

strate, metabolite, or enzyme, in an attempt to find significant parallelism between antimalarial potency and the effect of drugs on that system. Such studies may be of value in the search for clues as to mechanism of action and in the development of simplified laboratory assay methods for candidate antimalarials. Only two of the many examples of this field of experimentation are cited here. It has been observed that antimalarial drugs antagonize certain pharmacological actions of adenosine, a constituent of certain coenzymes, and that the antiplasmodial activity runs parallel to this antagonistic effect. Chloroguanide antagonizes adenosine only after it has been converted into an active metabolite in the blood (see below). A challenging finding is that antimalarial drugs *in vitro* specifically and powerfully inhibit the hemolytic action of an unsaturated fatty acid obtained from the plasma and tissues of animals. The acid is a very potent lysin and has been chemically identified as *cis*-vaccenic acid. The concentration of this acid in erythrocytes increases fiftyfold when they become parasitized. The tentative suggestion has been made that antimalarial drugs, by inhibiting hemolysis, may interrupt the erythrocytic cycle of plasmodial development by preventing the escape of the parasites from red blood cells.

It may be anticipated that continuing research will bring important new information concerning the mechanism of action of antimalarials and provide a more rational basis for the drug therapy and prevention of malaria. (See Symposium, 1946, 1951; Fulton, 1951; McKee, 1951; and others.)

QUINACRINE

History. Quinacrine (atabrine, atebine, mepacrine) is an acridine derivative introduced for malaria therapy by Schulemann in 1930. Its discovery was the result of an intensive systematic research program on synthetic antimalarials, conducted in the I. G. Farbenindustrie laboratories in Germany during the 1920's. This program involved the preparation and the testing of over 12,000 compounds and yielded pamaquine and quinacrine. Quinacrine was synthesized by Mauss and Mietzch on the basis of the clinical results obtained with pamaquine. The shift of research from the quinoline series to the acridine series was made with the view that the acridines could be thought of as pamaquine or quinine derivatives in which a benzene ring is fused to the quinoline nucleus. Another explanation credits the discovery of quin-

acrine to a historical accident. It is said that Paul Ehrlich found a laboratory preparation of dichloroparafuchsin to be highly trypanocidal; however, the manufacture of a larger supply by a different method resulted in a much less active substance. Re-examination of the original compound revealed its contamination with an acridine derivative, the subsequent study of which eventually led to the development of quinacrine as an antimalarial.

Although the use of quinacrine had become widespread prior to World War II, quinine still remained the chief antimalarial. With the shutting off of supplies of quinine to the allied nations by the Japanese invasion of the Southwest Pacific, it became imperative to manufacture quinacrine in the United States. The technical problems were quickly solved, and "American atabrine" was proven to be chemically and pharmacologically identical with the German variety. Whereas the prewar demand for the drug in the United States had been 1200 lb per year, production necessitated by the war rose to almost 1 ton per day.

Field experiences gained by the armed forces soon established the superiority of quinacrine over quinine, and quinacrine became the official drug for the treatment of malaria (see Office of the Surgeon General, 1943). However, the toxicity of quinacrine and its inability to cure malaria or to act as a true causal prophylactic provided the incentive for the search for more effective drugs (see Wiselogle, 1946). The accomplishments of the cooperative antimalarial wartime research program, conducted in an attempt to find compounds superior to quinacrine and quinine, are cited throughout this chapter. An important aspect of the program was the careful restudy of quinacrine in comparison with other antimalarials, and much additional information was thereby obtained. By the time World War II hostilities ended in 1945, it was already anticipated that chloroquine would replace quinacrine in the therapy of malaria; subsequent developments have substantiated this anticipation. However, a fairly detailed discussion of quinacrine is in order not only because the drug is still used in malaria and other diseases, but also because it is the prototype of a class of synthetic antimalarials which are effective, but neither prevent nor radically cure the malarial infection.

Chemistry. Quinacrine is 6-chloro-9-(1-methyl-4-diethylamino) butylamino-2-methoxyacridine, the structural formula of which is shown in Table 49. It is available as the dihydrochloride, designated *quinacrine hydrochloride*.

ride. The ready solubility of quinacrine in organic solvents permits its complete extraction from biological materials; subsequent quantitative determination is then possible by measuring the intensity of its fluorescence. With such procedures, the details of the absorption, distribution, fate, excretion, and plasma levels of quinacrine have been elucidated.

