

## CHAPTER XVIII

# Clinical Trials of Antimalarial Drugs

*Harry Most, M. D.*

Extensive military operations in various highly malarious regions during the Second World War stimulated intensive research in the chemotherapy of malaria. Interruption of the normal supplies of quinine from the Far East made it necessary, while conserving existing supplies, to reevaluate the efficiency of Atabrine (quinacrine hydrochloride) and other agents with known antimalarial properties and to widen the search for new drugs for the treatment, suppression, and possible cure of malaria.

Numerous investigations were carried out by civilian, military, and public health research groups under contract of the Office of Scientific Research and Development, Committee on Medical Research of the National Research Council, and integrated by the Board for the Coordination of Malarial Studies.<sup>1</sup> Approximately **15,000** compounds were studied, and the more promising were given detailed pharmacological and toxicological examination prior to testing in human beings. Important contributions to the knowledge of chemotherapy of malaria resulted from this comprehensive program. Quinacrine proved as good as quinine in most, and superior in some, aspects of treatment. New agents were found that proved superior both to quinacrine and quinine. In addition, other drugs which apparently produce definitive cure of malaria were later found.

The principal purpose of this chapter is to review briefly some of the clinical drug trials made during World War II in relation to their military application in the management of malaria. A note is added on some of these studies as continued, still under the auspices of the U.S. Army, and brought to significant conclusions in the immediate postwar period (p. **594**).

## PENICILLIN

The occurrence of acute attacks of malaria in military patients who were given large amounts of penicillin for surgical or other infections suggested very early in experience with this antibiotic that it would have no value in the treatment of malaria. Failures to terminate acute attacks with penicillin in amounts of **460,000** to several million units were reported. The im-

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<sup>1</sup> A Joint Body Composed of Representatives of the Office of Scientific Research and Development, the Army, the Navy, the U.S. Public Health Service, and the National Research Council, vols. I-VII. [Official record.]

from civilian studies that they were less toxic than quinine, particularly with respect to symptoms attributable to the special senses, and that these drugs singly or in combination, as in totaquine, should be approximately equivalent to quinine in antimalarial activity.

### Summary of Studies

Studies with cinchona alkaloids during the war were therefore of definite practical value. It was demonstrated that totaquine and its component alkaloids were as effective as quinine but more toxic, that the cinchona alkaloids were inferior to quinacrine in both suppression and termination of acute attacks of malaria, and that the loss of quinine was accordingly not a serious military problem. A rational method of assay of antimalarial properties of drugs was developed and the efficiency of the various cinchona alkaloids re-evaluated. No conclusive studies on the relative efficiency of parenteral quinine and quinacrine in the treatment of cerebral malaria were reported, and this problem still requires investigation before a final estimate can be made of the role quinine should play in the therapy of malaria.

### QUINACRINE HYDROCHLORIDE (ATABRINE) <sup>21</sup>

The extensive prewar literature dealing with the antimalarial properties and toxicity of quinacrine has been adequately reviewed.<sup>22</sup> Following the introduction of this drug in 1931, it became apparent that the originally advocated dosage schedule of 0.1 gm. three times daily for 5 days was in many cases, particularly in severe *falciparum* infections, inadequate for prompt and effective control of fever, symptoms, and parasitemia. There were numerous revisions in treatment plans, but there was no rational pharmacological basis for defining what dosage and treatment schedules were best for terminating acute attacks or for suppression. The relative efficiency of quinacrine versus quinine had not been established, and it was questionable whether we would be able to produce adequate amounts of effective antimalarial drugs. Numerous studies were conducted in many laboratories and hospitals in the various theaters. It is the purpose of this section to review briefly basic clinical and other observations that established quinacrine as a highly effective and satisfactory antimalarial during the war.

In 1941, American chemists succeeded in completely synthesizing quinacrine. Chemical, pharmacological, and clinical investigations sponsored by the National Research Council established the identity of the German and American drugs and found no appreciable difference between them as regards side reactions. Rumors that the American preparation was not identical with the German drug could be definitely dismissed. Finally, tremendously increased production assured an adequate supply at least for military use at first and later for civilian and lend-lease purposes.

<sup>21</sup> Formula : 3-Chloro-7-methoxy-9-(1-methyl-4-diethylamino-butylamino) acridine dihydrochloride.  
<sup>22</sup> See footnote 4 (7), p. 526.

### General Properties

Practical, highly sensitive, and accurate chemical methods for the estimation of quinacrine concentrations in the blood and tissues made it possible to study its physiological disposition in the human body.<sup>23</sup> It was shown that:

\*\*\*Atabrine is almost completely absorbed in the gastrointestinal tract and renal excretion accounts for very little of the daily dose. It may be concluded from these facts and the fact that its plasma concentration becomes stabilized after several days of drug administration at constant dosage, that it is disposed of by the body mainly by processes which result in its degradation. It follows, then, that the major factors which will relate drug administration and plasma drug concentration are those which condition the processes of distribution and degradation in the body.

\* \* \* It was found that the concentration of the drug in plasma, erythrocytes, and leukocytes is in the order of 1, to 1, to 100-200.

\*\*\* Studies \* \* \* in experimental animals indicated that the drug may achieve concentrations in the liver and spleen as high as 10,000-20,000 times those currently observed in the plasma. Localization in other tissues was found to be less extensive, but highly significant. An extension of these distribution studies to the human [subject] \*\*\* demonstrated that a major portion of the administered Atabrine is localized in the tissues of the body, leaving little in the plasma to exert a chemotherapeutic effect. It is in consequence of this that unless large initial doses of the drug are given the initial plasma drug concentrations are invariably low. However, the extensive localization, together with the low rates of degradation and renal excretion, lead to a low rate of decline of the plasma Atabrine concentration, and consequently a low rate of loss of the protection conferred by Atabrine, subsequent to the termination of drug administration.

It was apparent that a rational regimen of quinacrine therapy would have to be designed along the commonly accepted principles of chemotherapy; namely, the administration of sufficient drug when the diagnosis of malaria is made, or when exposure to malaria is anticipated, to obtain the desired plasma concentration, followed by the serial administration of small doses to maintain it.

The next step was to determine the plasma levels of quinacrine that would be effective in the prompt control of symptoms, fever, and parasitemia associated with acute attacks of *vivax* and *falciparum* infections. Infections with various strains of *P. vivax* and *P. falciparum*, transmitted by mosquitoes or introduced by blood, were established in volunteers and paretics, and different amounts of quinacrine in different treatment schedules were used to produce various plasma concentrations. It was found that if quinacrine concentrations of 30  $\mu\text{g}$ . per liter or more were maintained for 4 days in *vivax* infections there was complete termination of clinical activity and parasitemia. Levels between 10 and 30  $\mu\text{g}$ . per liter produced temporary or partial effects,

<sup>23</sup> (1) Brodie, B. B., and Udenfriend, S. : The Estimation of Atabrine in Biological Fluids and Tissues. *J. Biol. Chem.* 151 : 299-317, November 1943. (2) Mackie, Thomas T., Hunter, George W., III, and Worth, C. Brooke: *Manual of Tropical Medicine*. Philadelphia : W. B. Saunders Co., 1945, pp. 675-677. (3) Shannon, J. A., Earle, D. P., Jr., Brodie, B. B., Taggart, J. V., and Berliner, R. W. : The Pharmacological Basis for the Rational Use of Atabrine in the Treatment of Malaria. *J. Pharmacol. & Exper. Therap.* 81 : 307-330, August 1944.

and levels below 10  $\mu\text{g}$ . per liter produced little or no effect when maintained for 4 days. Infections with *P. falciparum* required approximately 50  $\mu\text{g}$ . per liter maintained for 6 days for termination of clinical activity and parasitemia.

With the treatment schedule for quinacrine commonly used before 1943 (0.1 gm. three times daily for 5 days), very low concentrations in the plasma were achieved during the first 2 or 3 days of therapy because of the extensive localization of the drug in tissues. If such dosage is continued for a period of days, the plasma levels will rise progressively, as more and more drug accumulates in the tissues, until ultimately they reach sufficient height to terminate the attack. The delay in the initial effect of quinacrine in such a dosage schedule had led to the belief that quinacrine therapy should be preceded by a 2- to 3-day course of quinine. Actually, such a course is undesirable because 24 hours or less after the last dose the plasma level of quinine is no longer effective. If parasitemia is still present, as it often is in cases so treated, there will be a reactivation of the disease during the next few days (of treatment with 0.1 gm. quinacrine three times a day) until the plasma quinacrine level in this schedule becomes effective.

