



Antimalarial Drugs: General Outline (1944)

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outbreak of the present war, an average of 2,330 kg. of quinine had to be imported annually.⁷ Some idea of the contribution of Latin America can be gained from relative figures on importation by the United States. The annual average of the total import of cinchona bark between 1937 and 1939 was 1,738,431 pounds. Of this amount, 23,855 pounds came from Latin America; i.e., about 1.4 per cent of the total.⁸

There is but little doubt that the discrepancy between the world requirements and the world supply of quinine was largely due to economic factors.^{4,9} The price of quinine was above the purchasing power of the indigent and in Italy, for instance, even before the last war, large scale use of the drug for the prophylaxis and treatment of malaria had to be subsidized by the government.^{10,40} Need existed, therefore, for a cheap antimalarial drug.¹¹ This need was partly met by the utilization of all the alkaloids found in cinchona bark; viz., quinine, quinidine, cinchonine and cinchonidine. The mixture was used in India and known by the name, "cinchona febrifuge."¹¹ At first it was produced from the red bark (*C. succiruba*) and had a relatively high content of quinine.⁸⁸ Later on, when quinine manufacturers preferred the yellow bark (*C. ledgeriana*), cinchona febrifuge was made from the quinine manufacturers' residues and was correspondingly low in quinine content. In either case it was, however, necessary to standardize the drug. This task was sponsored by the League of Nations which in 1931 gave the name, "Totaquina," to the standardized product.¹¹ The latter was adopted in 1932 by the British Pharmacopoeia

which defined it as containing "not less than 70 per cent of crystallisable cinchona alkaloids, of which not less than one-fifth is quinine."¹⁴⁹ In 1933 the Madras Government Cinchona Department produced nearly 2,000 kg. of totaquine,¹³ while in subsequent years other countries too promoted the sale of the drug.

It has been pointed out⁶ that if cinchona cultivation were extended in India, a preparation of the "totaquina" standard "could be produced at a cost of one-seventh that of quinine."

The U. S. Pharmacopoeia²⁵ included the following definition of "totaquina" in its twelfth revision of 1942: "It contains not less than 10 per cent of anhydrous quinine, not less than 25 per cent of cinchonidine and anhydrous quinine combined, and a total of not less than 70 per cent of cinchonidine, cinchonine, anhydrous quinidine, and quinine." In the fall of 1942 a new standard was envisaged,²¹⁴ requiring a quinine content of not less than 7 per cent and not more than 12 per cent, and 70 to 80 per cent of total crystallizable alkaloids. This change was to take account of the low alkaloid content of South American bark.

On the other hand, it must be realized that expensive as quinine might be, its price had, nevertheless, been reduced; in Germany, for example, it had fallen from several hundred marks per kg. in the eighties of the last century to 60 to 80 marks around 1926.¹⁴ These German figures were not without influence upon the search for quinine substitutes. The complicated structure of quinine made its chemical synthesis a very difficult task affording

little promise. Synthetic quinine would further depress the price of the natural drug and competition between the two, therefore, did not promise profitable results.¹³

With the virtual establishment of a quinine monopoly in the Netherlands Indies, the danger arose that in case of war the source of supply might be cut off. Campaigns in malaria-endemic countries have always held grave danger for foreign troops. During the last world war, this fact was experienced by the British and French forces in various theaters of the war, and particularly in Macedonia where malaria hospital admissions among the British Expeditionary Force in September and October 1917 reached monthly figures exceeding 15,000.¹⁴ But if the allied armies were hard hit by malaria, so were the German forces who, in addition, suffered from a shortage of quinine because of lack of cinchona bark.¹⁵

At the outbreak of the present war, it could be foreseen that the occupation of Java by an enemy power would create a serious problem. That such a possibility was reckoned with in this country is indicated by the sharp increase in imports of cinchona bark at least two years before Pearl Harbor. While imports amounted to 1,837,000 lbs. in 1937 and 1,349,000 lbs. in 1938, they reached 2,030,000 lbs. in 1939 and 5,418,000 lbs. in 1940.¹⁶ After Pearl Harbor efforts were made to plant cinchona seeds in Latin American countries and to secure bark from South America. Colonel A. F. Fischer succeeded in bringing some two million cultivated seeds out of the Philippines when these islands were occupied by the Japanese.¹⁴⁵

