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Drugs for Tropical Diseases: Problems of Utilisation, Research and Development (**)

Introduction

Tropical diseases are diseases which are now found mainly in the tropical and Third World countries. Fifty or more years ago they were found in practically every part of the world. Their disappearance from other parts of the world except the tropics coincided with the general elevation of the social and economic situation of those countries to a high level. A more realistic definition of these so-called tropical diseases would regard them as diseases of ignorance, poverty and squalor. Their persistence in the tropics is due to the existence in tropical countries of factors which promote spread of such diseases — poor personal and environmental hygiene, non-availability or limited availability of pipe-borne water and other potable water supplies, overcrowding and malnutrition. It is easy to see that a general improvement in the social and economic condition in these countries would be a giant step forward in the control of these diseases. Unfortunately, given the reality of the economic situation in these countries now and in the foreseeable future, there is no doubt that other methods of control would need to be employed if there is going to be any worthwhile reduction in the misery, suffering, morbidity and mortality resulting from these diseases in the near future.

Drugs constitute the obvious and most convenient tools for the control of diseases, and they are as relevant for tropical diseases as they are for the more cosmopolitan diseases. For a long time, therefore, drugs will be used to a considerable extent in the control of tropical diseases.

There is a wide variety of tropical diseases. However, the problems encountered in their control with drugs are similar for most of them and the

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problems can be discussed using any of the major tropical diseases as examples. In the rest of this paper, therefore, the problems will be discussed using malaria as a typical example of a tropical disease.

Use of Drugs in Malaria Control

Treatment of Individual Patients

This is a comparatively simple and cheap antimalaria activity. It is within the capability of every country, provided the drugs are made available and distribution channels simplified. The use of primary health care centres and schools for this activity in the rural areas would substantially increase the percentage of the population covered.

The effect of this activity depends on the endemicity of malaria in a given place. Similarly, the drugs used would be determined by the susceptibility of the parasites to the various drugs available and on whether clinical cure or radical cure is intended, the latter being determined by the malaria status of the affected locality.

In localities of high endemicity, prompt treatment of suspected or confirmed malaria reduces the mortality and suffering caused by the disease. It would have no impact on the transmission, incidence or prevalence.

In countries where endemicity is low or where, as a result of other antimalaria activities, prevalence and incidence have been considerably reduced, treatment of individual cases would aim not only to reduce mortality but also to stabilize transmission, and even reduce or eventually interrupt it. This is also true of countries where the disease is seasonal, focal, unstable and subject to epidemics. Such countries usually have a reasonable insecticide spraying programme, which is combined with chemotherapy of suspected or confirmed individual patients in the transmission season or during epidemics, to reduce mortality as well as transmission.

In some malarious regions of the world there are isolated localities where malaria has never existed or has been eliminated. In some of these localities, transmission does not occur and control consists of the treatment of imported individual cases to prevent mortality and suffering. In some, however, transmission is possible, and the control strategy is to prevent the reintroduction and re-establishment of malaria in the area. The control activities would usually combine the detection and treatment of individual cases with focal residual insecticide spraying.

The drugs currently used in the treatment of suspected or confirmed cases of malaria are:

(1) Chloroquine or amodiaquine;
(2) Sulphadoxine-pyrimethamine (S-P);
(3) Mefloquine or mefloquine-sulphadoxine-pyrimethamine;
(4) Quinine or quinine-tetracycline;
(5) Primaquine.

Chloroquine

Chloroquine is the drug of choice for the treatment of suspected or confirmed malaria in places where there is no known resistance or even in areas with RI levels of resistance. It has been customary in treating semi-immune subjects in Africa to use single-dose treatment with 10 mg/kg chloroquine. Although this dose may be enough to clear blood of the most susceptible parasites, it may not be adequate to completely remove the less sensitive parasites. There is also evidence that even in areas where there is at present no evidence of overt chloroquine-resistance, there is diminishing sensitivity to the drug (Walker *et al.*, 1984). In order, therefore, to reduce the possibility of hastening the appearance of chloroquine resistance and also ensuring adequate drug treatment for all patients in situations in which parasitological response cannot be monitored, it might be advisable to treat all patients with the full 25 mg/kg dose of chloroquine over three days. Other 4-aminoquinolines can be used in place of chloroquine. The best known of these is amodiaquine, which has been shown to be somewhat more active than chloroquine against sensitive strains of *P. falciparum* and also retains activity against some parasites with RI or RII resistance to chloroquine (Watkins *et al.*, 1984; Spencer *et al.*, 1984). The implication of the recent finding that amodiaquine behaves as a pro-drug in its use in malaria control is still to be determined (Churchill *et al.*, 1985; Salako and Idowu, 1985).