Structure-Activity Relationship. Of the thousands of compounds originally screened for antimalarial activity, quinacrine proved to be the most promising. It represents a substituted alkylamino derivative of acridine. The side chain is the same as that in pamaquine. The effects of ring and side-chain substitutions on activity in experimental avian and human malarial infections have been summarized by Blanchard and Schmidt (1946) and by Berliner and Butler (1946). The dextrorotatory form of quinacrine is apparently as potent as the racemic form; the claim that it is less toxic requires confirmation. The cooperative antimalarial research program conducted during World War II deliberately veered away from congeners of quinacrine because all available evidence indicated that causally prophylactic and truly curative compounds were not likely to be found in the acridine series. **Acranil**, 3-chloro-7-methoxy-9-(2-hydroxy-3-diethylamino)propyl amino-acridine dihydrochloride, a compound closely related to quinacrine, has had preliminary trial in the treatment of *Hymenolepis nana* and *Giardia lamblia* infections in children. The chemistry and the uses of other acridine derivatives are presented in connection with the antiseptic dyes.

Preparation, Dose, and Route of Administration. The preparation of quinacrine available for clinical use is **Quinacrine Hydrochloride (Mepacrine Hydrochloride)**, U.S.P. It contains approximately 80 per cent quinacrine base. The drug is a bright yellow, crystalline powder. It is odorless, bitter to the taste, and soluble in water 1:35. The chemical should be stored in tight, light-proof containers. Quinacrine hydrochloride is available in official tablets which contain 50 or 100 mgm of the drug.

The usual route of administration of quinacrine is by mouth. Each dose should be taken with a full glass of water and after a meal. The drug has also been given rectally, intravenously, and intramuscularly. The intramuscular route is preferred if parenteral therapy is necessary in patients with nausea and vomiting, and in certain emergencies, such as in fulminating falciparum malaria, cerebral or pernicious malaria, coma, delirium, etc. For this purpose, 0.2

gram of the powder is dissolved in 7 ml of sterile distilled water and injection is made in the gluteal region; the individual and total doses are generally the same as those for oral use. For intravenous administration, 0.1 gram is dissolved in 10 ml of sterile distilled water and the injection made **very slowly**. An alternative method is to give larger doses (0.4 gram) over a period of three to four hours by the intravenous drip technic. Parenteral therapy should be replaced by oral therapy as soon as possible. In infants, quinacrine may be given rectally in an aqueous acacia solution.

For therapy of the **acute clinical attack** of malaria, the dose of quinacrine for adults is 0.2 gram, with 1 gram of sodium bicarbonate, given by mouth with 200 to 300 ml of water, sweetened tea, or fruit juice. This is repeated every four to six hours for five doses, and then 0.1 gram is given three times daily for six days. For **suppressive therapy** in a malarious area, the dose schedule for adults is 0.1 gram daily, beginning two weeks in advance of exposure and continuing, after the individual leaves the area, for at least one month after the last possible exposure. In persons who have had attacks of vivax malaria within six months but have had no quinacrine for at least three weeks, the suppressive dose is 0.1 gram three times daily for three days, followed by 0.1 gram daily. Doses for children over eight years of age are the same as those for adults; for younger children, the dose is reduced according to age and weight.

Absorption, Fate, and Excretion. Absorption. Quinacrine is very readily absorbed from the intestinal tract. Even severe diarrhea does not interfere with absorption. The drug also quickly reaches the circulation from intramuscular sites of injection.

Distribution and Fate. Quinacrine is widely distributed in the tissues and very slowly liberated. Therefore, the drug progressively accumulates in the tissues when it is administered chronically. The marked avidity with which the tissues bind quinacrine can be appreciated from the fact that the parenchymatous organs of rats given 50 mgm of the drug daily for 60 days contain 6 to 17 grams per kilogram (Schmidt *et al.*, 1947). Comparable data for chloroquine and chloroguanide are given elsewhere. The highest concentrations are found in the liver, spleen, lungs, and adrenal glands; intermediate amounts are deposited in the kidney, pancreas, bone marrow, and intestinal wall; the lowest concentrations occur in the brain, heart, and skeletal muscle. The **concen-**

tration of the drug in erythrocytes is approximately twice that in plasma; in leucocytes, over 200 times that in plasma. The drug is deposited in the fingernails, where it can be detected by the brilliant greenish-yellow fluorescence under ultraviolet light; it may persist in the nails for as long as a year after discontinuing therapy. Quinacrine is also found in the hair; brunette hair contains five times more than blond hair. The compound passes through the placenta and reaches the fetus. The concentration in saliva is the same as that in whole blood; the concentration in spinal fluid varies from 5 to less than 1 per cent of that in the plasma.