If, on the other hand, total doses of 0.8 to 1.0 gm. of quinacrine are given orally during the first 24 hours of therapy, or by a combination of parenteral and oral routes, high effective plasma concentrations are quickly established and easily maintained by the serial administration of 0.1 gm. three times daily for 6 days. These considerations led to the adoption by the U.S. Army of a standard course of quinacrine therapy consisting of 2.8 gm. during 7 days (1.0 gm. the first 24 hours and 0.3 g.m. daily for 6 more days).<sup>24</sup>

### Clinical Use

In acute attacks.-Clinical experience in this country and overseas proved conclusively the efficiency of such a regimen in terminating acute attacks of malaria due to *P. vivax* and *P. falciparum*. It was found<sup>25</sup> that 2.8 gm. of quinacrine administered as recommended in Circular Letter No.153, Office of the Surgeon General, 19 August 1943, brought about cessation of fever within 22 hours in approximately 90 percent of cases of *vivax* malaria and in the remainder within 48 to 72 hours; approximately 80 percent of patients had negative smears within 48 hours and almost 100 percent at 96 hours. Relapses after treatment with quinacrine occurred in an average of 53 days, in contrast to 24 days and the many short-term relapses following treatment with quinine. In the treatment of acute attacks, there were no toxic manifestations similar to those induced by prolonged intensive treatment with quinine.

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<sup>24</sup> Circular Letter No. 153, Office of the Surgeon General, U.S. Army, 19 Aug. 1943, subject: The Drug Treatment of Malaria, Suppressives and Clinical.

<sup>25</sup> See footnote 15, p. 532.

In 291 patients, plasma levels were determined during and after 412 attacks of vivax malaria acquired in the South Pacific.<sup>26</sup> The average daily levels from the second to the eighth days of treatment with quinacrine were 41 to 52  $\mu\text{g}$ . per liter. The average increase in level 2 to 4 hours after a dose of 0.1 gm. on the second to seventh day was 6.8 to 11.3  $\mu\text{g}$ . per liter above the corresponding fasting level. The average level 4 weeks after completion of 2.8 gm. of quinacrine therapy was 8  $\mu\text{g}$ . per liter. It was found that this regimen produced plasma levels of 45  $\mu\text{g}$ . per liter within 24 hours after treatment was begun and that all symptoms and parasitemia were abolished within 72 hours in almost 100 percent of the patients. No correlation was observed between plasma levels and the occurrence or spacing of relapses.

The question arose whether plasma levels would be affected by such factors as jungle climate, fatigue, combat, and diarrhea. It was shown overseas that diarrhea or dysentery did not influence the pattern of the quinacrine plasma levels during therapy. In this country under simulated jungle conditions, and also overseas, it was shown that high temperatures, humidity, and fatigue did not adversely affect the absorption or stabilization of quinacrine in the plasma.

Quinacrine was found to be effective also in the treatment of delayed primary *vivax* malaria appearing after discontinuance of quinacrine suppression.<sup>27</sup> The continued use of this drug does not produce strains of parasites that are resistant to its action. It was noted that fever and sometimes parasitemia were not so promptly controlled in primary attacks as in relapses, although quinacrine was superior to quinine in both types of attack, and the rate of disappearance of parasites from the blood in a relapse was dependent on the degree of initial parasitemia rather than on the plasma level of quinacrine. This observation has no practical importance, however, since most patients are free of fever and symptoms before parasites have disappeared completely from the blood, and regardless of initial parasite density almost all patients have negative smears within 96 hours after the initiation of an adequate schedule of quinacrine therapy.

Attempts to enhance the response to treatment by increasing the initial or the total dose were made in several overseas installations. However, 2.8 gm. in 3 days, or 3.5 to 4.8 gm. in a week, proved no more effective in controlling the acute attack or affecting subsequent relapse rates than the standard schedule of 2.8 gm. in 7 days. In the control of relapses, short courses of treatment (1.2 gm. in 16 hours or 1.4 gm. in 12 to 16 hours) were effective in terminating acute attacks but, if not followed immediately by suppressive doses, might be succeeded by early relapse or in a malarious area by new infection because of the rapid fall of concentration in the plasma below protective levels. One-

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<sup>26</sup> Ellerbrook, L. D., Lippincott, S. W., Cateno, C. F., Gordon, H. H., and Marble, A. : Plasma Quinacrine Concentration in Treatment of Plasmodium Vivax Malaria Acquired in the South Pacific. Arch. Int. Med. 76 : 352-357, November-December 1945.

<sup>27</sup> London, I. M., Kane, C. A., Schroeder, E. F., and Most, H. : The Delayed Primary Attack of Virax Malaria. New England J. Med. 235 : 406-410, 19 Sept. 1946.

day treatment courses or less have only a slight advantage in insuring the administration of adequate amounts of drug in a short time, and little is gained in reduction of nursing care since patients with acute malaria are usually sick for several days. Moreover, unrecognized or severe *falciparum* infections may not be controlled with this amount of medication. A false sense of security may cause carelessness in observation of patients.

4 short course totaling 2.2 gm. in 3 days (1.0 gm. on the first day, then 0.6 gm. daily for 2 days) was found, in this country, as effective as 2.8 gm. in 7 days in terminating acute attacks of vivax malaria, with a similar spacing of the intervals to relapse. Many patients were symptom free in 3 days, and in some cases the period of hospitalization could be reduced. Relapse of previously treated *falciparum* infections, rarely seen in this country, would not constitute a hazard in 3-day treatment of vivax relapses here. Total doses in excess of 2.8 gm. or in periods of less than 7 days are not advocated except possibly in fulminating *falciparum* infections, since nothing is gained by excessive dosage and there is more risk of toxic reactions.

**In *falciparum* infections.**-The clinical studies discussed thus far have been concerned principally with *vivax* infections. It has been noted that experimentally induced *falciparum* infections were effectively controlled with quinacrine plasma levels in the range of 40 to 50  $\mu$ g. per liter. Plasma levels in that order are quite uniformly attained by initial doses of 1.0 gm. of quinacrine administered during the first day of treatment by the oral or combined oral and parenteral routes. It was to be expected, then, that standard quinacrine treatment would prove effective in the control of the majority of infections with *P. falciparum*.

In a report from India<sup>28</sup> summarizing the treatment of over 5,000 cases of malaria of which more than two-thirds were due to *P. falciparum*, it was stated that quinacrine was as effective as quinine in terminating them. This is of particular significance since early in that theater's experience the dosage of quinacrine was 0.1 gm. three times a day for 5 to 7 days. Undoubtedly, higher doses on the first day would have produced even more satisfactory results. In fact, 50 patients so treated responded promptly and were afebrile by the third day.

By contrast, patients treated with quinine for the first 2 days had a reactivation of fever on the third day when quinine was discontinued. It was stated that in this study the patients treated with quinacrine remained febrile a little longer than those treated initially with quinine, but the former had considerably less nausea and vomiting and no tinnitus or deafness. Treatment with quinine was associated with the development of blackwater fever in two patients. One patient developed a fatal diffuse bullous erythema after 1.95 gm. of quinine and another developed an extensive dermatitis after 15 gm.

Extensive experience in West Africa and in various Pacific islands where the majority of initial attacks of malaria were due to *P. falciparum* demonstrated the efficiency of standard quinacrine therapy in terminating uncomplicated attacks. In general, its value in the more severe forms of malaria is attested by the remarkably low death rate from this disease during the war in conjunction with the widespread use of quinacrine. Fulminating cerebral malaria was fortunately not common in most theaters.

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<sup>28</sup>Ware, R. E., Brem, T. R., and Crane, N. F.: Experiences With Malaria in India. [Official record.]