In highly endemic areas where chemotherapy is used to reduce mortality but not to reduce or interrupt transmission, only clinical cure is aimed at. Chloroquine is therefore the only drug given, there being no need for additional gametocytocidal therapy against *P. falciparum* or anti-relapse therapy against *P. vivax* and *P. ovale*.

Sulphadoxine-Pyrimethamine (S-P)

In areas with chloroquine-resistant *P. falciparum*, S-P is the drug of choice for the treatment of suspected or confirmed malaria as long as either there is no established resistance to this combination or resistance is low-grade or of low frequency. Unfortunately, deployment of S-P for malaria chemotherapy in areas with widespread chloroquine-resistant *P. falciparum* has been followed by the appearance or increase in the level or frequency of resistance to the combination. Moreover, *P. vivax* is intrinsically relatively insensitive to sulphonamides and rapidly develops resistance to pyrimethamine. Resistance by *P. vivax* to S-P is therefore relatively common. It would therefore be desirable, before deploying S-P for large-scale use for treatment in malaria control, to undertake a preliminary determination of the sensitivity of the local strains of *Plasmodium* to the combination.

S-P is an erythrocytic schizontocide active against all four human malaria species and is adequate treatment when used alone in situations where the aim is to reduce mortality and not transmission, subject to the above considerations.

Mefloquine or mefloquine-S-P

Where there is established resistance to chloroquine and S-P, recourse may have to be made to mefloquine. At present, this new drug has been registered for use in two countries, Thailand and Switzerland, although extensive clinical trials on it in many parts of the world have demonstrated its safety and its efficacy against chloroquine- and multi-resistant *P. falciparum*. The recommended therapeutic regimen in the adult is a single 750 mg dose with appropriate reduction in the dose for children.

Field trials of mefloquine have shown a few instances of resistance or reduced sensitivity to the drug. In some of these instances the resistance might be intrinsic and unrelated to exposure to mefloquine. Resistance has also been observed in experimental *P. berghei* infection in mice. It was shown in the latter case that combining S-P with mefloquine would delay the development of resistance. The combination of mefloquine with S-P has accordingly been subjected to extensive trial in man. These studies have shown that the combination is active against chloroquine-sensitive as well as chloroquine- and multi-resistant *P. falciparum* and is tolerated as well as mefloquine. Only time will tell whether it will live up to the expectation of delaying the onset of resistance to mefloquine. At the time of writing, mefloquine-S-P has not been approved for marketing in any country.

Mefloquine and its combination with S-P are erythrocytic schizontocides and can be used alone for chemotherapy in malaria control programmes in which the objective is to reduce mortality but not transmission.

Quinine

Treatment of suspected or confirmed cases of malaria poses a major problem to health authorities in places where *P. falciparum* is resistant to the drugs of choice: the 4-aminoquinolines and S-P. Since mefloquine-S-P has so far been registered for use but not for marketing in only two countries, the only other drug that can be used for this activity is quinine. Unfortunately, treatment with quinine is expensive; it is not widely available and is relatively toxic. It cannot therefore be distributed through the primary health care system for the immediate treatment of malaria. Its use has to be confined to the secondary and tertiary health institutions. In effect, only urban populations and severe cases referred from the rural primary health centres can benefit from the use of this drug.

For uncomplicated infections, quinine is given to the adult in a dose of 1.8 g orally in three divided doses daily for seven days. Alternatively, quinine could be given for three days and the treatment continued for another 5-7 days with tetracycline 2 g daily in three or four divided doses.

In severe, complicated or cerebral malaria, quinine is given initially as a slow intravenous infusion of 20 mg/kg over four hours. Treatment can be continued with i.v. infusion of 10 mg/kg quinine eight hourly but as soon as the clinical situation permits, oral therapy is instituted.