At present, the United States is cooperating with Bolivia, Colombia, Costa Rica, Ecuador, Guatemala, Mexico and Peru in their efforts to increase the output of cinchona bark.^{145,146} Apart from these enterprises, it was necessary to preserve the quinine supply in this country and to reserve it for the armed forces. Since June 1942, both quinine and totaquine may only be sold as antimalarial agents. The same is true for such secondary alkaloids as cinchonine and cinchonidine.¹⁷ Quinidine, on the other hand, is to be reserved for the treatment of certain heart diseases.¹⁴⁷ In February and March, 1943, druggists and physicians were urged to send quinine and other cinchona derivatives to the National Quinine Pool.^{18,19} It was pointed out that the civilian population was to receive totaquine which "while excellent for domestic use, is not as stable as is quinine and therefore not as suitable for shipment into areas of varying climatic conditions."¹⁸ At the same time an explanation was given as to why soldiers abroad might need quinine instead of the synthetic anti-malarial drugs.¹⁸ This country and our ally, Great Britain,¹⁸ were not the only countries to impose restrictions upon the use of quinine. Japan's partner, Germany, likewise had to limit its use to the treatment of malaria exclusively.²⁰

Economic and political motives thus largely explain the quest for a quinine substitute; i.e., a drug that would act as effectively as quinine. Besides, there existed medical reasons to look for a drug that would supercede or supplement quinine. Its bitter taste and toxic reactions were among the shortcomings known for a long time.

Doubts about its reliability as a prophylactically and therapeutically ideal drug had been voiced before the last world war. During and after that war, these doubts increased and biological and clinical studies as well as the invention of the synthetic drugs, plasmochin and atabrine, opened new vistas.

Before 1914, the opinion was wide-spread that quinine destroyed all forms of P. vivax, P. malariae and P. falciparum—except their gametocytes.²¹ This view influenced the prophylactic and therapeutic use of the drug. A sufficient quantity of quinine in the blood would kill the sporozoites introduced by the mosquito and destroy the schizonts developing in the blood-stream. Since, however, not all sporozoites or schizonts would be killed at once, it was believed necessary to give quinine over a certain period of time in order to prevent infection or relapses.

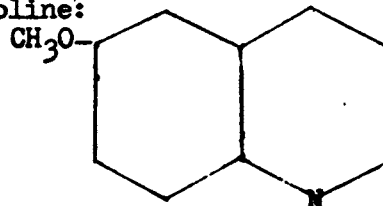
In contrast to present usage the period of prophylactic administration following the time of actual exposure to infection was relatively short;²¹ whereas, the period over which quinine was given therapeutically was relatively long. For instance, according to the treatment that Nocht²² introduced in 1904, 1.0 gm. (15 grains) of quinine hydrochloride were given daily to the adult patient during his febrile attacks and during 5 subsequent days. Then, for 6 weeks, 4 free days alternated with 3 days on which quinine was given, or a scheme was followed in which the number of free days gradually increased while the number of quinine-days decreased (2 free days—then 3 days of quinine, 3 and 3, 4 and 2, 5 and 2, 5 and 2).

Celli's statement: "He who takes quinine every day, and therefore has always a supply of quinine in the blood stream, can undergo with impunity inoculations of blood full of malarial parasites, and can expose himself with little or no danger to the bites of infected mosquitoes,"²¹ although often quoted was not generally accepted before the last war. The efficacy of quinine prophylaxis was a matter of considerable debate, its defenders usually accusing irregular or insufficient consumption of the drug for the apparent failures. If regularity were assured by the habit of taking a daily dose at a fixed time, the results would be excellent.²¹ When the British and French forces began to suffer heavily from malaria during the Macedonian campaign, the debate was continued along very similar lines without reaching any conclusive results.¹⁴⁴ Moreover, "some pessimistic papers were written during the war period by medical officers of the British Army as to the value of quinine in the treatment of malaria."²³ Although such pessimism was opposed by those who believed "that quinine properly administered and continued for a sufficient period of time, will cure any case of malaria infection, provided the patient can take the drug,"²³ there is yet little doubt that the first World War shook rather than enhanced confidence in the prophylactic and curative properties of quinine.

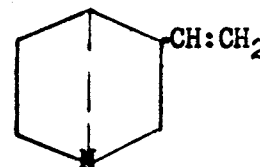
II. The Synthesis of New Antimalarial Drugs

Plasmochin. Chemically, quinine is the methyl ether of cupreine and has the formula $C_{20}H_{24}N_2O_2 + 3H_2O$. This formula can be considered as consisting of three parts:

the quinoline component, i.e., 6-methoxy-quinoline:

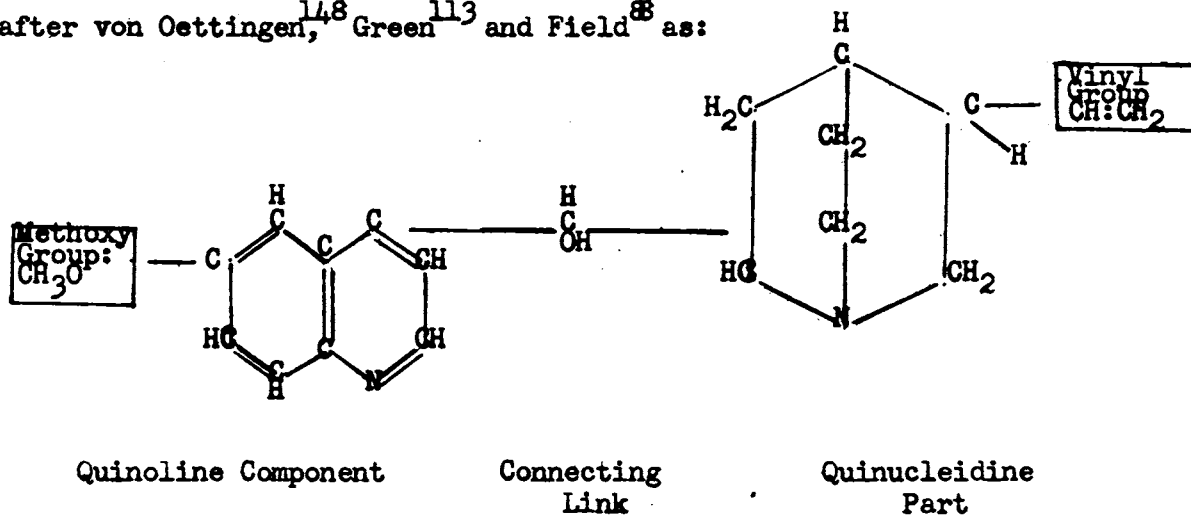


the quinucleidine part, i.e., a complex ring with a vinyl group



and the connecting link containing a hydroxy-group: HCOH

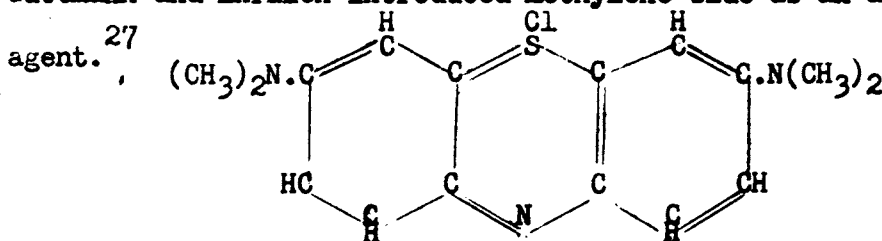
The structural formula of quinine can, therefore, be visualized after von Oettinger,¹⁴⁸ Green¹¹³ and Field⁸⁸ as:



The other cinchona alkaloids; viz., quinidine, cinchonine and einchonidine are also built after this pattern. Quinidine is an optical isomer of quinine; cinchonine and cinchonidine are optical isomers lacking the methoxy group.¹⁴⁸

Of the component parts of the quinine formula, the quinoline ring was known more than a hundred years ago.¹¹⁴ It is, therefore, not surprising that quinoline was among the early chemicals tried against malaria, to be followed by kairin, antipyrin, antifebrin, thallin, phenacetin and other antipyretic drugs, all of which failed.²⁷