The metabolic fate of quinacrine in the body is incompletely understood. Several of its degradation products have been isolated from urine in small amounts. When the racemic form of quinacrine is ingested, only the *l* isomer can be isolated in the urine. Whether quinacrine exerts its antimalarial actions per se or after metabolic transformation remains to be determined.

Excretion. Quinacrine is slowly eliminated from the body. Negligible amounts are excreted in the sweat, milk, saliva, and bile. Not over 11 per cent of the conventional suppressive dose (0.1 gram) is eliminated daily in the urine. Significant amounts of quinacrine can still be detected in the urine for at least two months after therapy is discontinued. Alkalinization of the urine by ingestion of sodium bicarbonate decreases the renal elimination of quinacrine (and chloroquine), whereas acidification by ingestion of ammonium chloride enhances renal excretion (see Trager and Hutchinson, 1946; Jailer *et al.*, 1947, 1948). The influence of urinary pH on renal excretion of drugs is also evident for the salicylates, nicotine, and other compounds. In general, a pH which permits a drug to exist in ionic form in the tubular lumen facilitates excretion, by limiting tubular reabsorption. In the case of quinacrine, renal elimination is so limited (largely because the drug is bound by plasma proteins) that the difference between the quinacrine excretion in acid urine (4 per cent of the amount ingested) and that in alkaline urine (0.2 per cent) is not reflected in any alteration of plasma level and does not reduce the effectiveness of a given oral dose. Consequently, acid salts are of no practical value in hastening elimination in cases of quinacrine poisoning. Indeed, acidosis temporarily elevates the plasma quinacrine level by altering the distribution of the drug between tissues and plasma.

Plasma Levels and Antimalarial Activity. Quinacrine present in the plasma is largely

bound to nondiffusible constituents; at drug levels known to be therapeutically effective, from 80 to 90 per cent is bound to plasma protein. The many variables influencing plasma quinacrine levels and the clinical efficacy of these levels have been exhaustively studied (see Shannon *et al.*, 1944; Ellerbrook *et al.*, 1945; Office of Surgeon General, 1946; Taggart *et al.*, 1948; and others). The major purpose of these studies was to develop dosage schedules designed to yield clinically effective plasma levels of the drug, on the assumption that there was a satisfactory correlation between oral dosage and plasma level on the one hand, and between plasma level and antimalarial activity on the other. It was found that the erythrocytic phase of *P. vivax* infection could be completely eradicated if the plasma quinacrine level was maintained above 30 micrograms per liter for not less than four days; *P. falciparum* infections required levels of approximately 50 micrograms per liter for a six-day period. Suppressing doses of quinacrine (0.1 gram daily) eventually result in plasma levels of 25 to 30 micrograms per liter. When quinacrine medication is stopped, the plasma level falls at the rate of approximately 50 per cent per week. However, the results of subsequent investigations have tended to minimize the role of plasma quinacrine levels as the all-important factor in therapy. It has been pointed out that the concentration of the drug in parasitized erythrocytes is the crucial factor and that it bears no relation to the plasma levels which fluctuate greatly despite constant dosage. In contrast, there is quite a good correlation between dosage and therapeutic effect (see Marshall and Dearborn, 1946; Marshall, 1946, 1952).

Toxicity. The vast majority of the hundreds of thousands of individuals who have received quinacrine experienced no untoward effects from the drug. Careful study of subjects for many months during oral administration of the compound has revealed no significant alteration in liver, renal, or hematopoietic functions. Conventional therapeutic or suppressive doses are benign to the cardiovascular system and do not alter the ECG. The urine becomes deep yellow (upon acidification) by the fourth day of medication, but renal function is unimpaired. The drug only rarely causes visual or aural disturbances. It lacks the oxytocic action of quinine and can be employed safely in any stage of pregnancy. **Mild untoward effects** from quinacrine include skin discoloration, nausea, vomiting, abdominal cramps, headache, diarrhea, vertigo, excessive sweating, fever, pruri-

tus, insomnia, and pains in the muscles and joints. Enormous doses of quinacrine may prove fatal; but even large doses, taken in attempts at suicide, have been survived. One individual ingested at least 6 grams and recovered without residual effects; his plasma level of quinacrine was 475 micrograms per liter (practically the saturation level). Despite its relative benignity, quinacrine does cause a variety of toxic effects, in which the skin, gastrointestinal tract, and central nervous system are prominently involved; some of these may be serious and even fatal. The toxicity of quinacrine, in relation to that of equally effective antimalarials, represents a major therapeutic drawback.

