Bull. Org. mond. Santé
Bull. Wld Hlth Org. } 1974, **50**, 243-249

Treatment of drug-resistant malaria in man*

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The progressive spread in Asia and South America of falciparum malaria resistant to 4-aminoquinolines, and the focal occurrence in all malarious regions of infections resistant to dihydrofolate dehydrogenase inhibitors such as pyrimethamine and proguanil, make it everywhere necessary to be alert to the failure of accepted curative, prophylactic, or sporontocidal chemotherapeutic agents. Resistance to 4-aminoquinolines may be met curatively with courses of treatment lasting 1–14 days, or more, the longer courses relying on quinine, often with a sulfonamide, or on tetracyclines, and the shorter courses on associations of sulfonamides or sulfones with pyrimethamine or trimethoprim. Suppressive prophylaxis of these infections is obtained by the injection at 3-month intervals of a repository mixture of acedapsone and cycloguanil, or by the weekly ingestion of sulfadoxine, sulfalene, or diformyl-dapsone associated with pyrimethamine, or the daily ingestion of dapsone with proguanil. Primaquine, although continuing to be an efficient sporontocide of P. falciparum *when pyrimethamine and proguanil no longer suffice, is becoming less effective in preventing relapses of* P. vivax *in countries around New Guinea.*

For practical purposes, drug-resistant malaria in man at the present time may be regarded as limited to infections caused by *Plasmodium falciparum*. Curative, prophylactic, and sporontocidal treatment of these infections depends upon the type and degree of resistance exhibited by the parasite strain involved. These attributes of the parasite may have been determined generally for the geographic area by earlier assessment of drug response, using the prescribed field clinic or reference centre tests (1), or may only just have been discovered by the failure of initial treatment in a given patient.

Although it is not relevant to this presentation to describe in detail the geographic distribution of drug-resistant falciparum malaria, it is necessary to be aware of the general situation in each region. The two main categories of resistance should be distinguished: first, and more important, to the 4-aminoquinolines with, in some cases, associated resistance to quinine; second, to the dihydrofolate dehydrogenase (" DHFR ") inhibitors (informally known as " antifols "). The former category, in which parasite resistance to chloroquine usually exceeds that to amodiaquine, has not yet become established in the Mediterranean area, Africa, or western Asia, although its dramatic increase in South-East Asia, the Western Pacific and South America (including Panama) is proving a growing deterrent to the routine use of chloroquine in individual cases and in mass drug administration campaigns. Resistance to the antifols, however, is present in scattered or confluent foci in all regions where endemic malaria exists, including Africa; tends to appear promptly when one of the antifols is used for mass drug administration; and is manifested usually as cross-resistance to all compounds of the antifol group.

Before the treatment at present available for these categories of falciparum malaria is described, one epidemiological aspect must be mentioned that may soon be of special concern in South-West Asia, particularly Iran and Iraq. In the past 2 or 3 years chloroquine-resistant *P. falciparum* has spread across Burma and may now be appearing in eastern India (2). It is carried readily by *Anopheles stephensi*, and could spread westwards across India to Pakistan and Afghanistan in the immediate future. With regard to Africa, we are finding on a research basis that this resistant parasite is transmitted efficiently by *A. gambiae*. Malariologists in Africa and South-West Asia should therefore be alert for the failure of falciparum infections to respond promptly and completely to chloroquine or amodiaquine, should be prepared to investigate the situation by use of the

* Presented at the Symposium on Malaria Research, Rabat, Morocco, 1–5 April 1974.

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WHO field tests for resistance (1), and if necessary should administer alternative types of treatment.

CURATIVE TREATMENT OF DRUG-RESISTANT FALCIPARUM MALARIA

Antifol resistance

Since antifols such as pyrimethamine and proguanil are not routinely used by themselves for the curative treatment of falciparum malaria attacks, the resistance to these drugs found in *P. falciparum* in many places in Africa and in other regions does not affect treatment with the drugs of choice, the 4-aminoquinolines. Where chloroquine or amodiaquine continue to be effective, the use of alternative anti-falciparum compounds such as the sulfonamides, sulfones, or tetracyclines is contraindicated on bacteriological grounds.

