REVIEW ARTICLE

Altered Membrane Transport of Malaria-Infected Erythrocytes: A Possible Pharmacologic Target

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In recent years, the incidence of malaria, one of the most ravaging diseases of man, has risen sharply in many countries. This global expansion of the disease has been attributed mainly to failure of vector control programs and the increasing occurrence and spread of antimalarial drug resistance. Most alarming is the status of treatment of the disease caused by Plasmodium falciparum, the most common species found in tropical areas. Previously reliable antimalarial drugs have become less efficacious and consequently, severe cases involving multiple organs and hyperparasitaemia have been reported. Undercurative and prolonged prophyllactic usage of drugs are thought to be the major factors responsible for emergence of drug resistance, while increased mobility of the human host has largely contributed to the spread of malaria across wide geographic areas. Short of immunopreventative and immunocurative treatments, chemotherapy remains the major weapon for reducing malaria morbidity and mortality.

There is an urgent need for safe and effective treatment. The mode of action of currently used antimalarials and the mechanism of drug resistance are presently being explored. The identification of potentially sensitive points in parasite physiology or biochemistry appears to be a rational target in the development of new drugs. For all types of malaria, the asexual stages associated with the erythrocyte are responsible for the clinical manifestations of the disease. Most curative treatments focus on these stages. The targets potentially affected by drugs may be found in any compartment of the parasitized cell (Fig 1), whether of parasite or host-cell origin. Currently used blood schizontocides are thought to act directly on the parasite to suppress intracellular parasite growth, but the actual biochemical target(s) within the parasite remain elusive. Consequently, the theories advanced to explain drug mechanisms of action are controversial.

Classical and novel approaches to the treatment of malaria will be discussed with a review of the current concepts of the mode of action of established antimalarials and the biochemical basis of drug resistance. Reflecting the search for new effective chemotherapeutic agents.

An early landmark in the search for antimalarials was the description of the antimalarial action of methylene blue in 1891 by Guttmann and Ehrlich. Thirty-five years later the first synthetic antimalarial, pamaquine, was introduced, and primaquine was synthesized 15 years later. Because of their tissue schizontocidal, sporontocidal, and gametocytocidal properties, structural congeners of 8-aminoquinoline were used as prophylaxis against the preerythrocytic forms of the four species of parasites that cause human malaria. These agents also reduced transmission of parasites. A cure could be obtained in those malarial species that retain tissue stages and produce genuine relapses, particularly when complemented with blood schizontocides. Claims for in vitro killing of P. falciparum have been made. However, therapeutic but nontoxic doses of primaquine fall short of reducing parasitemias in vivo.

The biochemical basis for the antimalarial action of the aminoquinolines remains to be elucidated. In contrast, recognition of the structural analogy of sulfanilamide to p-aminobenzoic acid (PABA), an obligatory substrate of a key enzyme of the folic acid pathway, dihydropteroate synthetase, led to the design of sulfonamides and sulphones as effective antagonists of PABA and potent bacteriostatic agents. The finding of analogous effects of those agents in malaria preceded the development of other antagonists of enzymes of the folate pathways including schizonticides of both blood and tissue forms. These have proved useful for suppressive prophylaxis of malaria. The antibiotics tetracycline and clyndamycin were adopted in the treatment of malaria, particularly in combination with other antimalarial drugs.
**Mode of Action of Blood Schizontocides**

The introduction of the in vitro culture technique of *P. falciparum* and the development of reliable assays for the in vitro assessment of drug sensitivity provided a basis for analysis of antimalarial agents. The mode of action of antimalarials, with the exception of the antifolates, remains largely unresolved.

**Antifolates.** The antimalarial action of pyrimethamine, cycloguanyl, and related structural congeners is due to inhibition of parasite dihydrofolate reductase (DHFR), a key enzyme in the pathway of deoxythymidine synthesis. The parasite enzyme is considerably more sensitive to these drugs than is the mammalian enzyme. The parasite DHFR has thymidylate-synthetase activity, an activity that resides in a separate enzyme in mammalian cells. The antifolates provide an example of rational chemotherapy based on a combination of antimalarial drugs with defined pharmacokinetic properties. By acting on sequential steps of an essential metabolic pathway, combinations of drugs such as sulfonamides and pyrimethamine potentiate the effect of each other, probably reducing the spread of drug resistance.