Skin and Mucous Membranes. A lemon-yellow pigmentation of the skin occurs in the majority of persons receiving suppressive quinacrine medication for more than a week. The color usually disappears within two weeks after the drug is withdrawn, but it may persist for several months. All tissues including the central nervous system are stained by the drug. The sweat, tears, and nasal secretions may also be colored deep yellow. The cutaneous discoloration is diffuse, but it is most prominent on the dorsum of the arms, hands, and feet, and in the folds of the skin. The face and forehead are also discolored and a golden circle may form around the mouth. When drug administration is prolonged beyond six months, a small percentage of subjects develop a grayish-blue coloration of the hard palate, cartilaginous structures of the ears and nose, and nailbeds of the fingers and toes. The pigment contains iron and may be hemosiderin; it disappears very slowly after withdrawal of the drug. Quinacrine pigmentation must not be mistaken for jaundice, from which it readily can be differentiated by testing for hyperbilirubinemia. Pigmentation of the sclera can be differentiated from that seen in jaundice by the fact that it is most marked around the limbus and fades toward the fornices; in jaundice, the reverse is true. Quinacrine pigmentation causes no symptoms and apparently no harm.

Quinacrine also produces various types of dermatitis. The incidence is less than 1 per cent of patients receiving the drug. Dose and duration of therapy do not appear to be contributory factors, except in the lichenoid type of dermatitis. Hypersensitivity to the drug is probably the basis of the lesions. The most common type is a "symmetrical eczematoid dermatitis," which can be protean in its manifestations. It may recur months or years later, upon exposure to heat, friction, or chemicals. Another

category, to which much study has been devoted, is an *atypical lichen planus* ("New Guinea or jungle rot"), a "fixed type" of drug eruption. It may be associated with the eczematoid form. At times the lesions may resemble psoriasis or lupus erythematosus. *Exfoliative dermatitis*, which may prove fatal, can develop as a primary reaction to the drug or as a secondary response to other types of quinacrine-induced eruptions. Contact dermatitis also occurs from the drug.

Treatment of quinacrine dermatitides consists in early withdrawal of the drug, mild local therapy for vesicular and pruritic lesions, and the systemic use of antibiotics for secondary infections. Lichenoid lesions are more refractory to treatment and subside slowly; in severe cases, sequelae which slowly regress include light brown pigmentation, depigmentation, atrophy of the involved skin, dystrophy of the nails, and partial alopecia. Hepatitis and severe anemia, which occasionally is aplastic, may accompany the more serious forms of dermatitis; they require appropriate treatment. Readministration of the drug to an individual who has previously had a quinacrine dermatitis frequently causes recurrence of cutaneous eruptions; these are often of the same type as originally experienced.

Gastrointestinal Tract. Daily suppressive doses of 0.1 gram of quinacrine occasionally cause mild gastrointestinal symptoms and headache. These are usually minimized when the drug is taken with a meal, and ordinarily disappear in a few days despite continued therapy. Single large doses (0.6 gram) may produce severe headache, nausea, vomiting, abdominal cramps, enhanced secretory and motor activity of the stomach, and slight diarrhea. Tolerance to the minor side effects of conventional suppressive amounts of the drug is best maintained when the interval between doses does not exceed more than two days.

Central Nervous System. Very large doses of quinacrine in man (causing plasma levels in excess of 100 micrograms per liter) produce *excitation of the central nervous system*, manifested in psychic stimulation, motor acceleration, restlessness, insomnia, increased work capacity, and a significant shift toward faster frequencies in the EEG (Engel *et al.*, 1947). *Epileptiform convulsions* can result from massive doses, or from therapeutic doses given to susceptible patients, such as those with dementia paralytica receiving the drug for the termination of induced malaria.