4-aminoquinoline resistance

When chloroquine-resistant falciparum malaria first appeared in South America and South-East Asia, cure could often be obtained by increasing the dose of chloroquine, particularly in the treatment of semi-immune patients. Claims continue to be made that standard courses of chloroquine cure infections in areas where the same drug fails as a prophylactic (3); in the cases described in such reports parasitaemia is cleared and the symptoms are resolved. However, since most of the patients concerned are followed only for 3 weeks, and since it is known that many RI-type recrudescences occur after 3 weeks, these claims of cure may be misleading. The use of amodiaquine instead of chloroquine has also been advocated, most parasite strains being somewhat more susceptible to the former, but this situation is now changing and resistance to the two compounds is levelling up. The use of any 4-aminoquinoline is contraindicated in acute attacks of chloroquine-resistant falciparum malaria in non-immune persons and in all children living in endemic areas, and should be recommended only with caution for the more easily cured semi-immune adults, it being safer to institute treatment with a schizontocide of more certain efficacy. The limited and imperfect range of antimalarials available for this purpose may soon be improved by the provision of several new groups of compounds such as 9-phenanthrenemethanols, 4-quinolinemethanols, and chlorinated lincomycin derivatives, which are in advanced stages of testing in man.

The courses of treatment of chloroquine-resistant falciparum malaria available at this time vary in duration (4, 1), and have for convenience been categorized as follows: long (14 days or more), intermediate (5–7 days), and short (1–3 days). Should the condition of the patient be serious, quinine dihydrochloride (10 mg per kg of body weight) may be given intravenously slowly, together with supporting measures, prior to commencement of the course of oral treatment. The selection of a particular course depends on local circumstances and preferences, an important consideration being the length of time that the patient is available for treatment under supervision. The doses given here are for non-immune adults, and where multiple should be administered in 3 or 4 parts during the 24-hour period. Any reduction in dosage appropriate for semi-immune persons must be determined on the basis of local experience, as this factor varies from place to place.

Long courses

These courses are based on the administration for 14 days of quinine dihydrochloride or sulfate, each day 2 g being given alone or, should asexual parasitaemia persist, in association with one of the following drug combinations:

(1) pyrimethamine (50 mg daily for the first 3 days of the quinine course) together with dapsone (25 mg daily for 30 days);

(2) pyrimethamine (50 mg daily for the first 3 days of the quinine course) with sulfafurazole or sulfadiazine (2 g daily for the first 6 days);

(3) sulfalene (1 g on the first day of the quinine course; if recrudescence occurs, the sulfalene may be given on days 1, 5, and 10 of a repeated 14-day course of quinine).

A daily dose of 2 g of the quinine salt approaches the limit of tolerance of some sick adults, and vomiting may occur, leading to treatment failure. For this reason the lowest daily dosage compatible with antimalarial efficacy should be given. We have found that 1.67 g daily in divided doses, for 14 days, has had as good an effect as 2.0 g against identical multi-drug-resistant strains of *P. falciparum*, sulfalene also being administered. The effects of these two regimens tested in 43 non-immune adults in Maryland, under research conditions including 60-day follow-up, and the effects of the new 4-quinoline-

methanol compound WR 30090 tested similarly in 39 men, may be summarized as follows:

Radical cure rates

quinine 2 g daily with sulfalene	89.6
quinine 1.67 g daily with sulfalene	87.2
WR 30090 690 mg daily for 6 days	97.5

Times from first dose to asexual parasite clearance

quinine 2 g daily with sulfalene	78 h
quinine 1.67 g daily with sulfalene	80 h
WR 30090 690 mg daily for 6 days	67 h