**4-Aminoquinolines.** Most theories are predicated on the assumption that drugs containing the 4-aminoquinoline moiety act by a common mechanism, although their cellular targets and mode of action remain unknown. There are some basic facts about the 4-aminoquinoline-containing drugs such as quinine, chloroquine, amodiaquine, and mefloquine, that are pertinent to their biologic effects. These drugs are weak bases that are positively charged at physiologic pH. Such drugs appear to move freely through membranes in their unprotonated form, and some move through the membrane even when positively charged (Fig 2). Drugs accumulate in parasitized RBCs to concentrations several-fold higher than in nonparasitized cells, but accumulation is not necessarily proportionate to the parasite susceptibility to individual drugs. Finally, parasite strains resistant to one particular 4-aminoquinoline are not necessarily resistant to another. These observations seem inconsistent with the classical idea that the antimalarial activity of 4-aminoquinoline-containing drugs is related to binding to nucleic acids.

Ferriprotoporphyrin has been proposed as a “specific” parasite drug receptor that confers malaria parasites’ high susceptibility to 4-aminoquinolines. Effective drug concentrations required for antimalarial activity are considerably lower than those required for cytotoxic activity in mammalian cells. Ferriprotoporphyrin was thought to arise from parasite-mediated degradation of hemoglobin and sequestration in the food vacuole as the malarial hemoglobin pigment. The antimalarial activity of chloroquine and other 4-aminoquinolines was attributed to formation of lytic complexes between drug and transiently free ferriprotoporphyrin. Although chloroquine-ferriprotoporphyrin complexes with potential cell lytic activity have been demonstrated in solution, the occurrence of free ferriprotoporphyrin in *P. falciparum* is still uncertain. No structural or functional damage of the food vacuole by putative chloroquine-ferriprotoporphyrin complexes has been observed, and there is no correlation between the degree of pigment formation and

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*Fig 1. Schematic representation of permeation pathways in the host membrane of malaria-infected cells. The major permeation pathways present in normal erythrocytes are depicted on the left side of the scheme, grouped as carriers, pumps, and channels (leaks). The parasite-induced or modified pathways (Neoporters) are depicted on the right side, some of which might display pore- or channel-like properties, and others are pathways for simple diffusion either through the modified bilayer of the host cell membrane (shaded areas) or parasite-derived or modified proteins (shaded circles). The new pathways can serve as pharmacologic targets for antimalarial drugs (AMD) or as routes for selective admission of AMDs into infected cells. Once inside the erythrocyte, the AMD can affect host-associated or parasite-associated functions, act on cytoplasmic enzymes, or act on food vacuole-associated functions (FV), while others may act at the level of the mitochondria or the nucleus (N). Phlorizin is an example of an AMD that enters only into infected cells, primarily via the new permeation pathways, and produces pleiotropic effects, both at the level of the host-cell membrane and at the level of the parasite.*
Fig 2. Models of drug resistance to chloroquine (CQ) in relation to the mode of drug accumulation in the parasite food vacuole. According to the lysosomotropic hypothesis, CQ accumulates in the parasite food vacuole (FV) after sequential crossing of the host plasma membrane (RBCM), the red cell cytosol (RBC), the parasitophorous vacuole membrane (PFVM), the parasite cytosol (PC), and the food vacuole membrane (PFVM). Each of the aqueous compartments has been assumed to have a characteristic pH that determines the ionic composition of CQ in that compartment and the degree of accumulation of CQ in the FV. The acidic pH of the vacuole is assumed to be produced by the H+ pump located in the PFVM (full circle). Model I, assumes marked differences in pH between the different compartments. CQ+ is assumed to be permeant to all membranes while CQ− is translocated only via a hypothetical carrier mechanism (solid circle), which is present at the PFVM of both CQ-sensitive and CQ-resistant cells. However, in resistant cells there is a carrier also operative in the FVM, whose presumptive function is to "extrude" the CQ− into the PC. Model II assumes that resistant cells have a relatively higher pH in their FV, due to the presence of additional translocators that effectively lead to alkalization of the FV by Ca/H exchange. The hypothetical translocators could be a combination of Na-Ca and H-Na antiporters, in conjunction with leak pathways for Ca (not shown here).

The susceptibility to chloroquine in strains with different sensitivities to the drug. The ability to form complexes with ferric protoporphyrin does not correlate with antimalarial potency of 4-aminoquinolone-containing drugs. Finally, prevention of chloroquine accumulation in parasitized cells can be accomplished by treating cells with ammonium chloride, an agent that has no effect on the ability of chloroquine to form complexes with ferric protoporphyrin in solution.