In India, of over 6,000 cases of malaria in native or foreign troops there were 140 cases of the cerebral form, or an incidence of about 2 percent of *falciparum* infections.<sup>29</sup> The death rate in American troops with cerebral malaria was 5 percent and in Chinese and other personnel, 33 percent. Quinacrine alone was said to have cured several cases. In another report,<sup>30</sup> it was stated that 1 death occurred in 8 patients with cerebral malaria treated with quinacrine intramuscularly, and 31 deaths occurred in 61 patients treated with quinine parenterally. In the latter group, eight patients had convulsions and died shortly after intravenous injection of quinine. Of five additional patients treated with a single infusion of quinacrine (0.8 to 1.0 gm.) for cerebral malaria, one died; this patient had also received more than 1.0 gm. of quinine intravenously.<sup>31</sup> In the four patients who recovered, parasitemia was controlled within 48 hours. The serum quinacrine levels 24 hours after the infusion was given varied from 100 to 320  $\mu\text{g}$ . per liter. The mortality for cerebral malaria in a series of 146 patients in the Southwest Pacific treated with quinine parenterally was 37 percent and was 21 percent for 19 patients treated with quinacrine.

Parenteral quinacrine treatment thus gave definite evidence of effectiveness in some cases of cerebral malaria. No comparative studies in sufficient numbers were reported on which to base definite conclusions with regard to the relative efficiency of quinacrine and quinine in severe cases with cerebral involvement. The surgeon in the India-Burma theater stated:

My conclusions as to the relative merits of parenteral quinine and Atabrine (in cerebral malaria) are that I am not certain that either possesses a distinct advantage over the other. Atabrine may have a slight advantage in that (1) it is probably less toxic, (2) its effect persists longer, and (3) it can be given intramuscularly. 911 data we possess indicate that when given in adequate amounts, it is at least as effective as quinine, and may be more effective. Moreover, if a rapid and prolonged effect is desired 0.8 gm. in a slow intravenous drip (over 4 hours) clears the blood of parasites as rapidly as any other method and a parasitocidal concentration remains in the blood for at least 5 days.<sup>32</sup>

Intramuscular injections of quinacrine were found useful in *vivax* and *falciparum* infections with severe vomiting as a means of attaining high plasma levels promptly. For example, single doses of 0.4 gm. given intramuscularly result in levels of 168, 327, 297, 155, 89, 60, 45, 37, and 20  $\mu\text{g}$ . per liter at 5, 15, 30, 60 minutes and 2, 3, 5, 8, and 24 hours, respectively, after injection. Serial injections of 0.2 gm. at intervals of 4 to 8 hours for 24 hours or more can be expected to maintain high effective levels until oral medication can be instituted.

Following a single intramuscular dose of 0.2 gm. of quinacrine, it was shown<sup>33</sup> that the number of motile parasites with finely dispersed pigment was reduced and the number of nonmotile parasites with clumped pigment was increased. Three hours after the injection when the plasma level of

<sup>29</sup> Fitz-Hugh, T., Jr., Pepper, D. S., and Hopkins, H. U. : The Cerebral Form of Malaria. Bull. U.S. Army M. Dept. No. 83, pp. 39-48, December 1944.

<sup>30</sup> See footnote 17, p. 535.

<sup>31</sup> Blumgart, Hcrman L., and Pike, George M. : History of Internal Medicine in India-Burma Theater. [Official record.]

<sup>32</sup> See footnote 17, p. 535.

<sup>33</sup> Trager, W., Bang, F. B., and Hairston, N. G. : Relation of Plasma Level of Atabrine to Morphology and Motility of Plasmodium Vivax. Proc. Soc. Exper. Biol. & Med. 60 : 257-258, November 1945.

quinacrine was falling rapidly the ratio of motile to nonmotile parasites returned to normal, and since the total parasite count did not change it was suggested the parasites had recovered after temporary damage. Similar changes during the first 3 hours after quinine at levels of 6 to 10 mg. per liter were noted. These observations emphasize the necessity for the continued serial administration of antimalarial agents in sufficient amounts and at properly spaced intervals so that adequate levels would be maintained sufficiently long to terminate clinical activity and parasitemia.

The value of single intravenous infusions of quinacrine in *falciparum* infections was studied at the 20th General Hospital.

Doses of 0.4 gm., 0.6 gm., and 0.8 gm. in 1,000 cc. of fluid were given intravenously to groups of 10 patients on each dosage schedule, and 1.0 gm. in a single infusion was given to each of 20 patients. The acute attack was terminated in all but one patient (given 0.4 gm.) without further treatment. The duration of fever in the various groups was 8 to 64 hours (average 27.2 hours) and smears became negative in from 1 to 3 days (average 2.2 days). Of the 30 patients treated with 0.8 or 1.0 gm., 19 were observed for a month or more after treatment and 4 relapsed within 3 to 5 weeks. Of the 20 patients who received 0.4 or 0.6 gm., 9 were followed for a month or more and 8 of the 9 relapsed within 10 to 23 days after termination of the attack by intravenous quinacrine. Three patients had brief periods of vomiting shortly after the infusion; one patient had a generalized convulsion; a fifth patient developed an acute state of exhilaration and excitement lasting 5 hours. Two patients with moderately severe cerebral malaria treated with 1.0 gm. of quinacrine intravenously responded well, being out of stupor in 18 hours. Twenty control patients treated for acute attacks of *falciparum* malaria with quinacrine by mouth all responded well although parasitemia and fever persisted in them a little longer than in the groups treated intravenously. In a comparison of the relative efficiency of single intravenous doses of quinine and quinacrine, it was reported that of 10 patients treated for acute *falciparum* malaria with 1.2 gm. of quinine in an infusion of 1,000 cc., the attack was terminated in only 5. The remainder continued to have high fever for 60 to 132 hours after treatment and required additional therapy. Three relapses occurred in the successfully treated group 6, 9, and 13 days, respectively, after infusion. Three patients who received single doses of 2.0 gm. of quinine in an infusion developed signs and symptoms of shock. It should be pointed out that these doses of quinine (1.2 and 2.0 gm.) are in the toxic range for this drug and are rarely if ever resorted to therapeutically. Further, a comparison of single doses of quinine and quinacrine does not take into account the rapid excretion of quinine. A more practical estimation would have been the serial administration of nontoxic amounts of quinine intravenously.

From these observations, it is apparent that although quinacrine given intravenously effectively terminates attacks of *falciparum* malaria such a procedure is not without danger and has little advantage over oral treatment in most cases. In cerebral malaria, comparably high effective plasma levels may be reached as quickly by serial intramuscular injections without the dangers inherent in intravenous therapy. Relapses, which occurred at short intervals after single doses of 0.8 or 1.0 gm. of quinacrine injected intravenously, are very common in *falciparum* infections after 2.8 gm. given in 7 days by mouth. Finally, the prompt response from intravenous quinacrine reported in Chinese patients with a high degree of immunity may not be

duplicated in nonimmune white American troops. The question of parenteral quinacrine versus quinine therapy remained unsettled.

**In suppression.**—The dosage of quinacrine for suppressive purposes recommended before World War II was based on evidence derived from malaria rates in various parts of the world, populated, for the most part, by immune natives. Daily doses of 0.05 gm. of quinacrine were considered inferior to a daily dose of quinine, but 0.4 gm. of quinacrine weekly in two divided doses was considered more effective than daily doses of quinine in suppressing clinical malaria.<sup>34</sup> Although numerous reports indicated varying success in the suppression of malaria with this divided dose of quinacrine, it was not known when we entered the war how effective such a schedule would be in nonimmune troops in highly malarious zones and under combat conditions.

Studies of the course of plasma levels resulting from 0.4 gm. and 0.6 gm. of quinacrine weekly as well as from larger amounts were conducted in England on volunteers, and in the United States on medical students<sup>35</sup> and at a military installation. Of 230 white soldiers observed in active training at Fort Knox, Ky., 100 men received 0.4 gm. of quinacrine weekly and another 100 received 0.6 gm. weekly. Thirty volunteers subjected to conditions simulating jungle climate were given 1.2 gm. during the first week and 0.6 gm. weekly for the next 11 weeks. It was shown that, with constant regimens, the plasma concentrations differed widely in individuals but that the group plasma level at any time was a function of the daily dose, the preexisting level, and the interval since the last dose. The group mean level rose progressively for 4 to 8 weeks to reach an equilibrium, which then remained substantially constant. The equilibrium level for the group given 0.4 gm. weekly was 1.2  $\mu$ g. per liter, and was 1.7 for the group on 0.6 gm. weekly. It was shown that a hot, humid environment did not influence the group equilibrium level and that suppressive therapy under such environmental conditions did not affect the rate of acclimatization and performance of the men. The time for reaching equilibrium levels could be reduced from 5 to 6 weeks to 1 week by administering high initial doses for a short period (0.2 gm. daily for 5 to 6 successive days). Similar results and conclusions were reported from studies in England and civilian installations in the United States.