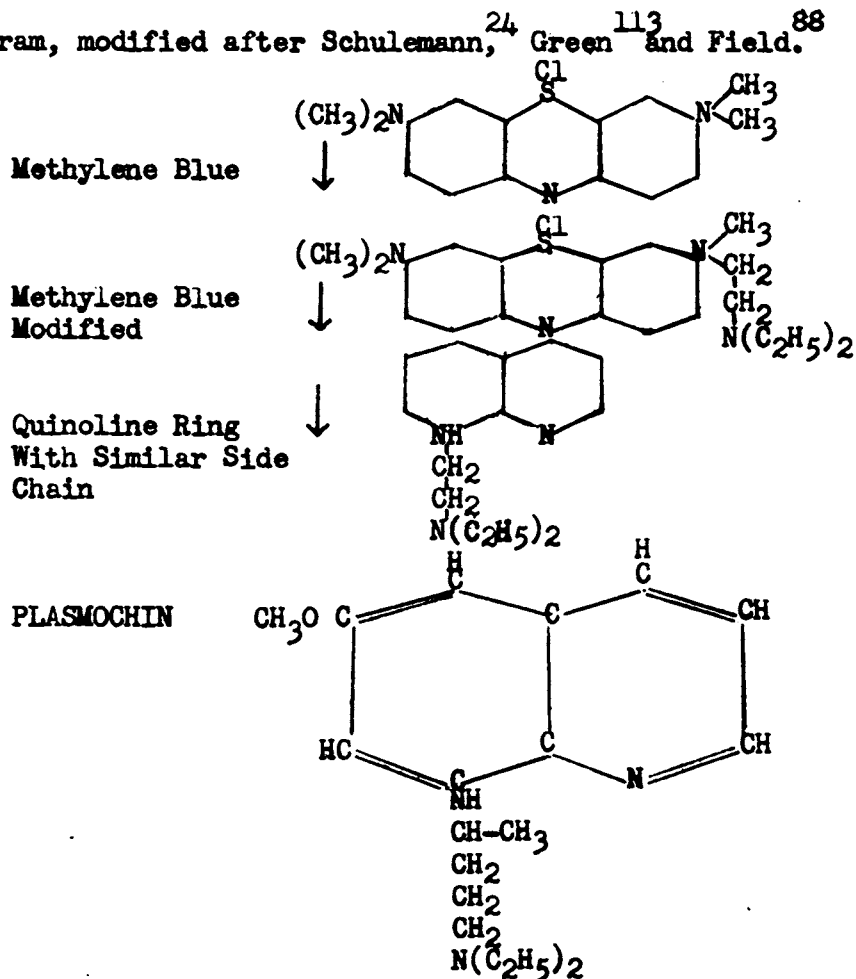
A new chapter in the history of antimalarials began in 1891 when Guttman and Ehrlich introduced methylene blue as an antimalarial agent.²⁷



Methylene Blue ²⁵

The fact that methylene blue was being used for staining plasmodia gave these authors the idea of trying its therapeutic effect in two cases of malarial infection (tertian and quotidian types). They administered the dye (in capsules) in doses of 0.1 gm. 5 times a day, continuing with the same dosage for 8 to 10 days. The febrile attacks stopped during the first few days of this medication and, according to the authors, the plasmodia disappeared from the blood "not later than 8 days" after the beginning of the treatment.²⁷

Methylene blue is not used much as an antimalarial drug nowadays nor are the arsphenamines which were tried for this purpose shortly after their invention by Ehrlich.²⁴ (See p. 99) Thus it can be said that no efficient synthetic antimalarial drug was in use before the first World War. Yet after the War, methylene blue became important again because Schulemann²⁴ and his coworkers used it as the starting point in their synthesis of plasmochin. An amino compound of methylene blue gave the first promising results. This, in turn, led to quinoline compounds containing nitrogen atoms in an aliphatic side chain and finally in 1924 to plasmochin, an 8-(4-diethylamino-1-methyl-butylamino)-6-methoxy quinoline. The sequence can be illustrated by the following diagram, modified after Schulemann,²⁴ Green¹¹³ and Field.⁸⁸



Plasmochin was the first synthetic antimalarial drug of major importance. Moreover, its synthesis was not due to chemical research alone. Chemist, biologist and clinician had worked together and had made systematic use of animal experiments as well as trials on patients undergoing malaria therapy. These new methods have become fundamental in the investigation of antimalarial drugs and their development up to the invention of plasmochin, as well as in more recent years, therefore, may be sketched briefly.

Danilewsky in 1886 realized that the plasmodia in man were related to the intracorpuseular sporozoa in lower animals,²⁹ and in 1899 Koch and Pfeiffer found that canaries were ready hosts to infection with plasmodia formerly found in sparrows.²⁶ Here then was easily available material that could be used for testing anti-malarial drugs. In the following decades a copious literature on the subject originated which was reviewed by Bishop²⁶ in 1942, as well as by Marshall.³⁰

During the early stage of the work on avian malaria, it was found that the inability to trace parasites in the blood of infected birds was no proof of complete recovery. On the other hand, birds which were still infected did not suffer from an acute attack, if reinoculated with plasmodia. While these findings pointed to the existence of latent infection and a state of "premunition"—to use a term introduced by E. and E. Sergent³¹—they made it all the more important to develop tests by which the final success of a cure could be established. The Sergents³¹ in 1921 described the following two tests as the most reliable ones. The immunity reaction

(réaction d'immunité) consisted in injecting infected blood into the peritoneum of the suspected bird. If the latter did not show definite signs of infection, it had still to be considered diseased. The "isodiagnostic" test varied from the above by the injection of blood of the suspected bird into the peritoneum of a healthy animal of the same species. Quinine was the main drug whose therapeutic and prophylactic effects were tried in birds. The experiments conducted by various authors up to the early twenties showed that therapeutically the drug had much the same action in birds as in man. It did not really destroy the parasites once the animal had been infected, although their appearance might be delayed.²⁶ Thus the doubts of clinical observers were strengthened by the results of laboratory investigations.