The lysosomotropic theory of weak base action described in mammalian cells was adopted in the field of malaria after identification of the food vacuole as the site of chloroquine accumulation in parasitized cells and the organelle associated with parasite hydrolytic activities. The main determinant of chloroquine accumulation in parasitized cells was shown to be the large pH gradient that exists between the acidic food vacuole and the external milieu. The proposed mode of action of chloroquine as an antimalarial was assumed to be the result of vacuole alkalization, caused by protonation of accumulated drug, which resulted in inhibition of vital parasite functions. This hypothesis found support in studies conducted with digitonin-lysed cells but was not supported by experiments done with intact cells. Moreover, the validity of this hypothesis was challenged by: (1) demonstration that alkalization caused by NH₄Cl of a magnitude greater than that caused by chloroquine was considerably less detrimental to parasite survival, and (2) the lack of correlation between the antimalarial potency of 4-aminoquinolines and their alkalization potential as estimated based on the pKa values of their protonatable groups.

Alternate theories have incorporated the possibility that the relatively high concentrations of 4-aminoquinoline attained in food vacuoles by virtue of their weak base properties interfere with hydrolytic activities by interaction with enzymes, membrane components, or both. The different drugs might show different spectra of activities based on subtle chemical properties. Remaining to be shown is whether the profiles of inhibitory potencies of various drugs on specific vacuolar functions correlate with their antimalarial potency.

Although not strictly related to the mode of action of drugs in question, transporters of 4-aminoquinoline (chloroquine permease) were assumed to be operative in the plasma membrane of the parasite and in the vacuolar membrane. Experimental evidence for carrier-mediated transport of chloroquine in erythrocytes has been presented. The rationale for the operation of such permease(s) resides on the assumption that protonated forms of 4-aminoquinolines are impermeant to membranes unless translocated by permeases. Recent theoretical considerations have led to a modified description of this permease (renamed the chloroquine carrier) as operative in the parasite plasma membrane. It is now thought to be selective for the diprotonated form of chloroquine, whereas the monoprotonated form of the drug may be membrane diffusible (Fig 2). These properties would seem to be more consistent with what is known about diffusion of lipophilic cations across membranes. Such a carrier in the food vacuole membrane of chloroquine-resistant cells might confer drug-resistance by virtue of its capacity to extrude the drug from the acidic vacuolar space into the slightly more alkaline cytoplasm. No kinetic or biochemical evidence in support of such a permease has been presented, nor has any physicochemical analysis supported the need for such entity.

**DRUG RESISTANCE**

Although records of failure of quinine to cure certain patients with *P. falciparum* in South America date back to the first decade of this century, experimental evidence of resistance of the malarial parasite, rather than the host to drugs, was not presented until decades later. Work with
animal models provided initial information on mechanisms of resistance. The advent of reliable tests for determining *P. falciparum* response to drugs in vitro \(^{38,39}\) facilitated the monitoring of drug resistance and the global assessment of its spread. Drug resistance is particularly acute in *P. falciparum*-afflicted areas, while the other human plasmodial species have apparently retained their susceptibility to the 4-aminoquinolines, particularly to chloroquine. \(^{34}\) Resistance to each type of drug may occur by a different mechanism and involve genes located at different loci. \(^{47,48}\) Although drug-resistant strains have emerged for chloroquine, quinine, and mefloquine, and the antifolates, \(^{46}\) there are no indications for a common genetic mechanism. Even in the case of chloroquine, alterations in several genes might each confer onto the parasite a discrete quantum of resistance. \(^{47}\)

Work with animal models has indicated that drug resistance to pyrimethamine may be due to spontaneous gene mutations. One of the factors associated with the resistance may be overproduction of a form of DHFR that has a demonstrably lower affinity for the drug. \(^{22}\) Resistance of *P. falciparum* to pyrimethamine may be acquired over a number of generations by exposure to increasing concentrations of the drug. In such experiments, several independent genetic changes appear to be involved. \(^{49,50}\) These include gene duplication with a five- to tenfold increase in the amount of DHFR and in pyrimethamine binding. The enzyme turnover rate has also been shown to be one fifth to one tenth that of the parent line (so that the total enzyme activity per cell remains the same). This mode of drug resistance that is based on modification of the target enzyme clearly underscores the concept that drug resistance need not be based on reduced accumulation of drug.