It was obvious that such plasma levels would give little or no protection during the first 4 to 6 weeks, or until maximum equilibrium was attained with these doses. Furthermore, marked variations in individual levels meant that the smaller weekly dosage (0.4 mg.) would frequently fail to protect significant numbers of men, especially if occasional doses were omitted. It was clearly necessary to give a large initial or priming dose before or when troops entered malarious zones in order to give immediate protection and

<sup>34</sup> The Treatment of Malaria ; Study of Synthetic Drugs, as Compared With Quinine, in the Therapeutics and Prophylaxis of Malaria. Fourth General Report of the Malaria Commission, League of Nations, Bull. Health Organ. 6: 895, December 1937.

<sup>35</sup> Minutes, Subcommittee on the Coordination of Malarial Studies, 3 June 1943, National Research Council. Bulletin on Malaria Research, pp. 99-105.

prevent clinical "breakthroughs." These data were collected during the early months of 1943. Shortly thereafter, these conclusions were translated in terms of the specific recommendations for suppression of malaria contained in Circular Letter No. 153 (p. 540).

In the meantime, numerous reports from overseas had been received which documented the development of the clinical disease in large numbers of troops shortly after their arrival in malarious areas and clearly demonstrated the value of priming doses and the superiority of from 0.6 to 0.7 gm. quinacrine weekly over 0.4 gm. for suppression. Valuable information was obtained on "breakthroughs" during suppression with 0.4 and 0.6 gm. weekly and the relation of such failures to plasma levels and quinacrine discipline. Brief reference to a few field experiences to elucidate some of the factors associated with poor and successful suppression follows.

The Americal Division, which was on New Caledonia from March to October 1942, was moved to Guadalcanal during October, November, and December, where it remained until March 1943.<sup>36</sup> The men were forced to live and fight in hypermalarious areas with little to no field control and no mosquito repellent. Quinacrine, 0.4 gm. weekly, was prescribed but the extent of its use was not known. The malaria rates on Guadalcanal were as high as 2,500 per 1,000 per annum. The ratio of *falciparum* to *vivax* infections was 3 to 1. Following removal of these troops to the Fiji Islands and mass treatment ending on 10 June 1943, the rates in August and October were still 4,220 and 2,948 per 1,000 per annum, respectively. In September, 613 men were placed on suppressive doses of quinacrine of 0.4 to 0.6 gm. per week. The malaria rate in this group fell from 219 per 1,000 per month to 23. In November, the Division was placed on 0.4 gm. weekly and this dosage was increased to 0.6 gm. on 12 December. The malaria rate fell from 2,948 per 1,000 per annum to 80 and after 2 months' combat in Bougainville the rate in March 1944 was only 97.1. The experience in this division showed that early suppressive doses of 0.4 gm. weekly were inadequate to control malaria in combat although a moderate degree of satisfactory suppression was obtained in a nonmalarious area under fairly good disciplinary conditions. On the other hand, 0.6 gm. of quinacrine proved highly effective both in malarious areas and in regions free from malaria (chart 29). Another example was the 43d Division, which had also been on 0.4 gm. weekly with a high incidence of malaria. Half the division was taken off suppression and had a malaria rate of 2,000 per 1,000 per annum. The other half was placed on 0.6 gm. weekly and their rate fell to 236 per 1,000 per annum. Again, a naval construction battalion of 840 men, on a suppressive regimen of 0.4 gm. weekly, arrived on Guadalcanal on 12 December 1942.<sup>37</sup> During the first 5 weeks, 123 men were down with malaria, about 95 percent of which was due to *P. falciparum*. In the same report it was stated that two combat infantry outfits on 0.4 gm. weekly entered a highly malarious area and within 2 weeks malaria was occurring at the rate of 40 to 60 cases a day, most of them caused by *P. falciparum*.

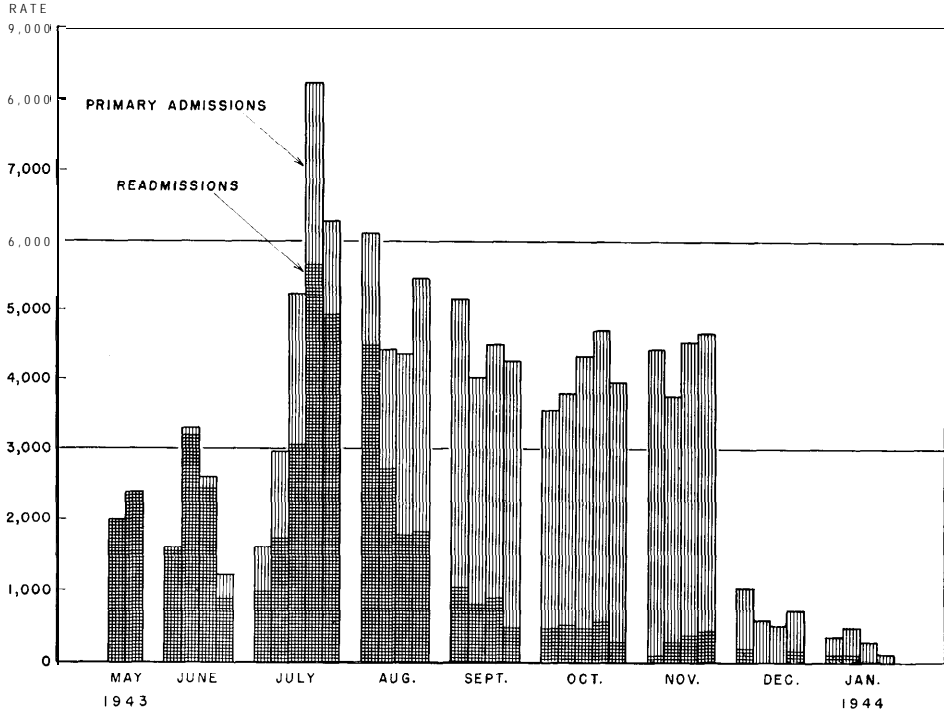
Although the great majority of initial infections in the Pacific islands were caused by *P. falciparum*, subsequent relapses were principally caused by *P. vivax*. When adequate amounts of quinacrine were used in termination of the attack of *falciparum* malaria and when suppressive medication of 0.1

<sup>36</sup>Essential Technical Medical Data, South Pacific Area, for April 1944.

<sup>37</sup>Lewis, R. A.: The Suppression of Malaria. [Official record.]

**CHART 29.**—*Malaria rates in an infantry regiment under various schedules of suppression with quinacrine hydrochloride, by week*

[Rate expressed as number of attacks per annum per 1,000 average strength]



gm. daily was continued, *falciparum* malaria rarely occurred on discontinuance of suppression.

In the Australian studies that have been referred to,<sup>38</sup> it was conclusively shown in volunteers infected with *P. falciparum* (New Guinea strain) transmitted by mosquitoes that, if 0.1 gm. of quinacrine were administered during the period of infection and for 23 days after the last infective bite, clinical malaria did not occur during suppression or after its termination. Actual cure was demonstrated by subinoculation of 200 cc. of blood into other volunteers. If subinoculation was done on the 9th to 11th days after infection, malaria developed in the recipients, indicating that quinacrine was not a causal prophylactic but effected a cure by permanently destroying the erythrocytic parasites after their appearance in the blood. Similar studies in England and in this country with other strains of *P. falciparum* also demonstrated the curative action of quinacrine suppression in such infections. In the Australian experiments along the same lines with *P. vivax*, there was shown complete clinical suppression during therapy but no curative effect, for all the volunteers developed *vivax* malaria at varying intervals after quinacrine was discontinued.

The practical inferences from these observations were that effective plasma equilibrium having been established, quinacrine administered *in doses*

<sup>38</sup>See footnote 12, p.529.

of 0.1 gm. daily without interruption would effectively suppress both *falciparum* and *vivax* malaria and that, if suppression were continued for about 3 weeks in troops leaving the malarious area, *falciparum* malaria would not develop. *Vivax* relapses would occur later and could be effectively terminated with quinacrine or delayed indefinitely if necessary by continued suppression. These results were seen in many studies overseas and in this country.