It was at approximately the same time that the use of malaria for the treatment of general paresis made it possible to observe the course of the disease under well defined conditions and to test antimalarial drugs in man. Malaria was usually transmitted from a well known strain, either directly from patient to patient, or through the intermediary of mosquitoes. The patients of countries where malaria was not endemic were usually free from previously acquired immunity and, therefore, presented material for testing drugs on newly infected cases. During the ten years following the introduction of malaria therapy by Wagner Jauregg in 1917, some observations were made which tended to round up the picture regarding the action of

quinine on the various developmental phases of plasmodia. Thus Yorke and Macfie in 1924 noticed that quinine given prophylactically was effective against inoculation with the blood of patients, but not against mosquito-induced infection.²⁶ The conclusion these authors drew was that quinine did not affect the sporozoites but the trophozoites. Hence, quinine did not really prevent infection; it only suppressed clinical manifestation of the disease.

When the research workers at the Elberfeld Laboratories of the I. G. Farbenindustrie approached the task which in 1924 led to the synthesis of plasmochin, they had to develop a method by which the many compounds suggested by the chemist could be tested in birds so as to find the most efficient combination. Roehl,³² who developed such a method, first of all had to invent a standard for comparison. Inoculating canaries with P. relictum (praecox) and testing their blood daily, he found that the parasites usually became visible after 4-5 days. If, however, quinine solutions were injected into the bird's stomach by means of a catheter, the parasites appeared after 10 to 12 days or even later. This delay in the appearance of the parasites was taken by Roehl as a test for the efficiency of a drug and a standard for comparison was elaborated with solutions of quinine hydrochloride. A solution of 1:200 (1 cc. per 20 gm. body weight) was efficient and yet tolerated by the bird; a solution of 1:800 was still definitely efficient, while a solution of 1:1600 was no longer efficient. Since, therefore, solutions from 1:200 to 1:800 represented the latitude where quinine hydrochloride was tolerated and effective, this drug then according to Roehl had a

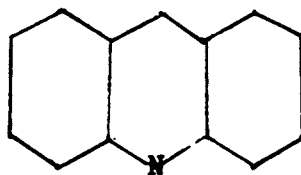
chemotherapeutic index ("Wirkungsbreite") of 1:4. Substituting the various suggested products for quinine hydrochloride, it was found that plasmochin was effective between 1:1500 to 1:50,000; i.e., that it possessed a chemotherapeutic index of approximately 1:30. In many cases according to Roehl, plasmochin prevented the appearance of plasmodia altogether. The birds remained healthy and their blood not infectious for other birds. Once the infection had become manifest, plasmochin did not effect a complete cure.

It was, of course, impossible to predict whether this drug, found promising in canaries infected with P. relictum, would also be effective in man infected with quite different species of plasmodia. The question was answered in the affirmative by Sioli³³ in the early part of 1925. In order to test the tolerance for plasmochin, he first tried it on 3 paralytics who were not yet undergoing malaria therapy. These preliminary tests suggested to him that further experiments might begin with doses of 0.05 gm. 3 times a day without exceeding this dosage. He obtained satisfactory therapeutic results with 4 daily doses of 0.02 gm. or 2 daily doses of 0.04 gm. given until 3 days after the disappearance of the fever and the plasmodia, and repeated on 4 days during each of the subsequent 2 or 3 weeks.

The final step was made by Mühlens³⁴ in August, 1925, when plasmochin was introduced at the Hamburger Tropeninstitut for the treatment of naturally acquired malaria. Doses of 0.05 gm. once or twice (in a few cases even 3 times) a day or 0.02 gm. 5 times a day were usually given on 5 to 7 successive days until the complete

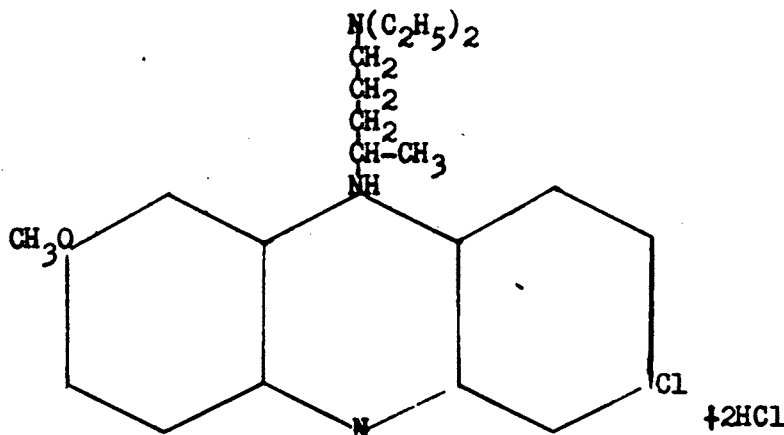
disappearance of all parasites" and continued for several weeks on 3 successive days following 4-5 day intervals. The whole cure lasted about 4-6 weeks. In cases suffering from tertian, quartan and tropical malaria, the febrile attacks very soon stopped after treatment with plasmochin had been instituted. The parasites of tertian and quartan malaria also disappeared in a few days. However, plasmochin treatment showed remarkable peculiarities in cases of tropical malaria. Regarding relapses, this drug was inferior to quinine, yet the gametes in M. tropica not affected by quinine disappeared almost invariably in the course of the plasmochin therapy. In order to avoid tropical relapses, plasmochin was combined with quinine as "plasmochin compositum."