Primaquine

Primaquine is a tissue schizontocide and gametocytocide. Gametocytes of chloroquine- and S-P-sensitive or resistant parasites are equally sensitive to primaquine. Primaquine is used sequentially with a schizontocide in *P. falciparum* infections in situations where chemotherapy is aimed at reducing or interrupting transmission since it makes the patient non-infective to mosquitos. This kind of treatment for *P. falciparum* is appropriate in areas of low endemicity where there are also vector control measures. It is also useful in areas with seasonal infection or in epidemics and to prevent reestablishment of the infection in areas from which it has been eliminated. In all these instances, chemotherapy is usually combined with vector control activities. Primaquine is given as a gametocytocide in a single dose of 30 or 45 mg after the full course of the schizontocide. At this dosage, primaquine is well tolerated even by patients with glucose-6-phosphate dehydrogenase deficiency.

Primaquine is also given as a tissue schizontocide to prevent relapse in *P. vivax* malaria. The administration of a tissue schizontocide is indicated only if the epidemiological situation favours the reduction of transmission by radical treatment of individual cases. The dosage of primaquine as a tissue schizontocide is 15-30 mg daily for 7-14 days. At this dosage level, adverse reactions are common, especially in patients with glucose-6-phosphate dehydrogenase deficiency.

Chemoprophylaxis

Experience has now shown that it is exceptional for large-scale prophylactic use of antimalarial drugs in a highly endemic area to have a lasting effect on the level of endemicity or rate of transmission of the disease. On the other hand, such a programme has often resulted in a diminishing sensitivity of the parasites to the administered drug or, even in some cases, to the appearance of drug resistance. In any case, for most of the malarious areas the logistics of covering the entire population invariably presents insurmountable problems. Consequently, chemoprophylaxis as a malarial control strategy should aim at reducing morbidity in non-immune visitors and in indigenous groups under high risk of severe and complicated malaria. Such groups include pregnant women and nursing mothers, and children under the age of five. It is controversial whether children between the ages of five and 14 come under this group.

Other high-risk groups for which chemoprophylaxis is desirable are semi-immune or non-immune personnel living in closed communities in endemic areas; for example, labour forces, police and army units, and refugees in camps. If chemoprophylaxis is combined with vector control measures, not only morbidity, but also transmission would be reduced in such isolated units.

The drugs currently used for chemoprophylaxis are:

(1) Chloroquine or amodiaquine;
(2) Sulphadoxine-pyrimethamine (S-P);
(3) Proguanil.

Chloroquine (or amodiaquine)

Chloroquine is the drug of choice for prophylaxis in areas where there is no resistance to it. The standard prophylactic dose of chloroquine is 300 mg weekly in the adult. Some workers have given the dose fortnightly or monthly and obtained a reasonable measure of protection. Chloroquine protects against all species of Plasmodium. The corresponding dose for amodiaquine is 400 mg weekly.

Sulphadoxine-Pyrimethamine

In areas with chloroquine resistance, S-P or some other sulphone/sulphonamide-antifolate combination like dapsone-pyrimethamine has been used for chemoprophylaxis where the parasites have retained sensitivity to these combinations. The dose of sulphadoxine-pyrimethamine is 500 mg sulphadoxine plus 25 mg pyrimethamine once weekly whilst that of dapsone-pyrimethamine is 100 mg dapsone plus 12.5 mg pyrimethamine once weekly.

Many areas with chloroquine-resistant *P. falciparum* are also endemic for *P. vivax* for which S-P resistance is common. It has, in recent years, been suggested that S-P might be combined with chloroquine to protect against *P. vivax* in such areas (Wernsdorfer, 1982). Recent observations have raised the suspicion of a possible association between the prolonged use of chloroquine plus S-P and severe and sometimes fatal skin complications like erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrosis. It might therefore be reasonable to avoid prolonged prophylactic use of chloroquine plus S-P until the issue of these possible toxic effects has been resolved. There is possibly little advantage, in any case, of prophylaxis against *P. vivax* for indigenous populations of an endemic area. Non-immune visitors on S-P prophylaxis for *P. falciparum* could be watched closely for early detection and treatment of infection due to nonsensitive Plasmodia.

In areas with chloroquine- and S-P resistant *P. falciparum*, there is at present no clear-cut prophylactic drug.