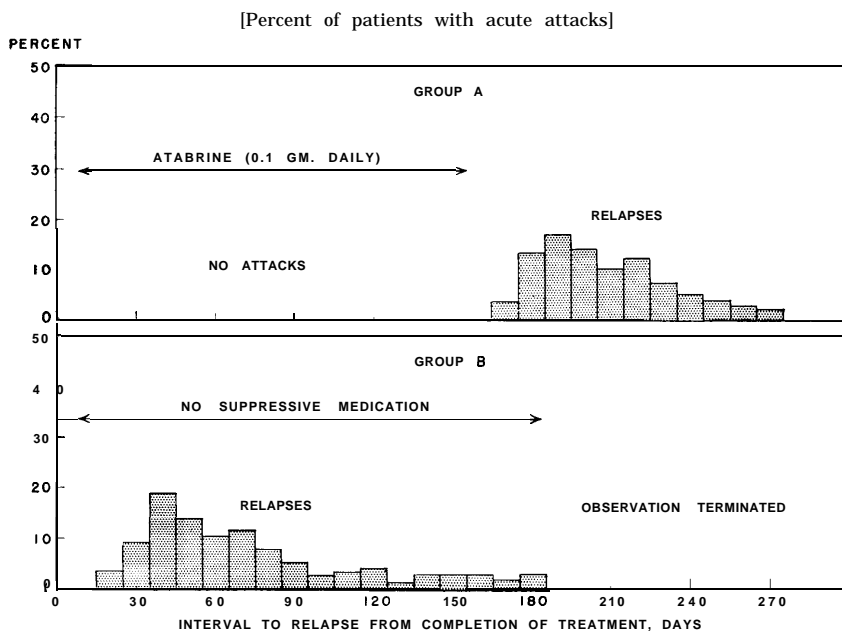
In one experiment, for example, 107 volunteers were taken to a highly malarious area in New Guinea where they were exposed to infection for 44 days. Initial priming doses were followed by 0.1 gm. of quinacrine daily administered 6 days a week during the period of exposure and for 10 days thereafter. No case of malaria developed during the period of suppression, whereas of 44 men who acted as controls and received no medication, 32 developed malaria (in 9 caused by *P. falciparum*). Subsequent to the discontinuance of suppressive therapy 25 cases of malaria due to *P. vivax* developed. No case of malaria caused by *P. falciparum* developed in the group receiving quinacrine either during or after suppressive treatment. This field study showed definitely the value of quinacrine in absolutely preventing clinical malaria due to *P. vivax* and *P. falciparum* during adequate suppression and the curative as well as suppressive action of quinacrine in *falciparum* infections.

In general, the plan of suppression with doses of 0.1 gm. daily was widely used with excellent results. In one oversea area, it was suggested that troops on patrol or in combat may fail to take occasional doses. Studies with single doses of 0.4 or 0.5 gm. twice a week carried out in the field showed that such a schedule would provide adequate protection and insure affective levels all the time.<sup>39</sup> This modified plan was not generally adopted but could be used under circumstances precluding regular daily suppressive medication.

By continuing quinacrine therapy for suppression following termination of acute attacks of *vivax* infections, it was possible to maintain effective fighting strength in combat units highly seeded with malaria. In this country, continued suppression for 3 months or more reduced the number of hospital admissions for relapses without interrupting training or rehabilitation programs. At one hospital in the United States, for example, 79 men treated with 2.8 gm. of quinacrine in 7 days for acute attacks of *vivax* malaria of Pacific origin were maintained on 0.1 gm. daily for 150 days after termination of the acute attack. No parasitemia or clinical attack occurred during the 5 months of suppression. In a similar sized group, also treated for acute attacks but not subsequently placed on suppressive therapy, 80 percent relapsed during the first 120 days' observation after treatment. The group given effective protection during 5 months by continued therapy was not thereby protected against subsequent relapse, for 82 percent relapsed during the 120-day period of observation after discontinuance of suppression (chart 30).

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<sup>39</sup> Duncan, G. G.: Quinacrine Hydrochloride as a Malaria-Suppressive Agent for Combat Troops. War Med. 8 :305-318, November-December 1945.

CHART 30.—*Distribution of relapses in two groups of patients after treatment for acute attacks of vivax malaria of Pacific origin*

The subject of "breakthroughs" or clinical attacks during suppression received attention at many oversea installations. In India, six patients supposedly taking 0.1 gm. of quinacrine a day were admitted to the 20th General Hospital and found to have plasma levels of 6, 7, 8, 12, 12, and 14  $\mu\text{g}$ . per liter, respectively. In every case, it was possible to show that the individual was able to absorb quinacrine normally, the reason for the low levels being failure to take the prescribed dose daily. In the Southwest Pacific, 80 percent of 116 men who had attacks while on suppression were found to have levels of less than 10, whereas only 25 percent of another group of 853 men had similarly low levels. Seventy-five officers having attacks while supposedly taking 0.1 gm. quinacrine daily were found to have low plasma levels and admitted not taking the drug regularly. On the other hand, four men with acute attacks were found to have levels of from 16 to 30  $\mu\text{g}$ . per liter when admitted. It is possible that self-administered medication for beginning symptoms may account for apparently adequate levels in some "breakthroughs." In a division in the Southwest Pacific, the average level for 1,021 men on suppression for a year or more was 13  $\mu\text{g}$ . per liter and varied from an average of 5 in men who "broke through" to an average of over 20 in companies with good discipline.<sup>40</sup>

<sup>40</sup>Schaffer, A. J., and Lewis, R. A. : Atabrine Studies in the Field. I. Relation of Serum Atabrine Level to Breakthrough of Previously Contracted Vivax Malaria. Bull. Johns Hopkins Hosp. 78 : 265-281, May 1946.

## Toxicity

*Effects of prolonged administration*

Toxic reactions, principally related to the gastrointestinal tract and nervous system, associated with the ingestion of quinacrine or its parenteral use had been reported before World War II. In an analysis of toxic reactions observed in 49,681 patients to whom quinacrine had been administered before 1941, it was concluded that neurogenic symptoms (headache, mental depression, delirium, psychoses, convulsions) occurred rarely (less than 1 per 1,000) and that gastrointestinal symptoms (nausea, vomiting, diarrhea) were uncommon and of little significance and were frequently related to the concomitant administration of other drugs. More serious reactions were poorly documented and could not be unequivocally related to quinacrine.

Following our entry into the war and the extensive use of quinacrine over prolonged periods for suppression and frequently for termination of acute attacks with larger amounts of drug than were previously used for either purpose, great interest was stimulated in the potential acute or chronic toxic effects of such medication. No attempt will be made in this section to review the voluminous studies made with various experimental animals. Brief reference will be made to observations on the effects of quinacrine not previously reported or to findings that were of significance during World War II.

Liver and kidneys.-Studies of hippuric acid synthesis, serum phosphatase, urea clearance, and liver biopsies (10 cases) performed on 101 men who had been on suppression from 8 to 36 months revealed no abnormalities. Similar negative findings resulted from detailed examinations of liver and kidney function of 43 Oxford University undergraduates who took 0.1 gm. of quinacrine daily over a period of 9 to 12 months.

Studies to discover subclinical hepatic damage in white and Negro American troops who had been taking 0.6 gm. quinacrine weekly for 18 to 24 months were done on various groups of 50 men. The icteric index, urinary urobilinogen, sulfobromophthalein excretion, fibrinogen, galactose tolerance, and cephalin-cholesterol flocculation tests failed to detect any evidence of subclinical hepatic dysfunction.<sup>41</sup> On the other hand, there were a few reports of varying degrees of liver disease believed related to quinacrine ingestion.

Four cases of hepatic dysfunction (two subclinical and two severe hepatitis, one of which ended fatally) believed related to quinacrine were reported from an overseas theater. An interesting feature in these cases was the association of corneal edema, manifested by blurred vision. In three of the patients corneal edema became less marked after discontinuance of quinacrine and was aggravated by its readministration. Impaired liver function did not become apparent until 3 to 6 months after the initial episode of visual disturbance. The observers of these patients felt that corneal edema and

<sup>41</sup>Gottfried, S. P., and Levine, A. C.: Liver Function Studies on Soldiers Under Prolonged Atribrine Administration. *J. Lab. & Clin. Med.* 30: 853-855, October 1945.

punctate erosions of the surface epithelium were due to quinacrine, that this was a rare manifestation of quinacrine toxicity, and that its occurrence may be followed by liver disease.