Atabrine. Plasmochin was not a mere substitute for quinine. It acted on those forms of falciparum malaria where quinine was least effective. However, there still remained the task of finding a synthetic drug which would act where plasmochin was inferior to quinine; that is, in the action upon the schizonts of P. falciparum. This pharmacological problem was approached by Mauss and Mietzsch³⁵ from the following stand point. From the experiments with plasmochin, they accepted the principle of introducing a basic radical by means of an aromatic amino group. On the other hand, they did not wish to use the plasmochin ring, but looked for another ring more similar to the quinoline ring of quinine. This they found in acridine which was relatively closely related to quinoline and which for years had been used for the preparation of more or less effective antimalarial drugs such as tryptaflavine, rivanol, etc.³⁵



Acridine

By choosing the acridine ring³⁵ they hoped to lessen the toxic properties of the compound as compared with quinine and plasmochin. This combination represented a type of chemical which obviously could be modified in many ways. Introducing the chlorine atom and a methoxyl group into the acridine ring, they obtained a dihydrochloride of 2-methoxy-6-chloro-9-(8-diethylamino- α -methyl-butylamino) acridine which received the name of atabrine and to which was given the following formula: 88,115



Atabrine

Synonyms: Mepacrine hydrochloride
Quinacrine
Acriquine

The chemotherapeutic action of atabrine was elaborated by Kikuth³⁶ in 1932. Following Roehl's method (cf., p.14), he did not find any particular advantages of atabrine over plasmochin. The chemotherapeutic index of the two drugs was about the same and in absolute figures atabrine was four times as effective as quinine, but fifteen times less effective than plasmochin. In experimenting on Haemoproteus orizivora, he found that the mode of action of atabrine was different from that of plasmochin. Haemoproteus infections occur in the Java paddy bird and the schizont cycle develops in the endothelial cells of the host; whereas, gametes appear in the blood. If the infected birds were given plasmochin, the gametes disappeared temporarily from the blood, only to reappear shortly after the end of the medication. According to Kikuth these relapses took place because plasmochin did not destroy the schizonts which continued to develop sexual forms. Quinine and atabrine, on the other hand, did not affect the already circulating gametes at all, since in Kikuth's opinion they acted upon schizonts. If these assumptions were correct, then plasmochin and atabrine given together ought to destroy the gametes as well as prevent relapses. The outcome of Kikuth's experiments confirmed his hypothesis, whence he took it for experimentally proved that atabrine, just like quinine, acted upon the schizonts of malaria parasites.

In July 1930, Sioli³⁷ tried atabrine upon general paretics treated with malaria (P. vivax) and advised oral administration of

0.1 gm. 3 times a day for several days. Peter,³⁸ in September of the same year, had an opportunity of trying atabrine upon patients naturally infected with malaria. In vivax malaria, he observed an effect upon all developmental stages of the parasite, although the gametes were the last to disappear. In falciparum malaria, however, the drug proved inefficient upon the gametes, while the ring forms disappeared quickly. He thus confirmed Kikuth's prediction that in infections with P. falciparum, atabrine would act upon the schizonts.

While Haemoproteus orizivora is not a malarial parasite, it has been found that various plasmodia occurring in other birds have an extra-erythrocytic cycle in addition to the erythrocytic cycle hitherto known. In particular, James and Tate³⁹ observed in P. gallinaceum Brumpt "a hitherto unrecognized schizogonic cycle of development occurring in reticulo-endothelial cells of the spleen, liver, kidneys and other internal organs and particularly, in certain cases, in the reticulo-endothelial cells which line the capillaries of the brain." These authors drew attention to the possibility that a similar cycle occurred in human malaria parasites and that this might account for the ineffectiveness of quinine in preventing primary attacks as well as relapses of the disease. The question of an exo-erythrocytic cycle has evoked a considerable amount of research without having as yet been solved conclusively with regard to human malaria.²⁶