Times from first dose to resolution of fever

quinine 2 g daily with sulfalene	88 h
quinine 1.67 g daily with sulfalene	79 h
WR 30090 690 mg daily for 6 days	66 h

Intermediate courses

Quinine may be administered by mouth for 10 days, particularly in paediatric practice, but when this is done the recrudescence rate of chloroquine-resistant falciparum malaria is much greater than following the 14-day course. Recently a 10-day course of quinine dihydrochloride given intravenously by slow drip has been tested in non-immune adults and found to be remarkably effective, in contrast to the same amount of quinine taken by mouth (5). Courses of intermediate duration not primarily involving quinine are as follows:

(1) 7-day courses: tetracyclines given for 7 days (but not for 5 days) provide radical cure of falciparum malaria. Tetracycline hydrochloride (1 or 2 g daily), doxycycline (0.2 g daily), or minocycline (0.1–0.4 g daily) are equally effective. It is important to note, however, that infections are slow to respond to tetracyclines and a more rapidly acting blood schizontocide, such as quinine, must be administered briefly at the beginning of the course.

(2) 5-day courses: pyrimethamine (50 mg daily for 3 days) with either sulfadiazine (2 g daily for 5 days) or dapsone (100 mg daily for 5 days). Failure of these courses implies that the parasite is antifol-resistant and the patient may have a metabolic defect interfering with the ability of the sulfonamide or sulfone to gain access to the parasite.

Short courses

The short courses of 1 or 3 days' duration depend for their effectiveness upon a potentiating action of antifol and sulfonamide or sulfone. Failure of these courses may occur for the reasons mentioned in the preceding paragraph.

(1) 3-day course: the antifol trimethoprim when given with sulfalene has a rapid schizontocidal action (6). However, a single day of treatment at the low dosages originally advocated is no longer considered adequate, more satisfactory results being obtained by use of a well tolerated 3-day course in which 1.5 g of trimethoprim and 1.0 g of sulfalene are given each day in three divided doses. In Maryland this regimen produced radical cures in 74.2% of 31 non-immune adults infected with chloroquine-resistant *P. falciparum* that was also resistant to pyrimethamine at the RIII level. Asexual parasitaemia and fever were not cleared in 2 of these patients, but in the remaining 29 the times from first dose to parasite clearance and resolution of fever were, respectively, 63 hours and 70 hours—shorter than the times involved when quinine was used in the long course.

(2) 1-day (single dose) course: pyrimethamine (50 mg, or 1 mg per kg of body weight) may be given together with either sulfadoxine (1 g, or 15 mg/kg) or sulfalene (2 g). Dapsone (200 mg) may be used instead of the sulfonamide. It is difficult to compare the effectiveness of these different combinations since many of the data have been obtained through treating patients whose immunity varied widely and who were subject to reinfection. The longer duration of sulfadoxine in the blood suggests, however, that the pyrimethamine–sulfadoxine association should be superior as an antimalarial although the occasional serious side-effects of long-acting sulfonamides must be remembered.

PROPHYLAXIS OF DRUG-RESISTANT FALCIPARUM MALARIA

Although *causal prophylaxis* of drug-resistant falciparum malaria has been demonstrated using tetracyclines (7), the necessary repetitive use of such short-lived antibiotics cannot be recommended in view of the dangers of inducing resistance in pathogenic bacteria and producing side-effects in the recipients. Our need is either for a long-acting causal or suppressive chemoprophylactic agent, the closest approach to which has been the repository combination of acedapsone with cycloguanil, or for an active immunization process. At the present time, short-

acting orally administered chemosuppressives and injectable acedapsone with cycloguanil are the only available agents.

