CHEMOTHERAPY OF MALARIA[1]

By G. Robert Coatney

The recent war, which carried troops into all the highly malarious regions of the world, gave great impetus to the search for better antimalarial drugs. The greatest concerted effort was put forth in the United States under the guidance of the Board for Coordination of Malarial Studies. The principal objective was the discovery of a drug of low toxicity which would also be at least one of the following against all types of human malaria: a true causal prophylactic, a better therapeutic or suppressive agent than was then available, or a truly curative agent. Under this coordinated program, over 14,000 compounds of various types were screened against several of the avian malarias. The pharmacology and toxicology of many of the compounds of promise were studied in lower mammals, and approximately 100 were finally tested against the human malarias. The principal practical results were the development of rational regimens for the use of quinacrine (atabrine), based on its physiological disposition and antimalarial activity; the development of chloroquine, a therapeutic and suppressive agent of great value; and the development of the curative agents pentaquine and isopentaquine. The British effort, although on a smaller scale, resulted in the synthesis and elucidation of the highly interesting drug paludrine.

The object of this paper is to set forth the general usefulness of the better chemotherapeutic agents when used for the suppression, alleviation or radical cure of human malaria. Any drug to be generally useful must be effective against *Plasmodium falciparum*, and it is now known that this species can be prevented by any of the recognized antimalarials and that it can be cured if diagnosed early. There is little information on the effectiveness of the newer chemotherapeutic agents against *Plasmodium malariae*, but this should occasion no great concern because of the low prevalence and limited distribution of this species. *Plasmodium vivax*, on the other hand, creates a major problem for it is found throughout the world and none of the antimalarial agents applicable to field use will prevent its establishment in the human host and only agents adapted to hospital use will cut short its pronounced predilection toward repeated relapses. As a consequence of the above, the main emphasis in this paper will be directed toward *P. vivax*.

QUININE

It is hardly necessary to spend much time discussing the use of quinine in the treatment of malaria for, although an effective antimalarial, it

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has definite limitations which are more or less well known. It has no causal prophylactic action even when given in dosages near the limit of tolerance (1, 2, 3, 4); its rapid elimination from the body allows for closely spaced relapses (4, 5, 6); and it is prone to produce more toxic reactions than commonly realized (4, 7).

In countries where cinchona is grown, and where, as a consequence, quinine and the other alkaloids (i.e., cinchonine, cinchonidine and quinidine) which have antimalarial activity roughly equivalent to quinine may be combined into a standard product, such as totaquine, at a price well below that of other antimalarials, its use should not be discouraged until better drugs can be made available. Otherwise, it is not to be recommended.

QUINACRINE

The value of quinacrine (atabrine) as an antimalarial was not fully appreciated until after our supply of quinine was cut off by military operations in the Pacific. Necessity led to crucial experimentation in which the work of Shannon and his collaborators (8) was outstanding. These investigators showed that quinacrine is extensively localized in the various body tissues and that the effectiveness of the drug is a function of its concentration in the plasma. These facts Shannon translated into a more logical system of therapy than the commonly recommended prewar regimen, 0.1 gram three times daily, by recommending large loading doses during the first day to obtain rapid saturation of the tissues. Action as prompt as with quinine was thereby attained. The slow release of quinacrine from the tissues following discontinuance of therapy results in the maintenance of suppressive levels long enough after the last dose of drug to delay relapses for 5 to 7 weeks. All the recent investigators employing the newer regimen of therapy have favored quinacrine over quinine (5, 9, 10, 11, 12).

In critically ill or vomiting patients, quinacrine may be given intramuscularly with resultant high plasma concentration within 15 minutes. The standard initial dose is 0.4 gram; this should be followed by oral administration, sufficient to provide 1.0 gram during the first 24 hours.