Sulfa Compounds, Simian Malaria and Immunity. In 1932, when discussions on the comparative effect of quinine, plasmochin and atabrine upon human malaria began to appear in great number in the medical literature, opinion tended to crystallize as follows: quinine and atabrine were considered predominantly "schizontocides," plasmodin, on the other hand, a "gametocide,"¹³¹ and none of them destroyed the sporozoites by which infection was transmitted in the natural way. The experimental work on avian malaria, however, did not allow such a relatively simple view. The literature reviewed by Marshall³⁰ reveals a considerable divergence of opinion and the same is true of the question whether any drug is really able to prevent infection in birds. Besides, the problem is made even more complicated by the different susceptibility to the drugs of the various species of parasites as well as strains. In addition, the species of birds acting as hosts also vary with regard to susceptibility. The large number of avian parasites as well as their main hosts (more than 130 species of birds have been found infected in nature¹⁴¹), chiefly used in experimental work, can be seen from the following list:

PARASITE	HOST
<u>P. relictum (praecox)</u>	Canary, Duck, Pigeon, Java Sparrow (?), Acanthis linaria, Spinus spinus, Fungilla linaria
<u>P. cathemerium</u>	Canary, Duck
<u>P. nucleophilum</u>	Canary
<u>P. circumflexum</u>	Canary
<u>P. roudi</u>	Canary
<u>P. elongatum</u>	Canary, Duck
<u>P. vaughani</u>	Canary
<u>P. gallinaceum</u>	Chicken
<u>P. lophurae</u>	Chicken, Duck
<u>P. paddae</u>	Finch
<u>Haemoproteus</u>	Finch

The importance of these problems for the research work on anti-malarial drugs was pointed out by Marshall³⁰ and formulated by him as follows: "What avian malarial species resembles most closely in its susceptibility to drugs the species producing infections in man? The answer to this question involves a study of the species and strain susceptibility to drugs of the parasites available for experimental infections and a comparison of the data obtained with what is known or can be found as to the action of the same drugs in the 3 types of human infections."

The number of other drugs besides quinine, plasmochin and atabrine tested on birds with equivocal success is so great that a few indications regarding sulfa compounds may suffice here. Neoprontosil made P. praecox (?) disappear in the infected Paddy bird and sulfapyridine gave positive results in canaries infected with P. circumflexum. Sulfanilamide, however, proved ineffective against various species of plasmodia in canaries. The same negative response also seemed to be obtained in P. lophurae infections of chickens and ducks until it was shown that, if these birds were treated by the drug-diet method, a positive action could be evoked.^{30,41} The drug-diet method aims at maintaining a more or less constant blood concentration of the drug.⁴¹ The dependence of the activity of a drug on the blood level is a recognized principle in bacterial chemotherapy.⁴¹ The positive results obtained with the drug-diet method are an indication that the same principle is also valid for the drug therapy of malaria.

The initial failure of sulfanilamide in birds stood in marked contrast to its spectacular effect upon the infection of monkeys with P. knowlesi. This parasite was discovered in 1927 in cynomologos monkeys in Java and it was found later that the rhesus monkey too was susceptible to this infection.⁴² A large number of parasites have been identified in a great variety of monkeys and apes. The literature on the subject of primate malaria has been collected recently by Ruch¹⁴² in a publication prepared at the request of the Board for the Coordination of Malarial Studies of the National Research Council.

Rhesus monkeys, if inoculated with P. knowlesi, succumb almost without exception to the infection, but a single oral administration of sulfanilamide, as Coggeshall showed in 1938, eradicates the disease entirely.⁴⁴ Although sulfanilamide (in contrast to other sulfonamide compounds) has but a slight therapeutic effect in human malaria,⁴¹ this discovery was of great importance. For man, too, is susceptible to infection with P. knowlesi and the study of this parasite might lead to the discovery of a drug of similar potency as sulfanilamide has in the rhesus monkey.⁴⁴ Fulton and Christophers used the Warburg manometer for measuring the respiration of P. knowlesi and found that quinine and atabrine inhibited respiration. In vitro experiments on plasmodia had previously given but little promise, mainly because of the inability to cultivate the plasmodia. Determination of the inhibitory effect upon parasites might, on the other hand, lead to

an evaluation of potential antimalarial drugs. With this aim in mind, Coggeshall and Maier⁴⁴ developed a method permitting comparison of various drugs. They found, however, that there was no uniform correlation between the inhibitory effect of various drugs and the response to these drugs in experimental animals. The method, therefore, was recommended by these authors only "as an adjunct to in vivo experiments."⁴⁴