For *suppressive prophylaxis*, in contrast to species-specific clinical treatment, provision must be made to combat all plasmodial species known to exist in the region. In Africa, western Asia, and Central America no serious problem arises since the 4-aminoquinolines are still effective against all species, including antifol-resistant *P. falciparum* and *P. vivax* wherever these occur. In South America and South-East Asia, the increasingly rapid spread of multi-drug-resistant *P. falciparum* is forcing us to introduce relatively untested combinations of chemosuppressive agents, and since the drug component effective against the falciparum parasite is ineffective against the other three species a second component must be introduced. For the suppression of *P. falciparum*, either sulfonamides or sulfones may be used, while for the suppression of other species the antifols or, less preferably (for reasons mentioned below), the 4-aminoquinolines are available.

Other combinations have been tested unsuccessfully. The addition of primaquine to weekly doses of chloroquine or amodiaquine helped somewhat, but in carefully supervised trials up to 50% of falciparum infections broke through and the combination was not always well tolerated. The new 9-phenanthrene-methanols and 4-quinolinemethanols are considerably less effective as suppressive than as curative agents (8), and the tetracyclines should not be used prophylactically for the reasons stated above.

The drug combinations shown to be reasonably effective act for differing periods of time, and consequently need to be administered at different intervals, as noted below.

3-month intervals: intramuscular injection

(*a*) Against *P. falciparum:* acedapsone

(*b*) Against other species: cycloguanil.

The combination may be administered by deep gluteal injection in doses of 7.5–7.9 mg per kg of body weight, the supplied preparation containing equal amounts of each of the two components. Multi-drug-resistant falciparum infections have been suppressed for 3 months following each injection, while few if any vivax infections have broken through. Local tissue reactions, generally of a mild nature, occur in up to 30% of the population receiving the injection.

1-week intervals: oral treatment

(*a*) Against *P. falciparum:* sulfadoxine (0.5 g), sulfalene (0.5 g), or " diformyl-dapsone " (DFD) [a] (0.4–0.5 g)

(*b*) Against other species: pyrimethamine (25 mg).

The combination used most widely is sulfadoxine with pyrimethamine; few infections break through in areas dominated by multi-drug-resistant *P. falciparum*. Sulfalene with pyrimethamine has been tested on a research basis and found to be equally effective. DFD with pyrimethamine protected 92% of non-immune adult volunteers exposed to mosquitos heavily infected with these falciparum strains, while *P. vivax* was not only suppressed but suppressive cures were obtained: when chloroquine was substituted for pyrimethamine, the effect on *P. falciparum* was similar but *P. vivax*, although suppressed during treatment, invariably appeared after treatment ended. For this reason, as well as because of potentiation and sporontocidal effects, pyrimethamine seems to be preferable to chloroquine or amodiaquine for combination with a sulfonamide or a sulfone.

1-day intervals: oral treatment

(*a*) Against *P. falciparum:* dapsone (25 mg)

(*b*) Against other species: proguanil (100 mg).

This combination administered every day under supervision has proved remarkably effective in suppressing multi-drug-resistant *P. falciparum* and other species being transmitted in endemic areas. Probably small doses of DFD could be substituted for the dapsone and pyrimethamine for the proguanil, but these combinations have not been tested on a daily basis and there is little need to improve on the well-known dapsone with proguanil regimen.

The choice of 3-month, 1-week, or 1-day courses of suppressive prophylaxis depends on local circumstances, but since all these courses rely on sulfonamides or sulfones for their anti-falciparum effect, a word about toxicity, about drug failure, and about antibacterial action is necessary. Although a minimum of side-effects occurs, rare cases of agranulocytosis and extremely rare cases of Stevens–Johnson syndrome have been observed following the administration of sulfones or sulfonamides. The occasional inability of these compounds to suppress

[a] *N,N'*-(sulfonyldi-4,1-phenylene)bisformamide.

