended for suppression. Resistance to proguanil has been reported also in the gametocytes and pre-erythrocytic forms of P.falciparum, and the possible inadequacy of the customary proguanil dosage for radical and gametocytocidal prophylaxis must be considered in areas where proguanil-resistance is suspected.

VI. THE PROBLEM OF DRUG RESISTANCE

Drug resistance from the adaptation of living organisms to substances which normally destroy them has been known for more than half a century, but only with the discovery a few years ago of acquired bacterial resistance to the sulfonamides and antibiotics has this resistance made any serious impact on chemotherapy. In malaria significant drug resistance is a recent phenomenon. No important anti-malaria drug used before the end of World War II was known to induce resistance. Quinine, pamaquin, and mepacrine, had never given serious cause for anxiety on this score, and it seemed that the malaria

organism might lack the capacity for adaptation which bacteria were then beginning to show to the sulfonamides and penicillin. But the discovery in 1947 of acquired resistance to proguanil in the avian parasite P.gallinaceum sounded a note of warning. The asexual blood forms of this species could be trained - if we may use the word "trained" with no implication of the mechanism involved - to resist high doses, and the resistance was stable enough to survive passage through mosquitos. In quick succession other species of Plasmodium, including P.falciparum and P.vivax infecting man, were shown to share this capacity for adaption to proguanil; and for the first time drug resistance in malaria appeared as a significant clinical problem.

Resistance to the common anti-malaria drugs

The drugs on which modern malaria chemoprophylaxis is based vary widely in their capacity to induce resistance in parasites exposed to their action. We may perhaps summarize the tendencies in this direction of the more important compounds.

Quinine - A lessened sensitivity to quinine has been reported from several parts of the world, but serious acquired resistance is rare, if indeed it occurs at all. Experimental attempts to induce resistance have either failed, or at most have achieved only a slight change in sensitivity. Whatever defects quinine may have as a preventive drug in malaria we may be assured that an acquired resistance in the parasites is unlikely to be one of them.

Pamaquin and primaquin - Prolonged exposure to pamaquin may induce a slight resistance in the asexual blood forms of certain avian and mammalian parasites, but acquired resistance in the species infecting man has not been reported. Primaquin, closely related chemically to pamaquin, is presumed to have similar tendencies. Pamaquin and primaquin are used mainly as gametocytocides in the treatment of the acute falciparum attack and for the radical cure of vivax infection; there is no evidence that resistance in the parasites is ever likely to impair their activity in these directions.

Mepacrine and chloroquine - Experimental attempts to induce resistance to mepacrine and chloroquine have failed, and the risk of an acquired resistance to these drugs seems to be small. There is an isolated report of a slight resistance to mepacrine in P.falciparum of New Guinea origin.

Amodiaquine - Amodiaquine, like chloroquine, is a 4-amino-quinoline. Resistance has not been reported and on chemical and pharmacological grounds any tendency in this direction seems unlikely.

Proguanil - Under experimental conditions a high resistance to proguanil may be induced in P.falciparum and P.vivax. This resistance is mainly in the asexual blood forms, but resistance has been reported also in the pre-erythrocytic forms and gametocytes of P.falciparum.

Pyrimethamine - Experimental evidence suggests that resistance to pyrimethamine may develop fairly early, resisting strains having been produced in P.cynomolgi and P.knowlesi of monkeys and in P.vivax of man. Pyrimethamine-resistant strains of P.falciparum have been reported from Malaya.