Proguanil

Proguanil is now enjoying a resurgence of interest as a prophylactic drug after a period in which it was considered of relatively little prophylactic value because of resistance to it by *P. falciparum* in most areas where the drug had been used on a large scale. However, recent observations have shown that proguanil given alone at a dosage of 200 mg daily or in combination with chloroquine at a dosage of 200 mg daily plus chloroquine 300 mg once weekly provides protection in a high percentage of non-immune residents of malarious areas. Proguanil has a weak blood schizontocidal action against all plasmodia species, but its prophy-

lactic action against falciparum malaria might be due mainly to the effect on the pre-erythrocytic stage of the parasite.

Controlled studies are urgently needed to re-evaluate the role of this drug as a prophylactic drug, but on the basis of presently available evidence it seems a useful prophylactic drug, alone or in combination with chloroquine, in situations in which chloroquine alone and S-P alone are unsuitable.

Although there have been trials attesting to the prophylactic value of mefloquine against chloroquine- and multi-resistant *P. falciparum*, the need to protect this drug, for as long as possible, against the type of deployment that could lead to rapid development and spread of resistance to it dictates caution in its use for prophylaxis. Quinine is, of course, too costly and too toxic for use in large-scale prophylaxis.

Malaria control through chemoprophylaxis might thus be inappropriate and unreliable in areas with multiple resistance. The control strategy in such situations would be early detection and radical treatment with schizontocidal and gametocytocidal drugs to reduce the transmission of drug-resistant parasites.

Problems from Drug Use in Malaria Control

From the foregoing discussion of the use of drugs in malaria control, a few questions come to mind. Three of these are:

1. Do the currently available drugs fulfil all the needs of individual or community malaria prevention and control? If not, why not?

2. Are the available drugs adequately distributed and utilised?

3. Are existing drugs optimally deployed?

It is clear, from my description of the situation with respect to the use of drugs for treatment of suspected or confirmed cases and for prophylaxis, that the existing drugs fall far short of the requirements for these activities in many countries. Malaria remains the greatest single infectious disease threat to the health of the world. The ideal drug for the control of such a disease should be readily available, cheap, effective in a single dose for treatment and have a long duration of effect lasting several months at single dose prophylaxis and should be well tolerated. None of the existing drugs fulfils all these criteria. The widespread resistance to some of the drugs (e.g., chloroquine and sulphadoxine-pyrimethamine) has sadly cut short their effective life span in many countries; a drug like quinine is too scarce and too expensive to make its deployment in mass control programmes a viable proposition; some like primaquine and even quinine are too toxic for use on a long-term basis and outside specialised referral centres; the multiple-dosage regimens required for the optimum effect of others (e.g., quinine, primaquine) create insurmountable logistic problems for their effective deployment in control programmes.

Unfortunately, it cannot even be said that within the limits of their usefulness the existing drugs are procured in adequate amounts, equitably distributed to ensure coverage of all those needing them and optimally utilised. The reasons for this situation are to be found in the poor economic status of many of the effected countries, the low priority that many developing countries give to health care and disease control, and the lack of basic public health infrastructure essential for ensuring the correct deployment of antimalarials in their territories. Some of the most essential elements for the efficient distribution and utilisation of antimalarials should ordinarily be within the capability of even the poorest countries — I refer to primary health care, school health and maternal and child health services. Failure of most affected countries to provide these services or to use them in disease control is clearly due to poor motivation and lack of commitment on the part of these countries.

Even if allowance is made for technical, biological, economic and logistic problems in the use of antimalarial drugs, another question still remains. Are we deriving the maximum therapeutic advantages possible from these drugs even within the limits imposed by the above constraints? It is now generally accepted that in order to maximise the use of a drug, as much advantage as possible must be taken of our knowledge of its pharmacokinetics. The last of the currently widely available antimalarials, pyrimethamine, was introduced into therapy about 30 years ago. At that time the science of pharmacokinetics was in its infancy and drugs were introduced with little knowledge of their rates of absorption, distribution, metabolism and excretion. Limited knowledge of these parameters made a rational approach to the route of administration and dosage difficult, especially in special groups like children and pregnant women, a situation in which maximum benefit could not be expected from the drugs.