or cure falciparum infections seems to be attributable to treatment failure rather than resistance by the parasite to the drug: careful serial studies suggest that a small proportion of people, possibly in the order of 5–10% irrespective of race, metabolize sulfonamides and sulfones in such a manner that expected concentrations of the drugs do not reach the parasite. Whether the drugs are acetylated unusually rapidly and promptly excreted, or are bound to plasma protein and held back, the result appears to be that subtherapeutic drug levels prevail in these persons. True resistance by *P. falciparum* to the sulfonamides and sulfones may indeed develop, just as it has in some plasmodia that have nonhuman hosts. As to the antibacterial action of these compounds, the risk of inducing resistance to pathogenic bacteria must be weighed against the need to suppress drug-resistant malaria. The repetitive use for long periods of small doses of the sulfonamides or sulfones (between which there has been shown to be a high degree of bacterial cross-resistance), in populations that contain some carriers of meningococcus, is contraindicated in regions where *P. falciparum* is still sensitive to chloroquine.

SPORONTOCIDAL TREATMENT

Fortunately all strains of multi-drug-resistant *P. falciparum* continue to be sensitive to primaquine, a single dose of 45 mg (base) of this compound remaining highly effective as a gametocytocide and an oocyst inhibitor. Pyrimethamine and proguanil are ineffective as sporontocides when the asexual stages of *P. falciparum* are resistant to antifols.

Having mentioned primaquine in connection with falciparum malaria, I would like, in conclusion, to digress briefly to *P. vivax*. Although *P. vivax* is not resistant to primaquine, it is well known that one strain—the Chesson, transmitted 30 years ago in New Guinea—tends to relapse unless 30 mg (not 15 mg) of primaquine is given to the patient for 14 days. This type of strain has recently been reported to be present in the Solomon Islands (9) and Sumatra [a]. The increasingly rapid spread of multi-drug-resistant-falciparum malaria westwards across Asia may be followed by a similar spread of vivax malaria that is relatively insusceptible to primaquine.

[a] Unpublished observations, 1973.

RÉSUMÉ

TRAITEMENT DU PALUDISME PHARMACORÉSISTANT CHEZ L'HOMME

En Asie et en Amérique du Sud, le paludisme à *Plasmodium falciparum* résistant aux amino-4 quinoléines, comme la chloroquine et l'amodiaquine, continue à s'étendre géographiquement, tandis que la résistance aux inhibiteurs de la dihydrofolate réductase, comme la pyriméthamine et le proguanil, est observée par endroits dans toutes les régions impaludées. Il importe donc d'être attentif aux échecs éventuels de la chimiothérapie antipaludique.

Dans le passé, on a pallié la résistance de *P. falciparum* aux amino-4 quinoléines en augmentant les doses de ces produits, mais cette méthode ne donne plus des résultats satisfaisants. On recommande actuellement 3 types de traitement curatif: traitement prolongé, de 14 jours ou plus, par la quinine ordinairement associée à un sulfamide; traitement de durée moyenne (5-7 jours) comportant l'administration de tétracyclines ou de pyriméthamine associée soit à la sulfadiazine soit à la dapsone; traitement de courte durée par le triméthoprime associé au sulfalène (3 jours) ou par la pyriméthamine associée à la sulfadoxine, au sulfalène ou à la dapsone (1 jour).

Le traitement suppressif des infections paludéennes peut être réalisé grâce à un schéma comportant l'administration d'une sulfone ou d'un sulfamide pour éliminer *P. falciparum* et d'un inhibiteur de la dihydrofolate réductase pour juguler les autres espèces. L'administration d'une préparation retard d'acédapsone et de cycloguanil, à 3 mois d'intervalle, a donné de bons résultats. Il en est de même d'un traitement hebdomadaire par la sulfadoxine, le sulfalène ou la diformyl-dapsone associés à la pyriméthamine et d'un traitement quotidien par la dapsone associée au proguanil.

L'activité sporontocide de la primaquine continue à s'exercer à l'égard de *P. falciparum* que ce dernier soit ou non résistant au proguanil et à la pyriméthamine. On a cependant observé, en Nouvelle-Guinée, aux îles Salomon et en Indonésie, qu'il est parfois nécessaire d'augmenter les doses de cet antipaludique pour prévenir efficacement les rechutes de paludisme à *P. vivax*.