In a large series of Chinese patients receiving quinacrine for suppression or treatment of malaria there were 5 with severe hepatitis and exfoliative dermatitis, 3 of whom died of this complication (incidence 1 in 2,000-3,000 Chinese).<sup>42</sup> The rash present in each case appeared as early as the 2d day and as late as the 10th day of medication and consisted of a scarlatiniform, maculopapular, dry, scaling eruption beginning on the face and involving the entire body. Conjunctivitis and exfoliation of the tongue were observed. Jaundice, which appeared several days after the rash, was accompanied by a high ("septic") fever, leukocytosis, proteinuria, and bilirubinuria. The liver was large and tender at first but shrank rapidly. Mental clouding was prominent and death followed in coma in the third to fifth week of the disease. At autopsy there was gross and microscopic evidence of severe hepatitis or necrosis of the liver. It was concluded that quinacrine in previously sensitized individuals was responsible for both the hepatitis and the severe dermatitis.

**Aplastic anemia.**-A small number of cases of aplastic anemia with and without atypical lichen planus had been reported from the Pacific area, and this was thought to be possibly ascribable to quinacrine. In an attempt to determine whether prolonged use of quinacrine was responsible for the production of pathological changes in the body, the Army Institute of Pathology (now the Armed Forces Institute of Pathology), Washington, D.C., instructed laboratory officers to furnish data of quinacrine ingestion with all autopsy protocols, regardless of the cause of death. For some time, nothing of significance was observed. Later, it became apparent that aplastic anemia was the cause of death in a disproportionately large number of cases represented by autopsy material sent from the South and Southwest Pacific Areas where an extensive regimen of quinacrine suppression was in force. Fifty-seven cases of aplastic anemia were the basis of a report<sup>43</sup> on the possible relation of this disease and quinacrine. The incidence of aplastic anemia per **100,000** men varied little (**0.1** to **0.3**) from **1942** to **1945** in the continental United States and all foreign theaters, exclusive of the South and Southwest Pacific Areas and the China-Burma-India theater, where it rose from zero in **1942** to a peak of 2.84 per 100,000 during the last 6 months of 1944. Quinacrine was the common drug in at least **47** cases, 9 others being excluded because of the possible role of arsenic, irradiation, or sulfonamides in the production of the aplastic state. In the group treated principally with quinacrine, the drug had been taken for a period of from 1 to 34 months; in the majority, from **4** to 9 months. Large doses were specifically reported in six cases. Four patients had increased the daily dose to 0.2 gm. for a period of from 3 weeks to 8 months; one patient took 20 to 30 tablets during 4 days before onset of symptoms and another was said to have ingested "massive doses" for 3 weeks before he became sick. Hepatitis was present in 10 cases

<sup>42</sup> Agress, C. M.: Atabrine as a Cause of Fatal Exfoliative Dermatitis and Hepatitis. J.A.M.A. 131: 14-21, 4 May 1946.

<sup>43</sup> Custer, R. P.: Aplastic Anemia in Soldiers Treated With Atabrine (Quinacrine). Am. J.M. SC. 212: 211-224, August 1946.

and the "quinacrine dermatitis complex" in 25. The liver lesions in five cases were indistinguishable from epidemic hepatitis. Cerebral hemorrhage was the immediate cause of death in 10 cases. The bone marrow in all cases was badly depleted of normal hematopoietic elements? often almost totally so without evidence of extramedullary hematopoiesis. Occasionally, the influx of lymphocytes, plasmocytes, and histiocytes attained such proportions that at first glance the fundamental hypoplastic state was not apparent. One man who received 65 transfusions and lived 10 months had extensive secondary fibrosis of the marrow cavity. Clinically, the onset was gradual in most cases, and purpuric manifestations were commonly seen early. In many cases, the red blood cell count could be maintained at fairly good levels by repeated transfusions, but the white cells and platelets remained uniformly depressed. In 20 cases, the "quinacrine dermatitis complex" preceded the anemia. Although this form of possible quinacrine toxicity has proved fatal in the great majority of cases, recovery has been reported.<sup>44</sup>

**Asymptomatic changes in the skin.**—Changes in the skin and mucous membranes resulting from the prolonged administration of quinacrine were the subject of numerous reports. They varied from asymptomatic pigmentary changes to severe and disabling forms of dermatitis.

The yellow discoloration of the skin associated with quinacrine ingestion was a common finding in the majority of men on prolonged suppression. The intensity of the discoloration, which is not a toxic manifestation of drug ingestion but rather an expression of its deposition in the skin, varied with duration and dosage of suppression, exposure to sunlight, and complexion, being most marked in subjects with dark skin and hair.

Attempts were made to correlate the degree of fluorescence produced by quinacrine in the skin and plasma levels with the use of a dermofluorometer. A high degree of correlation of induced palmar skin fluorescence with mean plasma levels was found in 33 volunteers on 0.2 gm. daily for 1 week and 0.1 gm. daily for 3 weeks. The peak of fluorescence in the skin was reached in 4 to 5 weeks after initial dosage and decreased slowly over a 12-week period after the drug was discontinued. It was believed that this instrument might be useful in the field in determining whether quinacrine suppression discipline was effective.

Quinacrine discoloration of the sclera, as observed in a small number of individuals, was described <sup>45</sup> as consisting of yellowish pigmentation, most marked around the limbus in the part of the sclera exposed in the palpebral fissure, and fading toward the fornices. On the other hand, in jaundice, the pigmentation is most marked in the fornices toward the equator of the globe and fading toward the limbus.

Ochronosis-like pigmentation of mucous membranes, skin, and cartilage was described in many individuals on quinacrine suppression. In a dental

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<sup>44</sup> Most, H., and Hayman, J. M., Jr. : Recovery From Severe Hypoplastic Anemia Associated With Atypical Lichen Planus. Bull. U.S. Army M. Dept. 5 : 339-342, March 1946.

<sup>45</sup> Hayman, J. M., Jr. : Atabrine Pigmentation of the Sclera. Bull. U.S. Army M. Dept. No. 82, pp. 120-121, November 1944.

survey of 1,000 men in the Philippine Islands, 300 showed bluish-purple pigmentation of the hard palate. The color varied from a light blue purple to intense blue black involving from 1 cm. to the entire palate.<sup>46</sup> In another report,<sup>47</sup> the incidence in 500 men in the Southwest Pacific Area was 31 percent. The majority of the men with pigmentation of the palate had been on quinnocrine suppression for at least 7 months. The nature of the pigment based on staining reactions of biopsy sections was considered to be hemosiderin. A detailed study of a small number of patients showed the ochronosis-like pigment to be distributed in the skin, hard palate, nail beds, the cartilages of the nose, ears, epiglottis, and trachea, the conjunctivae and corneoscleral limbus. Phenol and alkaptonuria were excluded as causative factors. Surveys at Harmon General Hospital, Longview, Tex., and Moore General Hospital, Swannanoa, N.C., likewise demonstrated an incidence of 15 to 30 percent of asymptomatic pigmentation as described above in patients who had been on prolonged quinacrine suppression overseas.

Atabrine dermatitis complex.—More significant changes in the skin were reported from overseas as causing disability and frequently serious prolonged illness. For security reasons and in order to maintain the morale of quinacrine suppression, the data accumulated were not made generally available at first. It was necessary in the beginning to collect information on the incidence of these reactions and to evaluate fully the relation of quinacrine to them. The possibility of substituting another suppressive agent for quinacrine had to be considered if this cutaneous complex proved to be widespread or if unfounded rumors as to its incidence and severity threatened a breakdown in discipline. Fortunately, this did not occur nor was it found that the incidence of the Atabrine dermatitis complex was very great. The following paragraphs from a report entitled "Evaluation of the Untoward Reactions Attributable to Atabrine" prepared by the Medical Consultants Division of the Surgeon General's Office<sup>48</sup> summarize the vast amount of clinical and other data collected overseas and in this country:

Medical officers in the Southwest Pacific Area called attention, in the latter part of 1943, to a characteristic cutaneous syndrome which was occurring in soldiers who had been evacuated from New Guinea and adjacent islands. Lt. Col. Charles L. Schmitt, MC, and Maj. (later Lt. Col.) Thomas W. Nisbet, MC, dermatologists stationed with general hospitals in that area, were the first to submit to The Surgeon General official reports in which they described the disease and its probable etiology. Later, similar cases were reported from all other theaters where suppressive atabrine medication was in general use as a control measure for malaria. This syndrome has been observed most frequently in New Guinea and adjacent islands and in Assam and northern Burma; in other areas only small numbers of cases have occurred.