Origin and spread

The drugs which excite resistance in the malaria organism seem to be those which act by inhibiting nuclear division. Proguanil and pyrimethamine are the two important examples. The underlying causes of resistance to these drugs are not fully known, but the exposure of large parasite populations to a significant but sub-lethal dose of drug is thought to favour the emergence of resistant organisms, and we may presume that irregular and insufficient dosage is an important exciting cause. Under artificial conditions, with deliberate under-dosage and a serial transfer of parasites to fresh hosts resistance may appear within a few months. The usual conditions of clinical or preventive practice are less favourable for the emergence of resistant organisms, and there is good reason to believe that resistance may not appear when treatment is efficient, and suppression regular and thorough. Even so we must grant that there will be a margin for error when suppressive drugs are used on a large scale, and experience with proguanil in Malaya under the difficult conditions of post-war social rehabilitation shows how a resistance problem may unfold within a few years. A single dose of 100 mg in 1947 would terminate acute falciparum attacks. The first recorded failure to single-dose therapy was in 1948 and the first failure with a full therapeutic course in 1949. By 1950 nearly half the falciparum infections failed to respond to a standard therapeutic course. Resistance in P.vivax appeared in 1951, but the incidence remained low. No resistance in P.malariae has been observed.

Proguanil suppression, started experimentally in 1946, has since been widely used in the rubber estates and by the Security Forces. There is good evidence that a dose of 100 mg twice a week was very efficient at first, but five years later in certain districts there were indications that a daily dose of 100 mg would sometimes fail. Resistance involved mainly the asexual blood forms but there was a clear indication in falciparum infections of a spread of resistance to the pre-erythrocytic forms and gametocytes. These changes occurred in small foci; throughout the country as a whole proguanil remains a very useful preventive drug.

Prevention

Drug resistant parasites cannot emerge in the individual subject if the schizogonic cycle in the blood is permanently interrupted by efficient treatment, or fully inhibited by thorough suppression. They cannot be transmitted and spread in the community if the continued development of the gametocytes is inhibited by adequate therapy, clinical or suppressive, for every infected person. The main stimulus towards resistance probably arises when a large parasite population is exposed to, but not eliminated by, the drug. A logical corollary is that acute infections should be treated by drugs which do not give rise to resistance. During suppression, resistance may appear when the plasma concentration of the drug falls to a level low enough to permit an active proliferation of parasites. Irregular dosage will be the common cause, and the key to prevention probably lies in a good suppressive discipline.

Suggestions for the suppressive use of proguanil and pyrimethamine, designed to discourage the emergence of resistant organisms, are summarized in Table 6. Acute attacks are best treated with some other drug.

TABLE 6. MALARIA PROPHYLAXIS WITH PROGUANIL OR PYRIMETHAMINE IN RELATION TO DRUG RESISTANCE

Status of resistance in prevailing parasites	Drug and dosage for clinical protection
Strains sensitive	Proguanil 100 mg daily, or pyrimethamine 25 mg weekly. With partial immunes proguanil 200 mg or even 100 mg twice a week.
Early resistance	Tighten suppressive discipline; if ineffective either double the dosage, or change to another drug.
Resistance established	No proguanil or pyrimethamine; prophylaxis based on one of the 4-amino-quinolines, or mepacrine.

The most difficult decisions arise when resistance is mild, when proguanil or pyrimethamine though still useful suppressives sometimes fail. What margin of failure might we consider tolerable in the light of the other virtues of these drugs? To what extent should we weigh in the balance their immense potential value as safe radical preventives in falciparum infection, and as non-toxic sterilizing agents for gametocytes. This is a problem which faces health administrations in some territories today, and there is not always a clear answer.

Cross-resistance

The fear that a resistance to one drug might confer on malaria parasites a general tolerance to other anti-malaria drugs, has proved to be unfounded. Cross-resistance certainly occurs, sometimes to a marked degree, but the phenomenon presents no clinical problem which cannot be simply met by a change of drug. The only drugs to which the malaria organism may show a significant cross-resistance are proguanil, pyrimethamine and sulfonamide.

Cross-resistance involving the sulfonamides has much theoretical interest, but the sulfonamides are not used as malaria remedies, and there is little danger of proguanil- or pyrimethamine-resistant malaria from sulfonamide therapy in other diseases.

The extent and significance in human malaria of a cross-resistance between proguanil and pyrimethamine has still to be assessed. The evidence of this cross-resistance though mainly experimental suggests that the use of either drug may well be unwise where a marked resistance to one of them is known to occur.