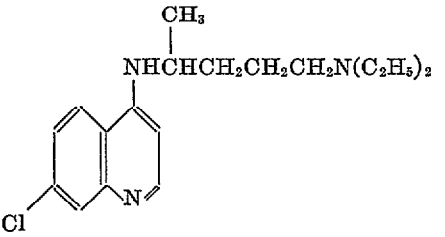
In dosage of 0.1 gram daily quinacrine has proved to be a highly effective suppressant. In Fairley's controlled studies (3) it was unquestionably superior to quinine, and in field practice it carried hundreds of thousands of individuals through highly malarious areas without evidence of infection until after the drug was discontinued.

The main advantages of quinacrine over quinine are that it can be manufactured in quantity, it is a more effective therapeutic and suppressive agent and, because of its slow elimination from the body, it results in relapses being more widely spaced.

CHLOROQUINE

As a result of postwar access to the records of German investigations, it was learned that the compound chloroquine (SN 7618), (7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline) (figure 1), had been synthesized by the Germans and studied under the name of "resochin" as early as 1934; but its antimalarial properties were not fully realized until after its independent development in the United States in 1944 (13).

FIGURE 1.—*Structural formula of chloroquine* (SN 7618)



Chloroquine rapidly alleviates acute attacks of *falciparum* (14), quartan (15) or *vivax* (14, 16, 17, 18) malaria. Like quinacrine, this drug becomes extensively localized in the tissues so that plasma concentrations cannot be built up rapidly unless a loading dose is given during the first day of therapy. Due to the longer time required for the concentration of drug to fall below an effective level after the last dose, relapses are delayed longer than after quinacrine. Three- or 4-day administration gives better results than a week's treatment with quinacrine. Treatment using only single doses of 0.3 gram (base) is surprisingly effective (19); the median interval to relapse among our 35 cases was 30 days.

As a suppressant, this drug appears to outrank all others. Our own studies in prisoner volunteers (19) resulted in the complete suppression of *P. vivax* when 0.3 gram (base) of chloroquine was given once weekly for 6 months or for one year. Clark (20), who has been carrying out field suppression studies in Panama, has found that 0.3 gram (base) given once weekly results in almost complete protection against all three species of human malaria. In dosages of 0.15 gram (base), it was also protective and well tolerated in infants and children.

Because of the pronounced effectiveness of chloroquine when given orally, we (19) considered it of practical interest to determine whether it could be given parenterally, as might be imperative in extremely ill patients. Chloroquine hydrochloride, in sterile aqueous solution, was administered intramuscularly during acute attacks of *P. vivax* in single or double doses (spaced 4 hours apart). Dosages ranged from approximately 2.5 to 5.0 milligrams per kilogram, i.e., 200 to 300 milligrams in

adult males. The parasites were cleared from the blood in one to 2 days. No local or systemic reactions were observed. Similar dosages have since been successfully employed against natural cases of *P. falciparum*. It is now believed safe to recommend the intramuscular use of chloroquine for subjects who may be comatose, vomiting or otherwise unable to take the drug orally. Single intramuscular doses have a prolonged effect. In practice, however, a complete course of therapy, i.e., 1.5 grams (base) in 4 days, is recommended, the oral administration to begin as soon as feasible.

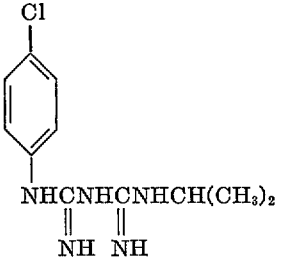
The main advantages of chloroquine over quinacrine are its pronounced rapidity of action, allowing for short-course or even single-dose treatment; once weekly administration results in suppression; relapses are more widely spaced; it does not stain the skin and eyes; and it does not produce gastrointestinal symptoms.

There are several other 4-amino-quinolines closely related to chloroquine which possess similar properties. Chief among these are sontochin (SN 6911), oxychloroquine (SN 8137), and camoquin (SN 10,751). All of these are effective and relatively non-toxic. From work with experimental malaria none of these appears superior to chloroquine and data from field trials are not sufficient for final conclusions.