The assumption that 4-aminoquinolines including chloroquine all act on the same target by a similar mechanism is untenable because resistance to one such drug is not necessarily accompanied by resistance to others as clearly shown by study of *P. falciparum* in vitro. \(^{15}\) The food vacuole has been identified as the locus associated with drug accumulation, but theories differ as to the mode that drugs affect this organelle (see above). The fact that chemically induced alkalization of the food vacuole renders cells resistant to short-term treatment by chloroquine \(^{42,43}\) suggested a drug-resistance mechanism based either on an impaired acidification of the food vacuole or an increased leakage of hydrogen ion (Fig 2, II). The prediction that chloroquine-resistant cells would have a more alkaline vacuole found support in a survey of *P. falciparum* strains with various degrees of resistance. \(^{46}\) However, drug accumulation varied only slightly among the most resistant and most sensitive strains.

Several observations \(^{51,52}\) suggested the existence of a transporter analogous to the anticancer-multipath drug resistance (MDR) transporter of mammalian cells \(^{29}\) that might operate in the food vacuole of resistant cells (Fig 2, I). Sensitive and resistant strains show a similar initial rate of chloroquine uptake, but resistant strains exhibit an approximately 40-fold higher efflux. \(^{51,52}\) Resistance to chloroquine could be experimentally reversed if otherwise-resistant cells were treated with verapamil, other calcium channel antagonists, or anticalmodulin agents \(^{51}\) similar to what has been demonstrated with a variety of drug effectors on the mammalian drug-resistance transporter. In analogy to what has been found in mammalian cells, \(^{53}\) verapamil, other calcium channel antagonists, and a series of mammalian cytotoxic agents markedly reduce the egress of chloroquine from resistant, but not from sensitive cells that have been loaded to the same levels with the antimalarial drug. \(^{52}\) There is no doubt that with present immunochemical and genetic technology it should be possible to ascertain whether or not an MDR like protein is expressed in parasitized cells and whether its level of expression differs between drug-sensitive and resistant strains, although it may prove considerably more difficult to assess its function either in situ or in an isolated system. Irrespective of the modus operandi of these drugs, the recent finding that the antidepressant desipramine and other basic hydrophobic agents reversed chloroquine resistance in vivo \(^{54}\) opens the road for the use of combinations of drugs as means to overcome drug resistance. This approach relies on one drug facilitating the action of the other by subserving its accumulation in otherwise-resistant cells. In mammalian cells, the drug effector is thought to compete with the anticancer drug for common sites on an ATP-dependent pump, the multidrug-resistant carrier, which is apparently expressed in the plasma membrane. \(^{55}\) An immediate analogy with that system in malaria-infected cells is not obvious and not easily reconcilable with the kinetics of aminoquinoline entry in parasitized cells. \(^{56}\)

Two additional hypotheses have been formulated to explain how chloroquine resistance might be reversed by compounds that affect calcium transport or calcium-dependent proteins. \(^{18,19}\) One hypothesis assumes that a chloroquine permease (MDR transporter?) \(^{49}\) is present in the plasma membrane of both sensitive and resistant cells, but only in resistant cells is this permease retained in the food vacuole (Fig 2, II). Calcium antagonists have been proposed to affect the permease activity either by acting directly on the food vacuole or via calmodulin. The second alternative hypothesis is based on the observation that resistant cells have more alkaline vacuoles (as described above). Increased efflux in resistant cells might then be the result of an increased gradient of unprotonated, diffusible chloroquine (Fig 2, II). The reversal of drug resistance by calcium antagonists would then be explained by the ability of this agent's action to induce acidification of the vacuole due to inhibition of a hydrogen ion egress pathway; eg, a hypothetical H-Ca antipporter, a combination of Na-H and Ca-Na antiporters in the various parasite membranes. Clearly, neither of these two hypotheses incorporated the simple notion of a direct inhibition of the transporter by verapamil and other drugs.

**NEW TRENDS IN DRUG DEVELOPMENT**

*Host Cell Membrane Is a Pharmacologic Target/Vehicle*

The membrane of RBCs infected with malarial parasites undergoes major alterations in structure and function. \(^{21,55,56}\) One of the earliest changes detected in the membrane after *P. falciparum* invasion is permeabilization without compromise of cell integrity. \(^{20-22}\) The described changes in permeability are not a direct nor an immediate result of parasite invasion,
but one of the sequelae of intracellular parasite activity. For some substrates the permeability changes are detected as early as six hours after invasion, while for others the appearance is delayed. The changes in permeation have been found to be cumulative and concomitant with parasite growth, depending on de novo protein synthesis. No changes in permeation or transport occurred as long as the protein biosynthetic machinery was suppressed. Several questions are in order: Are the parasite-invoked changes in permeation of functional significance for parasite development? Can they be used as pharmacologic targets? Can they provide selective access routes for targeted delivery of cytotoxic agents?