<sup>46</sup> Summer, S. : An Oral Manifestation of the Use of Atabrine. [Official record.]

<sup>47</sup> Lippard, V. W., and Kauer, G. L., Jr. : Pigmentation of the Palate and Subungual Tissues Associated With Suppressing Quinacrine Hydrochloride Therapy. *Am. J. Trop. Med.* 25 : 469-471, November 1945.

<sup>48</sup> Evaluation of the Untoward Reactions Attributable to Atabrine. *Bull. U.S. Army M. Dept.* 4 : 653-659, December 1945.

This skin disease which has acquired the name atypical lichen planus is characterized by various \* \* \* types of lesions. \* \* \* Almost all patients have both violaceous, hypertrophic lichenoid plaques and some form of cutaneous eczematoid reaction. During the course of the disease, a considerable number of these patients have acute, "explosive" generalized exacerbations, manifested by oozing eczematoid dermatitis having a predilection for the flexors, groins, axillae, extremities, and neck. Such exacerbations resemble exfoliative dermatitis \* \* \* which is as severe as the cases of primary exfoliative dermatitis described below. The seriousness of such a state and the need for expert management of these patients cannot be overemphasized.

Usually the disease is characterized by the onset of localized violaceous or erythematous eczematoid plaques \* \* \* followed by generalization of the lesions with subsequent appearance of the lichenoid plaques and mucous membrane lesions. \* \* \* Any part of the cutaneous surface may be involved, but there is a predilection for the lower legs, forearms, dorsal surface of hands and feet, face, buttocks, lower anterior surface of the neck, genitalia, mucous membranes of the mouth, eyes, and eyelids. Residual effects and lesions which develop later in the course of the disease include: atrophy; hyperpigmentation (melanin) and depigmentation; diffuse follicular accentuation over the upper back, shoulders, and extremities; changes in the nails; moth-eaten, patchy alopecia; and marked disturbance in sweating function.

\* \* \* A characteristic type of eczematoid dermatitis which also has occurred in individuals taking suppressive Atabrine \* \* \* is characterized by bilateral, symmetrical, violaceous-tinged, vesicular, eczematoid and oozing plaques involving the hands, arms, feet, legs, and sometimes other parts of the body. Secondary pyogenic infection is common. The nail bed and skin of the nail folds are usually involved, frequently resulting in exfoliation of the nails without true suppurative paronychia. With experience, on clinical grounds, one can in most cases distinguish between this eruption and other forms of eczematoid dermatitis. Tentatively the term "symmetrical eczematoid dermatitis" has been used \* \* \*.

It does not seem advisable to make a sharp distinction between the so-called atypical lichen planus and the symmetrical eczematoid dermatitis syndrome. From a broad point of view, it seems that all of these patients have either a lichenoid cutaneous reaction or an eczematoid cutaneous reaction or a combination \* \* \*. A small percentage of the total group have lichenoid lesions alone; a larger group have a combination of lichenoid and eczematoid lesions; and a still larger group have eczematoid lesions that are not accompanied by lichenoid lesions.

\* \* \* reports of general Army experience \* \* \* indicate that Atabrine is the essential etiological factor. The mechanisms resulting in the lichenoid reaction and the eczematoid reaction are probably different. For example, it was observed in a carefully controlled series of cases at Moore General Hospital that the time interval preceding exacerbations of eczematoid lesions is much shorter than with the lichenoid lesions. The fact that the incidence has been so very much higher in New Guinea and adjacent islands and in Assam and northern Burma suggests that climatic or geographic factors may play a contributory role in the etiology. There is evidence that various forms of cutaneous trauma may contribute to the onset and localization of the lesions, particularly the eczematoid phase of the eruption. The sequence of events in many cases suggests that individuals taking suppressive Atabrine have a tendency to acquire chronic eczematoid dermatitis on contact with external allergens (such as certain jungle plants and trees) rather than self-limited contact dermatitis which is the usual course \* \* \*. It appears that cutaneous reactions are more frequent in individuals who have been taking Atabrine in dosages above the recommended suppressive amount (0.7 gm. per week). It should be emphasized that the incidence of these cutaneous diseases has been relatively low, even in New Guinea, and, from the military point of view, has not been an important handicap.

Since available evidence indicates that we are dealing with one complex, it is suggested that it would be best to group these cutaneous reactions attributed to Atabrine under one heading "Atabrine dermatitis complex" and classify the various manifestations as follows: (1) lichenoid dermatitis; (2) lichenoid and eczematoid dermatitis (both including cases heretofore referred to as "atypical lichen planus"); (3) eczematoid dermatitis (including cases heretofore referred to as "symmetrical lichen dermatitis"); (4) exfoliative dermatitis secondary to (1), (2), or (3).

The treatment of these conditions depends for the most part on early recognition of the trouble and discontinuation of Atabrine. In many instances, it is difficult to decide whether or not a given case of eczematoid dermatitis is due to Atabrine. It is necessary to study such cases carefully, with careful observation after withdrawal of Atabrine and possibly cautious trial readministration of the drug (do not attempt readministration of Atabrine to a patient who has had exfoliative dermatitis or a severe generalized eczematoid exacerbation). \*\*\* When possible, such patients should be seen by a competent dermatologist, and every effort should be made to rule out other etiological factors. Parenteral administration of penicillin is indicated in patients with secondary pyogenic infection. Local treatment should be bland and nonirritating, and should consist of preparations such as 1: 9,000 potassium permanganate soaks, Burow's solution soaks, 5 percent aqueous solution of tannic acid spray for oozing intertriginous sites, and application of borated cold cream if a grease is indicated. Preparations such as salicylic acid ointment, tincture of iodine, and sulfonamide ointments should not be used. Arsenicals and bismuth have been tried in some cases without affecting the course significantly; they should not be used. Superficial X-ray therapy, if indicated, should be used only under the direction of a competent dermatologist and in small doses (not more than 75 r and not to exceed a total of more than 375 r to 450 r). At least some of these patients have some degree of light sensitivity. Therefore, exposure to sunlight should be avoided and ultraviolet light therapy should not be used. All patients should be studied from the general medical standpoint, including studies of blood, serum proteins, and liver function. Therapeutic agents such as plasma, liver extract, multiple vitamins, and intravenous glucose should be used when indicated.

The prognosis varies from individual to individual. In general it is excellent, especially if the patient is hospitalized early in the course of the disease \*\*\*. The lichenoid lesions involute slowly, but they do not tend to recur; the eczematoid phase of the eruption may involute rapidly, but it tends to recur and is responsible for the prolonged disability which occurs in some cases. In general, recovery is a matter of weeks and months. Residual hyperpigmentation, depigmentation, and atrophy at the sites of lesions become less pronounced as time goes on and the hypohidrosis which occurs in many patients also improves spontaneously. The course is usually prolonged in all cases of exfoliative dermatitis because of frequent exacerbations. It should be noted that these patients have not been followed for a sufficient length of time to make final statements in regard to the prognosis of these cutaneous reactions.

Another major type of cutaneous reaction which has been attributed to Atabrine is primary exfoliative dermatitis, not secondary to the lichenoid-eczematoid syndrome. This is characterized by acute fulminating exfoliative dermatitis, demonstrably associated with true hypersensitivity to Atabrine. It is in every respect similar to exfoliative dermatitis due to other agents such as arsenicals. This type of cutaneous reaction \*\*\* is believed to be associated with Atabrine, much less commonly with quinine. Hypersensitivity of this degree may constitute a dangerous state in either instance.

#### *Acute reactions to short-term administration*

The principal toxic manifestations from therapeutic amounts of quinine usually employed in terminating acute attacks of malaria or from small

initial doses early in suppression are related mainly to the skin, gastrointestinal tract, and central nervous system.