PALUDRINE[2]

Paludrine[2], N_1-(*p*-chlorophenyl)-N_5-isopropylbiguanide (figure 2), developed during an intensive investigation which began with certain pyrimidine derivatives and extended into the structurally related biguanides (21), possesses unusual antimalarial properties against the human

FIGURE 2.—*Structural formula of Paludrine*



malarias. The drug is apparently destructive of the pre-erythrocytic stages of *P. falciparum* and, hence, acts as a causal prophylactic against this species, but not against *P. vivax* (22). It exhibits a wide range between the minimum effective dose and the maximum tolerated dose. For example, clinical cures of *vivax* malaria have been reported with dosages as low as 6 to 12 milligrams (base) daily for 4 days (23), and we

[2] American nonproprietary name, chlorguanide; British, proguanil.

(19) have found 1.5 to 3 milligrams per day slowly effective if continued for several days. On the other hand, 1.4 grams per day have been given for as long as 28 days without ill effects (24). Antimalarial action against *P. vivax*, however, is much slower than with other drugs (19, 25), 7 to 9 days being required to clear the blood of circulating parasites even when the drug is given at high dosage. Paludrine is not curative of *vivax* malaria; the interval to relapse is greater than that following treatment with quinine but less than that after treatment with either quinacrine or chloroquine. Paludrine has also been shown to be effective in relieving acute attacks of quartan malaria (26, 27).

Paludrine acts as a suppressant of all forms of malaria. In our own studies (19), under controlled conditions, patients received 0.3 gram (base) once weekly for either 6 or 12 months. This regimen gave complete suppression of *P. vivax* although acute malaria developed in all subjects after the drug was stopped. The interval from cessation of treatment to overt malaria was less in those who had received paludrine than in those of a comparable group who had received chloroquine. Field experiments in Panama (20) have shown that paludrine is suppressive of all three species.

The chief virtue of paludrine is its therapeutic and suppressive action against all forms of malaria at dosages far below those which produce toxic effects. Its chief disadvantages are the slowness of its action against *vivax* malaria and the reported variability of response to the drug by various strains of *P. falciparum*. In practice it does not appear to do anything that cannot be done as well, or even better, with chloroquine. Furthermore, accumulating examples of acquired resistance to the drug in the malarias of lower animals (28, 29, 30, 31) suggest that such resistance might become a problem if complete reliance were placed upon paludrine in the field.

PAMAQUINE

When it was realized, in 1944, that radical cure of *vivax* malaria did not result from the improvement of compounds whose main action was against erythrocytic parasites, the search for qualitatively different drugs led to a thorough re-examination of pamaquine (plasmochin), which had been described by earlier investigators (32, 33, 34) as having prophylactic or curative activity. Because of its toxicity, dosage regimens of pamaquine had been gradually reduced over the years until the amounts being given during 1941 through 1944 were inadequate to do more than clear persistent gametocytes of *P. falciparum*. Studies carried out during and following the recent war (19, 35, 36, 37, 38) confirmed the earlier demonstrations that pamaquine, when properly used, does have prophylactic and curative properties and that these actions are potentiated by quinine.

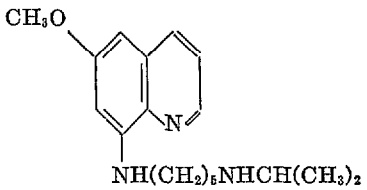
It seems reasonable to point out that, even under identical regimens of pamaquine plus quinine, one may encounter considerable variation in relapse rates. Early and heavy infections may require as much as 90 milligrams (base) of pamaquine daily for 2 weeks, given concurrently with quinine (36); this dosage may be seriously toxic. On the other hand, for light or late infections 30 milligrams (base) daily, plus quinine, suffices (35). Toxic reactions can be expected in any series of cases where the subjects are given effective dosages.