REFERENCES

1. WORLD HEALTH ORGANIZATION. Chemotherapy of malaria and resistance to antimalarials. Geneva, 1973 (WHO *Technical Report Series*, No. 529).
2. CLYDE, D. F. ET AL. *Journal of tropical medicine and hygiene*, **76** (3): 54-60 (1973).
3. LEWIS, A. N. ET AL. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **67** (2): 310-311 (1973).
4. CLYDE, D. F. *American journal of tropical medicine and hygiene*, **21** (5): 736-743 (1972).
5. HALL, A. P. *American journal of tropical medicine and hygiene*, **21** (6): 851-856 (1972).
6. MARTIN, D. C. & ARNOLD, J. D. *Journal of the American Medical Association*, **203**, February 12 1968: 476-480.
7. RIECKMANN, K. H. ET AL. *Proceedings of the Helminthological Society of Washington*, **39** (Special Issue): 339-347 (1972).
8. CLYDE, D. F. ET AL. *Antimicrobial agents and chemotherapy*, **3** (2): 220-223 (1973).
9. MAFFI, M. & MCDONNELL, M. *Parassitologia*, **13** (3): 455-503 (1971).

DISCUSSION

DONNO: Why does Professor Clyde suggest the use of 2 g of sulfalene rather than 1 g of sulfadoxine, since, according to their pharmacokinetic characteristics, the daily calculated dosage of the two drugs should be about equal.

CLYDE: The various dosages presented have been based on a review of other investigators' reports. Some of the dosages may be out of line, but there has been a lack of uniformity in the use of these drugs throughout the world. One gram of either drug should be used.

JEFFERY: The discussions have not been directed particularly at the evaluation of chloroquine, but the questions of retinal toxicity and of the possible existence of chloroquine resistance in Africa have been raised. In regard to the former, there has been a rather ominous hint that the reported accumulation of chloroquine on eye tissue may be indicative of retinal toxicity. I believe that several valid investigations have shown that this is not the case. The uncorrected statement might cause undue alarm.

VAN DER KAAY: Editors of medical journals should check carefully all reports of chloroquine-resistant falciparum malaria from Africa prior to publication.

DE ZULUETA: Is it safe, particularly from the point of view of eye damage, to use 600 mg chloroquine weekly?

JEFFERY: Although a 600-mg weekly dose has been used in many areas, 300 mg is a reasonable dosage.

CANFIELD: The findings of a study on the eye examination of US foreign service personnel, some of whom had been using chloroquine for up to 30 years, indicated a lack of correlation between the use of chloroquine as a chemosuppressive and eye pathology. The study concluded that the abnormalities detected were related to age and not to the use of chloroquine.

BRUCE-CHWATT: There is a gap in the factual data concerning the relationship between eye damage and the use of chloroquine. I am aware of only two well-documented cases reported from France, in which retinal toxicity was associated with long-term use (8–10 years) by two missionaries who took chloroquine at a dose of 100 mg daily. It is also known that patients with collagen diseases who are treated with chloroquine at a dosage of 500 mg daily do not develop serious and permanent eye defects if the treatment lasts for only a few months. A definitive study should be made at the international level to resolve this important question.

DONNO: The regimen mentioned by Professor Clyde —quinine for 14 days combined with pyrimethamine for 3 days—may be too toxic and should not be used.

CLYDE: This combination was favoured for a while in Vietnam, but may well be obsolete. I certainly do not advocate it.

EDESON: I agree with Professor Bruce-Chwatt that daily doses of a chemoprophylactic are to be preferred to weekly or monthly doses, as the omission of one or two daily doses is not as significant as that of a weekly or monthly dose. Furthermore, the regular taking of antimalarials is perhaps more important than the type of antimalarial used. Drugs used for the treatment of acute cases, such as chloroquine, should not be used in chemoprophylaxis.