Toxic psychoses occur in approximately 0.2 to 0.3 per cent of quinacrine-treated cases of

malaria. The psychosis is caused by the drug itself and not by the malarial infection or concurrent factors. Large, rapidly repeated doses appear to enhance greatly the possibility of psychotic episodes. Indeed, the incidence is quite low in patients receiving the conventional dosage of quinacrine. Two types of reactions are observed. The more frequent reaction is characterized by a sudden increase in motor and psychomotor activity; auditory and visual hallucinations, delusions, and, occasionally, ideas of reference are present. The other type is more insidious in onset and is characterized by gradual clouding of the sensorium, disorientation, amnesia for recent events, and confabulation. The clinical picture is probably determined by the prepsychotic personality of the patient. The duration of the psychosis is usually two to four weeks, and the course is relatively benign. Only symptomatic therapy is indicated. Rarely does readministration of quinacrine produce a recurrence of the psychosis. Despite the possibility of convulsions and psychoses from the drug, neuropsychiatric manifestations of malaria readily yield to quinacrine therapy.

Vision. Quinacrine in conventional amounts does not adversely affect vision. If suddenly attained, excessively high levels of plasma quinacrine may be associated with scotomas and enlargement of the blind spot. In a few hypersensitive patients, bilateral superficial corneal edema may occur and impair visual acuity. Occasionally, severe hepatitis subsequently develops in these patients. The corneal involvement subsides completely when the drug is withdrawn and vision returns to normal in two to four weeks.

Blood. It has been claimed and denied that quinacrine causes a mild eosinophilia in the peripheral blood. Aplastic anemia is a rare and usually fatal manifestation of quinacrine hypersensitivity; it usually occurs in association with severe dermatitis or hepatitis. Hemolytic anemia from quinacrine is practically unknown; consequently, the drug has been substituted for quinine in cases of blackwater fever. Agranulocytosis from quinacrine therapy is very rare. Prolonged administration of large doses of the compound produces hematological changes in various laboratory animals, such as anemia, leucopenia, and basophilic inclusions in lymphocytes. Unlike pamaquine, the drug does not produce methemoglobinemia.

Tissue Changes. Large doses of quinacrine administered to experimental animals produce generalized yellow discoloration, hepatic necrosis, fibrosis and necrosis of the myocardium

and skeletal muscles, lesions of the adrenal cortex, kidney, and reticuloendothelial system, leucocytosis, and basophilic granules in renal and hepatic cells. The pattern of pathological changes varies with the species employed. Death usually results from liver or myocardial damage. Diet modifies the toxic response to quinacrine. A high-protein diet apparently lessens the retardation of growth and the injury to the liver; conversely, fasting enhances the toxicity of the drug.

Combined Toxicity. The concurrent administration of quinacrine greatly enhances the toxicity of pamaquine by increasing fivefold to tenfold the concentration of pamaquine in the plasma and by prolonging its sojourn in the body; quinacrine likewise increases the toxicity of pentaquine, particularly with respect to methemoglobinemia and hemolysis of erythrocytes (see below). Such combinations should not be employed in therapeutics.

Pharmacological Actions. In conventional doses, quinacrine exerts few pharmacological actions in the body except those on malarial and certain other parasites. The toxic actions are discussed in detail above. Certain miscellaneous actions require comment.

Quinacrine has been found to **inhibit a number of enzyme systems**. For example, concentrations of the drug in the range of those which accumulate in tissues during therapy have been found to depress oxygen consumption of rat liver, brain, and kidney slices, probably by an interference with the yellow enzyme systems. Quinacrine is also a strong inhibitor of cholinesterase. It has been suggested that such inhibition may be a factor in the toxic symptoms produced by the drug. The **cardiovascular system** is influenced by quinacrine; toxic doses, or high blood levels such as are transiently attained during rapid intravenous injection of otherwise innocuous amounts, cause depression of the respiratory and vasomotor centers, peripheral vasodilatation, hypotension, impaired contractile power of the heart, decreased cardiac output, bradycardia, prolonged A-V conduction time, and arrhythmias. Doses of quinacrine in the therapeutic range restore normal sinus rhythm in dogs with experimental atrial fibrillation, probably by a mechanism similar to that of quinidine; on this basis, the drug has had a preliminary trial in cardiac arrhythmias in man. Quinacrine has also been reported to prevent ventricular fibrillation induced by epinephrine in dogs under chloroform anesthesia.