Negative answers to all the above questions indicate that we can still obtain more value from the existing drugs by undertaking more studies on them: pharmacological research to obtain more information on their pharmacokinetics, metabolism, mode of action and toxicity; pharmaceutical research to obtain more useful dosage forms and delivery methods, and operational research to find better methods of procurement and distribution which would ensure ready availability to all those who need the drugs.

In spite of the obvious need for more research to optimise the use of existing drugs, there is no doubt that there is equally a need for the development of totally new drugs for malaria. This need has certainly been recognised for a long time, and yet one can still with a feeling of despondency ask the following questions:

1. Is there enough activity in the areas of research and development for new antimalarial drugs, and in particular, are the pharmaceutical companies doing enough in this field or have they just simply abandoned the field?

2. Are the lessons gained in control programmes utilised for improved drug research?

3. Are basic and applied scientists providing enough leads for drug designers?

4. Are leads being adequately investigated before being discarded?

An examination of the chronology of the discovery of antimalarial drugs shows that since 1955 no new antimalarial has been developed to the stage where it can be released for unlimited clinical use or be officially sold through regular commercial channels. Of the two most promising new additions, mefloquine or its combination with other drugs has been approved for use in only Switzerland and Thailand whilst qinghaosu (including its derivatives) is used only in China. The first cases of resistance to chloroquine were reported in 1959 (WHO, 1973) a state of affairs which should normally lead to intensified activity to find a substitute. However, until quite recently the only organization that took up the challenge of finding new antimalarial drugs with the pertinacity that the situation demanded was the United States Army. Although the US Army authorities would argue that this effort represents a United States national contribution to the overall objective of improved health throughout the world, it is reasonable to conclude that even they would not have embarked on this effort but for the fact that protection of their troops against malaria was an essential military strategy in their Indo-China wars.

The US Army antimalarial drug development programme was begun in 1963. Twenty years later and after an expenditure of over $150m, only one product, mefloquine, was developed to a possible commercial level (Rapmund, 1983). It is well known that however brilliant a university or governmental research institution may be, the final development and commercial production of new drugs require the participation of the pharmaceutical industry. This has been lacking for antimalarial drugs until recently, when Hoffmann-La Roche took up mefloquine for final development and production.

A number of reasons have been advanced for the lack of interest of the pharmaceutical industry in the development and production of tropical disease drugs in general and antimalarial drugs in particular. One of these is the unprofitably short life of many antiparasitic drugs due to early development of resistance to the drug. Another reason is that financial returns on a new antimalarial which might have to be sold cheaply to some of the poorest countries in the world would not cover the amount invested in its development, much less turn out any profit, which is essential for the survival of private enterprises. The enormous funds that have to be committed to a programme of antimalarial drug development, especially using the traditional approach of random screening of chemical compounds and molecular manipulation of existing compounds, was forbidding for many companies. For example, since the inception of the US Army antimalaria programme more than 250,000 compounds have been screened and the programme has succeeded in coming up with only one drug, mefloquine. The enormity of that effort and the paucity of the results were enough to dissuade many companies from entering the race. Actually, apart from mefloquine the US Army programme also produced many interesting leads which could have been

followed with some reasonable expectation of a favourable outcome if there had been enough motivation and commitment on the part of pharmaceutical industries. Restrictive legislation permitting only government or other agencies to import and distribute the drugs in many target countries, and lack of respect of patent in a few others, also seriously reduce the financial returns on the drugs, contributing still further to their unattractiveness as business ventures.

Antimalarial drugs can thus be regarded as "Orphan Drugs" in need of foster parents. It seems unavoidable that the development of antimalarial drugs will have to be spearheaded and sponsored by national research organizations, United Nations Agencies like the World Health Organization and UNESCO, and private voluntary research foundations. Direct Government subsidy to pharmaceutical industries within their domain would also help, as also would collaboration between all the above.

Drug research and lessons learned in control programmes

One of the most frustrating lessons learned from the use of drugs in malaria control is the development of resistance to the drugs. It is therefore imperative that work must be intensified to find out how parasites become resistant to drugs and how to retard or prevent the process. Implied in this is the need for more work on the mechanisms of action of antimalarial drugs, the mechanisms and genetics of resistance and ways of interfering with its development and spread. Such knowledge should ultimately be useful in designing new drugs effective against resistant parasites.