CLYDE: The question has been raised whether the wide distribution of chloroquine-resistant falciparum malaria is due to spread or to development *in situ*. As regards Asia, centrifugal spread from Thailand and Malaysia, westward to Burma and eastward to the Philippines, mediated through migrants, is suggested by the epidemiological evidence. In Latin America, the picture is more confusing.

EDESON: Certain unfounded doubts exist concerning the use of prophylactic drugs in areas where resistance to these drugs has developed. Thus, proguanil resistance was reported from Malaysia as long ago as 1948–49. In spite of this, security forces using proguanil regularly have encountered few problems with malaria.

NÁJERA: The recent outbreak of chloroquine-resistant falciparum malaria in North-Eastern Surinam appears to have spread from previous outbreaks in the south of the country.

VAN DER KAAY: In 1972, an outbreak of falciparum malaria resistant to chloroquine was observed in Alalaparoe, Surinam. The outbreak was contained, thanks chiefly to the cooperation of the local population and to the presence in the village of a health post manned by a public health nurse. A standard course of chloroquine was used to treat all the laboratory-confirmed cases. If the case was still positive by day 7, a second course of chloroquine (2.7 g) plus primaquine was given. If, after this, the case was still positive, then a course of sulfadoxine plus pyrimethamine was given. Mass chemoprophylaxis of the entire local population was undertaken by administering to each person a weekly dose of 600 mg of chloroquine combined with 50 mg of pyrimethamine, and movement of the population was voluntarily restricted. In addition, house-spraying with malathion was carried out. By March 1974, no more positive cases were reported.

DE ZULUETA: With ever-increasing travel, malaria is becoming once again a problem for people in the European region. There is therefore a need for recommendations on prophylactic regimens, particularly for travellers to countries where there is drug resistance. This type of information should be made readily available.

BRUCE-CHWATT: Proguanil administered daily is a valuable prophylactic because it allows for better discipline in malaria prophylaxis. When the Australian troops in Vietnam began having increasing problems with malaria, 25 mg of dapsone were added to the daily dose of proguanil. This resulted in a marked improvement of the situation.

GRAMICCIA: Considerable confusion exists in the field of prevention and treatment of resistant falciparum malaria. The appearance of resistance and an increase in resistance should be differentiated. Thus, in areas of northern Malaysia, where the massive use of chloroquine is practised, there has been a definite increase in the level of resistance.

Two foci of natural chloroquine-resistant falciparum malaria have been identified: one in Asia and the other in South America. The appearance of these strains in countries such as Nepal and Sabah (East Malaysia), probably indicates that they have spread. However, these are places where malaria has been largely suppressed, although they still have a high potential for malaria transmission from resistant imported cases. It is important that field workers should be provided with guidelines as to what to do when confronted with the emergence of chloroquine resistance.

The special issue of the *Weekly Epidemiological Record* cautions travellers to ask about the local malaria situation and what drugs to obtain from their medical advisers.

PARISI: In field operations, rational use is being made of drugs. Combination drugs should be reserved for use only in case of resistance to chloroquine. All cases in the Syrian programme are currently followed up after treatment. Areas in which large amounts of chloroquine are used, e.g., in East Africa, should be monitored carefully for the presence of chloroquine-resistant strains and the indiscriminate use of drugs should be discouraged.

BRUCE-CHWATT: Antimalarial regimens for prophylactic use can be reasonably grouped into three categories: (1) true causal prophylactics, such as proguanil and pyrimethamine. The former is preferred because it is less likely to be forgotten when daily administration is used; (2) in areas of high drug resistance to antifolates, either 4-aminoquinolines or a combination of sulfadoxine and pyrimethamine may be used, although the latter should preferably be reserved for the treatment of overt malaria; and (3) in areas where drug resistance to 4-aminoquinolines is hardly a problem, chloroquine will still be useful. Delayed primary attacks from relapsing malaria may still occur when chloroquine administration has ceased, 9–12 months after the patient has left the malarious area. The traveller should be informed of this so that he can advise his physician in the event of a febrile illness.