Antimalarial Actions and Potency. During the decade following the introduction of quina-

crine, its antimalarial value was firmly established by numerous extensive field trials (see Bastianelli *et al.*, 1937; Fourth General Report, 1937; and many others). Because quinacrine closely resembles chloroquine in its spectrum of antiplasmodial actions and because it is no longer the antimalarial of choice, extensive discussion of its antimalarial activity is not necessary.

In **avian malarias**, quinacrine is from 2 to 15 times more potent than quinine. It acts mainly on the erythrocytic phase of development. It exerts very little effect on the sexual parasites of *P. falciparum* but destroys those of *P. vivax* and *P. malariae*. The pre-erythrocytic tissue forms are not affected. In **human malarias**, both experimentally induced and naturally acquired, quinacrine is more potent, more effective, and better tolerated than quinine. The huge experience gained by the Allied Armed Forces during World War II unequivocally proved the superiority of quinacrine over quinine. In terms of plasma drug concentration necessary to produce a permanent interruption of the erythrocytic phase of vivax malaria, quinacrine (25 micrograms per liter) appears to be approximately 200 times as active as quinine (5 mgm per liter), and a similar ratio exists between the two drugs with regard to suppressive activity (Shannon *et al.*, 1948; Taggart *et al.*, 1948). However, on the basis of oral doses required to produce comparably effective plasma concentrations, quinacrine is only five times as effective as quinine.

Quinacrine is neither a true causal prophylactic nor a radically curative agent for malaria, but it is highly effective as a suppressive drug and for the treatment of the overt clinical attacks. Daily suppressive therapy can be continued for a year or more without harm in the vast majority of individuals. However, when such medication is discontinued, overt malaria usually appears within a few weeks to months in most persons infected with vivax malaria. Resistance of erythrocytic forms of plasmodia to quinacrine apparently does not occur clinically, and overt attacks which develop despite suppressive therapy respond promptly to adequate doses of the drug. In the clinical attack, quinacrine quickly checks the progress of the disease by destroying the asexual erythrocytic trophozoites in all types of malaria. The period of treatment is shorter than for quinine and the relapse rate is somewhat lower. Quinacrine is especially superior to quinine in the treatment of *P. falciparum* malaria, and frequently cures this form of infection. The drug adequately controls symptoms, fever, and parasitemia in

all types of malaria, but it is less prompt than chloroquine in these respects; furthermore, the latent period for relapse is longer after therapy with chloroquine, and the latter drug is easier to administer and better tolerated than quinacrine. (See Most *et al.*, 1946; Pullman *et al.*, 1948; Young and Eyles, 1948; and others.)

In both mosquito- and blood-induced malarias in human subjects, prophylactic therapy with quinacrine completely protects against falciparum malaria but does not prevent vivax malaria (see Fourth General Report, 1937; Cooper *et al.*, 1949). Closer analysis indicates that the protection against *P. falciparum* is not due to an action on sporozoites or pre-erythrocytic forms because a mild transient parasitemia can be observed 7 to 10 days after mosquito-induced infection; the apparent prophylaxis is thus explained by a curative schizonticidal action of quinacrine (Fairley, 1945).

THERAPEUTIC USES

Therapeutic Status in Malaria. Quinacrine is an effective agent in malaria for suppressive therapy and for the control of overt clinical attacks. It is neither a true causal prophylactic nor a radically curative agent. It does not prevent relapses in **vivax** malaria; but, for reasons given above, even suppressive doses may be curative in many cases of **falciparum** malaria. In all these respects it resembles quinine and chloroquine. It is more effective and less toxic than quinine, but less effective and definitely more toxic than chloroquine.

Uses **Other Than in Malaria.** Quinacrine has been tried in various parasitic infections other than malaria. A number of clinical reports testify to its therapeutic efficacy in **Giardia lamblia** infection. The dose schedule is that employed for the overt attack of malaria. The organisms disappear from the stools, and symptoms referable to the infection rapidly clear. Although the parasite is considered by some authorities to be nonpathogenic, the preponderance of evidence indicates that it can at times cause gastroenteritis, especially in infants, and that quinacrine is a specific chemotherapeutic agent in the disorder. It has been both contended and denied that local infiltration therapy with quinacrine is useful in **cutaneous leishmaniasis (oriental sore)**. Quinacrine has also been used as a **taeniafuge**. Some investigators are of the opinion that quinacrine is the agent of choice in **Taenia saginata** (beef tapeworm) infestation, and that it may be of some limited value in **Hymenolepis nana** (dwarf tapeworm) infesta-