The scourge of resistance also should increase effort towards the improvement of the available *in vitro* and *in vivo* techniques for testing the susceptibility of the parasites to antimalarial drugs. This would make laboratory screening of potential drugs easier and more specific and would make field monitoring of the parasites' sensitivity to drugs easier.

Future Chemotherapeutic Research

The empirical approach to drug development has been the most extensively used method for research and development for new antimalarial drugs. Whilst it still remains a useful method, it is time-consuming, costly and uncertain, and more rational approaches are required. Two of such approaches are: the study of parasite biochemistry and the study of natural products.

Parasite Biochemistry: Early in this century, Paul Ehrlich advocated rational drug development for parasitic diseases through a study of the biochemistry of the parasites. His assertion that a thorough knowledge of the different chemoreceptors is a *sine qua non* for success in chemotherapy is as true today as it was in Ehrlich's time. The aim of research on parasite biochemistry would be to discover metabolic pathways or enzyme systems which are peculiar to the parasites and which could then be exploited for drug development.

Any metabolic activity of the parasite could present biochemical targets for

drug action, but the potential of this approach to antimalarial drug development would be illustrated by examples from three metabolic processes: folate metabolism, nucleic acid synthesis, protein synthesis.

Folate Metabolism

It is well known that sulphonamides inhibit the synthesis of dihydrofolate by inhibiting the condensation of PABA with pteridine pyrophosphate to form dihydropteroate (DHP). This is due to inhibition of the enzyme dihydropteroate synthetase (DHP synthetase).

The next enzyme, DHF synthetase, which in bacteria adds glutamate to DHP to form DHF, has not been reported from malaria parasites (Ferrone, 1977).

It has generally been believed that the malaria parasite, like bacteria and in contrast to the host, uses PABA and not folic acid for the synthesis of folate-based cofactors. Recently, studies with *P. falciparum in vitro* show that both folic acid and PABA interfere with the activity of sulphadoxine. These results suggest that another metabolic pathway may exist in the parasite by which, in the absence of plasma folates and PABA, the parasite is capable of utilising red blood cell folate present in the form of polyglutamated 5-methyl tetrahydrofolate to synthesise folate-based cofactors. Further studies on this may reveal new targets for anti-folate action of antimalaria drugs.

Nucleic acid synthesis

During intraerythrocytic growth, the nucleic acid content of plasmodia increases approximately 20 fold. The guanine-cytosine composition of RNA from malaria parasites is typically protozoan, being 35% in contrast to the host g-c composition of 65% (Sherman, 1983). This specificity of nucleic acid base composition might well constitute useful targets for drug design.

The purines used by plasmodia for nucleic acid formation cannot be synthesised *de novo* but are obtained preformed, the preferred purine being hypoxanthine from the host. The appropriate nucleotide is obtained from this via purine salvage pathways similar to those of the host (Hitchings, 1978).

In contrast, pyrimidines are synthesised *de novo*. The enzymes essential for the synthesis of thymidylate have been identified in several malaria species, in particular the three enzymes of the so-called thymidylate cycle. One of these is serine hydroxymethyltransferase, which synthesises the necessary cofactor N^5, N^{10} methylene tetrahydrofolate (MTHF) from tetrahydrofolate (THF) with the accompanying conversion of serine to glycine. Another is thymidylate synthetase (TS), which converts MTHF to dihydrofolate (DHF) with the simultaneous conversion of dUMP to dTMP. In order to sustain the "thymidylate cycle", DHF has to be converted back to THF, a reaction catalysed by DHFR, and is associated with a simultaneous conversion of NADPH to $NADP^+$ (Ferrone, 1977). The inhibition of one of these enzymes, DHFR, has already been shown to be the basis of the antimalarial action of pyrimethamine, proguanil and other antifolates. The DHFR of plasmodia is exceptionally susceptible to pyrimethamine — IC_{50}

of 0.5 nM for the parasite enzyme compared with 1.0 uM for the erythrocyte enzyme. DHFR inhibition interferes with the formation of thymidylate, and by blocking DNA synthesis, merozoite development is crippled (Hitchings, 1978).

The precursor of thymidylate is deoxyuridylate (dUMP), and all the enzymes necessary for the *de novo* synthesis of dUMP have been identified in plasmodial extracts (Hill *et al.*, 1981). Some of the enzymes have been identified in *P. falciparum*, and have been shown to be different from those in the host. This aspect of parasite metabolism is clearly a promising target for drug design.