Analogues of pamaquine which have greater effectiveness and somewhat less toxicity are now available. As a consequence, pamaquine should be used only when the newer drugs cannot be obtained and where precautions can be taken to detect and treat the occasional hemolytic reactions which may occur.

PENTAQUINE AND ISOPENTAQUINE

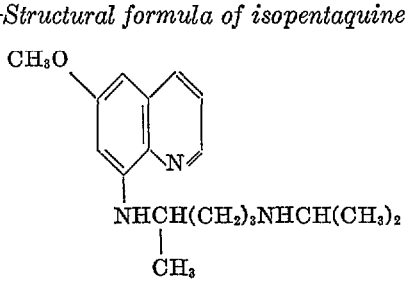
Since the toxicity of pamaquine so seriously limited its usefulness, a major portion of the American effort, from 1944 on, was directed toward finding related compounds which would exhibit a wider margin of safety. Several hundred pamaquine analogues were screened in lower animals and about 40 were tried in man. Two of these, pentaquine (SN 13,276), 8-(5-isopropylaminoamylamino)-6-methoxyquinoline (figure 3), and

FIGURE 3.—*Structural formula of pentaquine* (SN 13,276)



isopentaquine (SN 13,274), 8-(4-isopropylamino-1-methylbutylamino)-6-methoxy-quinoline (figure 4), have presented definite advantages (38, 39, 40, 41). In experimental *vivax* infections of a severity sufficient to present approximately 100 per cent relapse rates following quinine,

FIGURE 4.—*Structural formula of isopentaquine* SN 13,274)



quinacrine, chloroquine or paludrine, relapse rates were reduced to 26 per cent by pentaquine plus quinine and to 20 per cent by isopentaquine plus quinine. Dosages were 60 milligrams (base) of pentaquine or isopentaquine and 2.0 grams of quinine sulfate daily for 14 days. In natural *vivax* infections, relapse rates have been reduced to approximately 11.5 per cent (37) when this regimen of pentaquine plus quinine was continued for 10 days. In another series of infections, of several years' duration, the number of relapses has been reduced to practically zero (42), following a regimen of 30 milligrams (base) of pentaquine daily, plus quinine, for 14 days.

Alving (38), who has had wide experience with the 8-aminoquinolines in experimental *vivax* infections, considers isopentaquine superior to both pentaquine and pamaquine, its chief advantage being in the greater margin of safety between therapeutic and toxic dosages. Close medical supervision, however, is necessary with any of these 8-aminoquinolines, largely because of the occasional occurrence of acute intravascular hemolysis, which is more frequent in heavily pigmented races. Though such reactions are uncommon, they are dangerous and unpredictable. Their prompt recognition, however, by routine urine and blood examinations, with discontinuance of therapy permits their control.

The routine administration of pentaquine or isopentaquine plus quinine to cases of *vivax* malaria is not recommended. The chief value of these curative regimens would seem to be for stubbornly relapsing infections, particularly in individuals who have left malarious areas and are not longer subject to reinfection.

SUMMARY AND CONCLUSIONS

In view of the lack of complete information on the response of the different strains of malaria to drugs, dogmatic statements on the chemotherapy of malaria are unwarranted. But, as a corollary to the information presented in the discussion, it seems advisable to offer a few recommendations for the choice of drugs under various situations.

(1) For the routine therapy of acute attacks of malaria, chloroquine (SN 7618) is the drug of choice.

(2) For the critically ill or vomiting patient, intramuscularly administered quinacrine (atabrine) or chloroquine is indicated, followed by oral administration as soon as feasible.

(3) For the field suppression of malaria, weekly doses of chloroquine are recommended. Weekly doses of paludrine may prove equally efficacious.

(4) For the radical cure of relapsing *vivax* malaria, a regimen of pentaquine (SN 13,276) or isopentaquine (SN 13,274), plus concurrent quinine, offers the greatest chance of success.