Functional role of new permeation pathways. The RBC membrane is endowed with a battery of transporters (Fig 1) that either handle substrates associated with essential metabolic functions of the cell such as glucose, phosphate, lactate, certain amino acids, and nucleosides, or subserve some systemic function (eg, chloride/bicarbonate exchange that facilitates CO2 removal from tissues and its release in the lungs). Other pathways are merely remnants from the erythroblast stage such as those that handle choline and certain amino acids. Following parasitization, intracellular metabolic activities increase significantly. Nutrients must be acquired from external milieu and waste products disposed of expeditiously. The RBC membrane responds accordingly by increasing its transport capacity both in quantitative and qualitative terms. This response applies to a variety of substrates from essential amino acids including glutamine, glutamic acid, cysteine, and isoleucine; to building blocks of phospholipids including choline, myo-inositol, and fatty acids; and to nucleosides, lactate and perhaps iron, and other trace metals. Correlations have been found between inhibition of parasite growth and blockage of the following permeation systems: glutamine by plant alkaloids (Na-artesunate, piperine) and entry of a variety of substrates by bioflavonoid-glycosides (phlorizin and phlorizin derivatives, cosmetin, etc.).

Selection of pathways and their biophysical nature. The permeability changes apply to a variety of substrates for which the RBC is either impermeable or permeable to different degrees. These include hexitols (notably myo-inositol), acidic and neutral amino acids (notably glutamine), a variety of small inorganic ions, organic acids, and others, all of which undergo marked increases in permeation typical of simple diffusion systems. There is slight augmentation of potassium, sodium, and calcium leaks and the pumping efficiencies of these cations are reduced but not to an extent that affects cell osmotic competence. In parallel, specific carriers for glucose, nucleoside, and tryptophan undergo apparent activation, probably as a result of changes in the lipid composition of the host-cell membrane. Iron was recently shown to be acquired by the parasite from serum transferrin, although studies do not support these observations.

This discussion will focus on the parasite-induced diffusion pathways that admit neutral and ionic substances. These are the most prominent permeation pathways in the RBC membrane after parasitization with P falciparum and are the most pertinent to the present discussion. All permeant substances were once thought to be accommodated by a single pathway with pore-like (Stokesian) properties and exclusion limits of 7 nm diameter. Patch clamp recordings of infected cells have demonstrated the operation of voltage-dependent ionic channels of 90 pS conductance that were blocked by phlorizin (Stutzin and Cabantchik, to be published). However, a thorough analysis of available data that encompassed a wide repertoire of substances, led to the rejection of the pore model in favor of another, based on hydrocarbon partitioning of solute across the membrane. The biochemical character of the pathway deduced by this model was a mesophase of lipid absorbed to proteins of parasite that intercalated in the host-cell membrane.

Two interconnected questions arise when considering the properties of selection for the new pathways and their biophysical nature: Are there one or more pathways involved for all permeants? Are the selectivity properties of the new pathways conserved throughout parasite development? Most of the available transport data lack the requisite accuracy or reliability for proper quantitative analysis and are insufficient to resolve these questions unequivocally. This applies to tracer methodologies in which metabolic conversion or entry into the parasite rather than transport into the RBC could be rate-limiting and affect the accuracy of the measurements. The different volumes of distribution of various substrates in the highly compartmentalized infected cell is a limitation of the isoosmotic-lysis technique. Phlorizin and other bioflavonoid-glycosides at micromolar concentrations block uptake of the most highly hydrophilic permeants including hexitols, glutamine, serine, and threonine; whereas uptake of other substrates (thiourea, glycerol, nucleosides, and cysteine), although markedly enhanced upon parasitization, are not affected by the phlorizin and other bioflavonoid-glycosides. The same is apparently the case for nucleosides. The simplest explanation is that more than one diffusion pathway is induced in the parasitized cell.