Protein synthesis

There are 3 potential sources of amino acids for the erythrocytic stages of plasmodia: (i) CO_2 fixation, (ii) the free amino acid pools of the blood plasma and erythrocyte, and (iii) red cell haemoglobin. Of these, haemoglobin is generally presumed to be the main source of amino acids for plasmodial protein synthesis. Malaria parasites obtain their amino acids by proteolysis of haemoglobin, and the parasite-specific cathepsin D and aminopeptidases that have been identified could be targets for new drug design.

Antimalaria Drugs from Natural Sources

The first effective antimalarial drug, quinine, was a product of a traditional herbal remedy used for the treatment of febrile illnesses, and traditional herbs are still a very attractive source for the development and production of new antimalaria drugs. All cultures in which malaria is endemic abound in varying numbers of herbal remedies which are used by the indigenous populations for treatment. In many countries these remedies have been and are still being investigated for antimalaria activity using modern biomedical research techniques. The best results in this regard have been achieved by the Chinese. They have isolated qinghaosu (artemisinine) from a medicinal plant *Artemisia annua* (Qinghao), which has been used for treating fever by the Chinese for over a thousand years. Qinghaosu has a structure which is different from that of any other known antimalarial. It is a sesquiterpene lactone in which the peroxide bridge is essential for activity. Qinghaosu has been found in many clinical trials to be active against drug-sensitive and multiresistant *P. falciparum*. Two derivatives of artemisinine have also been produced and clinically tested. One of these, artesunate, is water-soluble and may be particularly useful in cerebral and other severe or complicated forms of falciparum malaria. The other, artemether, is lipid-soluble. Both derivatives are more active antimalarials than the parent compound, and all three appear to be more active and more rapidly acting than chloroquine or quinine.

Conclusion and Prospects for the Future

In spite of all the problems discussed above, it nevertheless still makes sense to conclude on an optimistic note. In the last 5-10 years, thanks largely

to the efforts of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, substantial progress has been made in improving the efficacy and safety of existing drugs and in designing new candidate drugs of potential use in malaria control.

Thus, advances in the last 5 years on the pharmacokinetics and metabolism of the existing drugs have provided rationale for the more effective use of these drugs (Salako, 1985). Progress has also been made on methods to modify the chemical molecules of drugs in order to prolong their release characteristics. For example, converting cycloguanil to its pamoate salt considerably prolonged its action. Unfortunately, this formulation could not be deployed for field use because of local tissue reaction at the site of injection and cross-resistance problems. The studies with cycloguanil have, however, shown that the method is valid and can therefore be applied to other drugs.

Finally, the leads provided from studies on plasmodial biochemistry have already been exploited to produce a number of chemicals which are now undergoing tests for activity against malaria parasites. Only time will tell how many of these will ultimately reach the stage of being used in man. However, if the present interest and activity can be sustained, there is justification to be hopeful that we will soon be able to have at our disposal better and safer drugs in our effort to achieve better malaria control worldwide.

The situation described in the preceding paragraphs for malaria is typical for other tropical diseases. There are usually no effective drugs, and whatever is available is under-utilised because of inadequate pharmacokinetic and pharmacodynamic characterisation. Basic and applied research to define parasite physiology and biochemistry comprehensively and precisely is at a low level. Hence, information needed to evolve control strategies and to develop drugs which are selectively active against the parasites is largely unavailable. Where promising leads have been identified for potential drug development, these are not pursued with any great enthusiasm because of limited economic prospects on such drugs.

Control, and eradication where possible, of tropical diseases should be a global concern for which the industrial countries should devote financial and human resources as an essential element of their national policy. As a beginning, through the aegis of the United Nations and its specialised agencies, particularly the World Health Organization, a new global legal definition of "Orphan Drugs" should be produced, so that research and development with regard to drugs for tropical diseases could come under the operation of "Orphan Drugs" legislation. National and international efforts should then be geared towards assisting universities, national research institutes, pharmaceutical companies and other interested organisations in pursuing programmes which would lead to the development of better and safer drugs for the control of tropical diseases. Only then can we begin to make really serious efforts towards the attainment of the goal of "Health for all by the year 2000" as far as the Third World countries are concerned.

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