**Skin.-**Acute reactions in the skin related to hypersensitivity or reactivation of eczematoid dermatitis following small amounts of quinacrine have been discussed. In addition, urticaria and pruritus have been described as an uncommon toxic manifestation of quinacrine ingestion. In a report<sup>49</sup> from India, 12 cases of pruritus and urticaria, particularly of the palms, were described in the course of quinacrine suppression. In 2 patients, symptoms began within 3 days after suppressive medication was started and, in the other 10 patients, within 2 to 3 weeks. The symptoms subsided in three patients while they were still on the drug and in nine within 4 days after the drug was discontinued. Six patients had no recurrence when quinacrine was readministered, and, in the three who had a recurrence, symptoms disappeared with continued medication.

**Gastrointestinal tract.-**Gastrointestinal symptoms (nausea and vomiting) are rarely encountered with quinacrine during therapeutic termination of acute attacks of malaria. Frequently, these symptoms when present are due to malaria rather than to ingestion of the drug. The administration of quinacrine in colored capsules to patients who stated they could not take it because of gastrointestinal symptoms completely forestalled the development of such symptoms.<sup>50</sup> Likewise, giving the drug after meals or with sweetened fluids during an attack of malaria reduced the incidence of nausea. Nausea, vomiting, and diarrhea were reported in large numbers of men on initial suppressive doses of 0.2 gm. twice weekly in some series and not at all in others. Symptoms usually disappeared after three or four doses and occurred only infrequently in the 0.1 gm. daily schedule. Psychological factors, field sanitary conditions, and other reasons were held mainly responsible for gastrointestinal symptoms. The consensus was that these reactions were never severe and almost invariably disappeared if the drug was continued.<sup>51</sup>

**Central nervous system.-**Before World War II, mental disturbances were reported as occurring in approximately 1 to 2 of every 1,000 cases of malaria treated with quinacrine orally or intramuscularly, and various aberrations of the central nervous system attributed to quinacrine were reported in a number of cases during the war.

In 7,604 patients treated with quinacrine in a period of 7 months at an oversea general hospital, 35 cases of toxic psychosis were observed.<sup>52</sup> Total doses of 2.1 gm. quinacrine in a week were routine. The greatest number of reactions occurred within 6 days of completion of therapy, although one was observed after only 0.9 gm. had been given and one developed as late as 12 days after therapy. There were two main types of onset. The most frequent

<sup>49</sup> Essential Technical Medical Data, India-Burma Theater, for August 1945, inclosure 3 thereto.

<sup>50</sup> See footnote 15 (1), p. 532.

<sup>51</sup> The Drug Suppressive Treatment of Malaria. Bull. U.S. Army M. Dept. No. 73, pp. 29-34. February 1944.

<sup>52</sup> Gaskill, H. S., and Fitz-Hugh, T., Jr.: Toxic Psychoses Following Atabrine. Bull. U.S. Army Al. Dept. No. 86, pp. 63-69, March 1945.

(65 percent) was marked by excitation, hallucinations, and delusions. The other (35 percent) began with retardation, disorientation, and amnesia for recent events together with confabulation. No constant physical or laboratory findings were obtained. The course of the psychosis was benign in most instances. Sixteen patients were subsequently (after 16 to 210 days) retested with quinacrine and only one showed any untoward reaction, consisting of mild excitement which cleared within 24 hours. There was no evidence that the men who developed toxic quinacrine psychoses were unstable psychologically. Two patients who did not recover developed typical schizophrenic reactions. There was no evidence of latent psychosis in the previous behavior of these two patients. Treatment consisted of restraint, sedation, supervision, and nursing care. The authors believed that the psychoses represented a quinacrine sensitivity reaction following which there was an unreactive period.

In another report from overseas,<sup>53</sup> 28 cases of quinacrine psychosis were observed in the American Division. The degree of malarial infection and the great number of relapses treated in this division would indicate the incidence of this reaction to be extremely low. Two patients gave a history of previous psychotic reactions to quinacrine, and in two additional patients it was believed that schizophrenia was induced by the drug. Only one case was noted during the standard course of 2.8 gm. of quinacrine in 7 days. The remainder developed during or after larger total doses, 18 patients receiving more than 3 gm. Confusion was the prominent clinical feature of the psychosis in 27 patients. Hallucinations occurred in eight cases. Recovery was complete within 10 days in 16 patients. By the use of the Koh's block test, these authors showed that there was evidence of confusion in 7 of 31 patients treated with 4.5 gm. quinacrine during 9 days, while no such changes could be demonstrated in 27 patients treated with 2.1 gm. in 7 days. Additional cases of quinacrine psychosis were reported from various installations overseas and in the United States, but their incidence was an insignificant fraction of the total number of psychoses that occurred in the U.S. Army.

Convulsions were reported in six patients treated with "massive" amounts of quinacrine orally<sup>54</sup> and in two who were treated intravenously. The convulsions occurred during treatment or on the following day, with unconsciousness for 5 to 15 minutes followed by confusion. Within 24 hours, these patients were all mentally clear. Plasma levels determined in three cases were from 180 to 280  $\mu\text{g.}$  per liter. Studies were stimulated by observation of high plasma levels with parenteral quinacrine therapy and by reports in the literature before World War II<sup>55</sup> of mental changes associated with parenteral medication. A group of 13 volunteers were given 0.9 gm. of quinacrine

<sup>53</sup> Newell, H. W., and Lidz, T. : The Toxicity of Atabrine to the Central Nervous System. I. Toxic Psychoses. *Am. J. Psychiat.* 102 : 805-818, May 1946.

<sup>54</sup> Newell, H. W., and Lidz, T. : The Toxicity of Atabrine to the Central Nervous System. II. Convulsions. *Am. J. Psychiat.* 102 : 805-818, May 1946.

<sup>55</sup> See footnote 34, p. 545.

daily for 7 days. Peak plasma levels were from 156 to 420 with a mean of 286  $\mu\text{g}$ . per liter. No symptoms or signs related to the nervous system were observed. Electroencephalographic studies revealed only small and inconsistent changes not characteristic of those observed in convulsive disorders of the brain. In another study, five normal subjects were given sufficient quinacrine by mouth during 7 to 10 days to produce plasma levels in excess of 100  $\mu\text{g}$ . per liter. In all cases, there was evidence of marked psychologic stimulation (motor acceleration, restlessness, sleeplessness, and increased capacity for work), and the electroencephalogram showed a significant shift toward faster frequencies. These manifestations appeared by the third day and persisted for 6 to 8 days after the drug was discontinued. The authors considered the data convincing evidence that quinacrine acted as a cortical stimulant.

### Summary of Studies

An experimental approach to the chemotherapy of malaria led to a rational use of quinacrine for effective treatment of attacks and for suppression. The development of chemical methods for estimating quinacrine in biological fluids and tissues resulted in a better understanding of the limitations of treatment and suppressive schedules in use before and early in World War II. Clinical and field studies carried out on a large scale demonstrated that quinacrine if properly used was superior to totaquine or its component alkaloids for treatment or suppression of malaria due to *P. vivax* or *P. falciparum*. Quinacrine produced more prompt control of fever, symptoms, and parasitemia; was less toxic; and provided a longer interval to relapse than quinine, sulfonamides, or heavy metals. Quinacrine was shown to induce definitive cure in *falciparum* infections and to provide effective suppression of relapsing malaria when priming initial doses were followed by daily doses of 0.1 gm. Failures in suppression (breakthroughs) were shown mainly due to poor discipline and failure to take the drug. Parenteral use of quinacrine was found effective in severe *falciparum* infections, but no conclusive comparative study was reported between quinine and quinacrine given parenterally. Toxic reactions known before the war were encountered, these consisting of minor gastrointestinal symptoms and toxic psychoses. In addition, prolonged quinacrine ingestion produced edema of the cornea in some cases, and in a large number of cases, the following reactions were described: (1) Ochronosis-like pigmentation of skin, mucous membranes, and cartilage (possibly with hepatitis), (2) urticaria and, more significantly, a dermatitis complex (atypical lichen planus and/or eczematoid dermatitis), and (3) aplastic anemia. It was only shown that long-continued suppression produced these reactions in only a small proportion of men taking the drug and that on the whole no significant disturbances in organ function resulted. The proper use of quinacrine made possible effective military operations in highly malarious areas.