Biochemical nature of the pathways. The appearance of new permeation pathways follows the developmental pattern of “remodeling” of the host-cell membrane of intracellular parasites. Proteins of parasite origin become associated with host-membrane components either by deposition on the inner aspect of the membrane, or by transient or more permanent insertion into the membrane. Chemical modification of membrane components including oxidative damage, changes in lipid composition and organization, or alteration in membrane fluidity may induce increases in the permeability of RBC membranes analogous to those observed with parasitization. Addition of inhibitors of protein synthesis after parasitization does not affect presently developed pathways for a few hours, but does inhibit the development of new pathways. These observations are most consistent with synthesis of new membrane components rather than modification of existing host membrane proteins by a parasitic enzymatic activity. Radiolabeled phlorizin, an inhibitor of many of the new permeation pathways, binds to fewer than 1,000 sites per cell. Use of covalent-binding forms of phlorizin in current experiments may identify the relevant targets.
Pharmacologic applications. The new permeation pathways in parasitized RBCs might serve as specific targets for drugs. Alternatively, the pathways might provide a means for selective delivery of cytotoxic agents preferentially into parasitized cells. Phlorizin, a naturally occurring substance present in plant bark roots, arrests in vitro parasite growth with the same efficacy as it blocks the permeation pathways. Although phlorizin inhibition of sodium-dependent glucose transport in the intestine and in the kidney precludes its clinical use, this limitation can be overcome by appropriate chemical modification of the dihydrochalcone to yield analogues with both improved antimalarial activity and higher specificity.

The plant alkaloid piperine and certain Chinese traditional drugs inhibit glutamine uptake by parasitized cells, but correlation with antimalarial activity is very poor. Chemically synthesized glutamine analogues have been tested and shown to inhibit glutamine uptake by infected cells but appear to be rather nonspecific.

The use of new permeation pathways as routes for selective delivery of cytotoxic drugs into infected cells has also been considered. The properties of an effective agent would include preferential uptake via the new permeation pathways, the ability to inhibit some aspect of parasite metabolism or function, and specificity with respect to either uptake or inhibition of the many other carriers, pumps, and channels that exist within the normal RBC membrane (Fig 1). In some cases, these properties can be achieved by modification of existing drugs. For example, phloretin, like many other bioflavonoids and aromatic alcohols, is toxic to parasites but enters most cells readily. After glycosylation to yield phlorizin, the drug is rendered permeant only to infected cells but with no impairment of its antimalarial activity. Conversely, the cytotoxic agent tubercidin, which enters mammalian cells via the nucleoside carrier, was shown to specifically affect parasitized cells when administered together with nitrobenzylthioinosine, an agent known to efficiently block the carrier but not the parasite-induced pathways.

The metal chelators, desferrioxamine and dipicolinic acid are preferrentially admitted by infected cells. Both have antimalarial activity. Other chelating agents could be modified so as to be preferrentially admitted by infected cells. An interesting possibility is the design of "specifically permeant" agents that modify the erythrocyte environment in infected cells, rendering it inhospitable to parasites. This approach uses various RBC genetic variants as potential models for specific modification of parasitized cells.

The approach of "permeatherapy" in malaria is at the stage of design and synthesis of "permeadrugs" and their in vitro testing on the permeation pathways, parasite survival, and the biochemical systems affected either at the RBC or parasite level. However, considerably more basic information will be required on the selectivity of the new permeation pathways and on potential sensitive targets in infected cells before such an approach to drug design will prove itself useful and profitable. The possibility that resistance to these classes of compounds exists, particularly in multidrug resistant strains hasn't been thoroughly evaluated. However, as in the case of the recently introduced blood schizonticides, mefloquine and halofantrine, development of resistance in malaria parasites seems to be more the rule than the exception.

NOTE ADDED IN PROOF

In two recent studies, Wilson et al (Science 244:1184, 1989) and Foote et al (Cell 57:91, 1989) concluded that P. falciparum contains at least two genes which show sequence homology to mammalian MDR genes. One of these genes appears to be present in higher copy number and is expressed at higher levels in one P. falciparum strain that is resistant to chloroquine-like drugs.

REFERENCES

17. Peters W, Richards WGH: Antimalarial Drugs. Handbook of


60. Anelcin ML, Vial HJ: Quaternary ammonium compounds efficiently inhibit Plasmodium falciparum growth in vitro by...
84. Luzzatto L: Genetics of red cells and susceptibility to malaria. Blood 54:961, 1979
Altered membrane transport of malaria-infected erythrocytes: a possible pharmacologic target

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