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QUIMIOTERAPIA DEL PALUDISMO (*Sumario*)

La reciente guerra, que hizo llegar tropas a todas las regiones altamente palúdicas del mundo, dió gran impulso a la búsqueda de nuevas drogas antimaláricas. El mayor esfuerzo concentrado fué realizado en los Estados Unidos bajo la guía del Consejo de Coordinación sobre Estudios Palúdicos. El principal objetivo fué descubrir una droga de baja toxicidad, la cual poseyera también por lo menos una de las siguientes cualidades contra todo tipo de paludismo humano: Ser un profiláctico verdadero; un mejor agente terapéutico o supresivo que los ya existentes; o un verdadero agente curativo. Bajo este programa coordinado se investigaron más de 14,000 compuestos de varios tipos, ensayándolos en varias de las infecciones maláricas en aves. La farmacología y toxicología de muchos de los compuestos que mostraron alguna promesa, fueron estudiados en mamíferos inferiores y aproximadamente 100 fueron finalmente ensayados contra el paludismo humano. Los principales resultados prácticos de estas investigaciones fueron el desarrollo de regímenes racionales para el uso de la quinacrina, basados en su disposición fisiológica y actividad antimalárica; el desarrollo de la cloroquina, un agente terapéutico y supresivo de gran valor; y el desarrollo de los agentes curativos pentaquina e isopentaquina. El esfuerzo realizado en Inglaterra, aunque en menor escala, resultó en la síntesis y elucidación de la muy interesante droga, paludrina.

El objeto de este trabajo es el de presentar la utilidad general de los mejores agentes quimioterapéuticos, cuando se emplean para la supresión, alivio, o curación radical del paludismo humano. Para ser útil en general, una droga debe resultar eficaz contra el *Plasmodium falciparum*, y se sabe ahora que esta infección puede prevenirse por cualquiera de los antipalúdicos conocidos, y que puede curarse si se diagnostica precozmente. Existe poca información sobre la eficacia de estos agentes quimioterapéuticos nuevos contra el *Plasmodium malariae*, pero esto no debe ser motivo de gran preocupación debido a la baja prevalencia y distribución limitada de esta especie. El *Plasmodium vivax* por otra parte, crea un problema mayor, pues se encuentra distribuído en todo el mundo y ninguno de los agentes antipalúdicos aplicables en el campo, puede prevenir su establecimiento en el huésped humano, y solamente agentes apropiados para uso en los hospitales pueden impedir la marcada predilección de esta especie de producir recidivas. Como consecuencia de lo anterior, el énfasis principal de este trabajo será dirigido hacia el *P. vivax*.

Repasa el A. las características, posología, toxicidad, etc. de la quinacrina, cloroquina, paludrina, pamaquina, pentaquina, e isopentaquina, llegando a la conclusión de que en vista de la falta de una información completa sobre la respuesta de los diferentes plasmodios a estas drogas, no se puede aun hacer afirmaciones definitivas sobre la quimioterapia del paludismo y solamente pueden hacerse ciertas recomendaciones sobre la elección de una u otra droga, bajo situaciones diferentes: (1) Para la terapia corriente de casos agudos de paludismo, la cloroquina (SN 7618), es la droga de elección; (2) Para los casos gravemente enfermos o con vómitos, está indicada la administración por vía intramuscular de quinacrina (atebrina) o la cloroquina, seguida de su administración por vía oral tan pronto como sea posible; (3) Para la supresión del paludismo en el campo se recomiendan dosis semanales de cloroquina. Dosis semanales de paludrina pueden resultar igualmente eficaces; (4) Para la curación radical de las recaídas de paludismo producidas por *vivax*, la mayor probabilidad de éxito corresponde al uso de la pentaquina (SN 13276) o isopentaquina (SN 13274), conjuntamente con quinina.