tion. The drug has also received favorable trial in human infestation with *Oxyuris vermicularis* (pinworm). The taeniocidal value of quinacrine requires further investigation. The drug has also been reported of value in **intestinal amebiasis** and as a **trichomonicide**, but other agents are usually to be preferred. On the basis of the observed ability of quinacrine to restore normal sinus mechanism in dogs with experimental atrial fibrillation, the drug has had a preliminary trial in patients with **cardiac arrhythmias** refractory to quinidine and procaine amide; encouraging results have been obtained particularly in atrial fibrillation and in an occasional case of paroxysmal ventricular tachycardia. This use of quinacrine requires further study. The drug has been used to advantage in selected patients with **chronic discoid lupus erythematosus**, but it must be employed with great care because of the hypersensitivity to drugs exhibited by patients with this disorder (see Kierland *et al.*, 1953).

CHLOROQUINE

History. Chloroquine (SN-7618; aralen; resoquin) is one of a large series of **4-aminoquinolines** investigated in connection with the extensive cooperative program of antimalarial research in the United States during World War II (see Wiselogle, 1946; Elderfield, 1946; Loeb, 1946). The objective was to discover more effective and less toxic suppressive agents than quinacrine. Although the 4-aminoquinolines had previously been described as potential antimalarials by Russian investigators, serious attention was not paid to the group until the French reported that 3-methyl-7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline (SN-6911; santochin; sontoquin) was well tolerated and had high activity in human malar-ias. Beginning in 1943, a large number of these compounds were synthesized and tested for activity in avian malaria and for toxicity in mammals; 10 of the series were then examined in humans with experimentally induced malar-ias. Of these, chloroquine proved most promising and was released for field trial. When hostilities ceased, it was discovered that the chemical had been synthesized and studied under the name of **resoquin** by the Germans as early as 1934.

Chemistry and Preparations. Chloroquine is 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline, the structural formula of which is shown in Table 49. The compound is generally available as **Chloroquine Phosphate**, U.S.P. (**Aralen Phosphate**, N.N.R.).

It is a white, bitter, water-soluble, crystalline powder. Approximately 60 per cent of the (di)phosphate represents the base. A solution of the drug is acid to litmus (pH about 4.5). The degree of inhomogeneity is less than 4 per cent. The phosphate is marketed as 0.25gram tablets for oral use.

Structure-Activity Relationship. Chloroquine contains the same alkyl side chain as quinacrine; it differs from the latter in having a quinoline instead of an acridine nucleus and in lacking the methoxy radical. Chloroquine also bears close resemblance to pamaquine and pentaquine; it differs from them in the position of the alkyl side chain and in having a chlorine instead of a methoxy nuclear substituent. The **d**, **l**, and **dl** forms of chloroquine are indistinguishable in potency tests in duck malaria, but the **d** isomer is somewhat less toxic than the **l** isomer in mammals. The 4-aminoquinolines showing the most marked antimalarial activity in both bird and human malar-ias have a chlorine atom in position 7 of the quinoline nucleus. The details of the structure-activity relationship of chloroquine and its congeners are discussed by Blanchard and Schmidt (1946), Berliner and Butler (1946) and Berliner and co-workers (1948).

Absorption, Fate, and Excretion. In general, the absorption, fate, and excretion of chloroquine and related 4-aminoquinolines are similar to those of quinacrine (see Blanchard and Schmidt, 1946; Berliner *et al.*, 1948). Chloroquine is almost completely absorbed from the gastrointestinal tract and only small amounts are found in the stools; it is absorbed somewhat more rapidly than quinacrine. Because the tissues bind less of the drug than of quinacrine, the plasma concentrations of chloroquine are substantially higher on any given dose schedule. Approximately 55 per cent of the drug in the plasma is bound to nondiffusible plasma constituents. Excretion of chloroquine is quite slow; only 10 to 20 per cent is found unchanged in the urine under ordinary conditions. However, the rate and extent of renal excretion of the drug may be appreciably influenced by the concurrent administration of acid or alkali; the excretion of chloroquine is increased by acidification of the urine and decreased by alkalization (Jailer *et al.* 1947).