Apart from the possibilities which investigation of P. knowlesi offered for the discovery of new antimalarial drugs, it helped to elucidate our concepts of immunity to malaria. As mentioned above, the existence of a latent infection where no clinical symptoms appeared while the blood was still infectious had been clearly recognized. Clinical observations as well as experiments on birds had proved that some degree of immunity did develop. The question remained, however, whether such immunity was due to cellular or humoral factors. Both possibilities were envisaged, but at first only a cellular response could be proved.^{42,45} During and after the crisis, the parasites were destroyed in the spleen, liver and bone marrow by the macrophages. This helped to explain the splenomegaly in patients suffering from malaria, particularly in endemic regions. Proof of the existence of humoral immunity was provided by studies of rhesus monkeys infected with P. knowlesi. Whereas, sulfanilamide completely eradicated the parasites, quinine and atabrine had no such radical effect, although they changed the otherwise fatal disease into a chronic infection. Monkeys treated with these latter drugs

showed a high degree of immunity to reinoculation with P. knowlesi. Immune serum from these animals transferred passive immunity and the same effect could be reached with immune serum from man inoculated with the same species of plasmodia. Thereby the existence of specific protective antibodies was proved. Every relapse increased the potency of the immune serum and might, therefore, be considered as a beneficial "process of auto-hyperimmunization" in the terms of Coggeshall.⁴²

In addition to the action of specific protective antibodies, the existence of complement-fixing agglutinins and precipitins could also be ascertained⁴² and utilized for a number of diagnostic tests.⁴⁵ Cellular and humoral responses, moreover, seem to act cooperatively in building up the immunity of the infected host.

The different action of sulfanilamide, on the one hand, and quinine and atabrine, on the other, on P. knowlesi infections shed some light on the question of how long immunity to malaria persists. An animal which was given sulfanilamide in the very early stage of the infection was cured without retaining any appreciable degree of immunity. If, however, an animal was allowed to acquire immunity by treatment with quinine or atabrine and the infection then eradicated by means of sulfanilamide, it survived renewed inoculations during the ensuing six months. From these experiments it followed that some amount of immunity remained after a complete cure of the disease and that it was more than "premunition" in the meaning of the brothers Sergent.

Although results obtained in experimental work on animals could not always be immediately transferred to problems of human

malaria, they agreed very well with observations made on therapeutic malaria. Here an ever increasing degree of immunity develops, if the infection is induced by mosquitoes and after several recurrences attempts at reinfection fail. However, the immunity extends to the same species only and is not even complete against different strains of the same species.⁴⁶ This fact already ascertained in 1931, harmonized with the observation in infections with P. knowlesi; viz., that no permanent cross immunity could be obtained even with closely related strains of the same parasite.⁴²

New Principles of Treatment. The hope of curing human malaria with immune serum has so far not been fulfilled. But the realization that a complicated immune process goes on in the infected patient has led to important conclusions as to the relationship of immunity to the drug therapy of the disease. At the end of the twenties, clinical experience with both naturally and therapeutically acquired malaria, experimental work on avian malaria and the introduction of new synthetic drugs had combined to throw doubts upon any of the standard treatments of the disease. In its third¹² and fourth¹³ general reports, published in 1933 and 1937 respectively, the Malaria Commission of the Health Organisation of the League of Nations took a stand on some of the most urgent problems. The third report¹² was mainly concerned with "Principles of treatment based on the results of controlled experiments." Conceding that the evaluation of the new synthetic drugs was still in an experimental stage, the Commission concentrated on a closer examination of the procedure to be followed during the various stages of malaria:

prophylaxis, cure of the attack, prevention of relapses and prevention of spread of the disease. Throughout the report great emphasis was laid upon local and individual peculiarities. "It seems probable," the report states, "that the therapeutics of malaria, like every other aspect of the disease, is much more a local and individual problem than has hitherto been thought." Briefly summarized, the Commission arrived at the following conclusions: "True causal prophylaxis" was impossible since there existed as yet no drug which, if taken in harmless doses, would destroy the sporozoites. For clinical prophylaxis, suppressing the effects of the infection, quinine in a daily dose of 0.4 gm. to be taken throughout the sojourn in a malarious region and for several months afterwards was recommended. "Atebrin taken in a daily dose of one tablet (0.1 gm.) is also effective as a clinical prophylactic, but it cannot ordinarily be used for the purpose, as even this small daily dose quickly colours the skin yellow." Acute attacks of malaria should be treated with either quinine or atabrine depending upon the response to the local strains of parasites. In general, it was pointed out, these two drugs were about equally effective in benign tertian and quartan malaria, with atabrine superior in cases of malignant tertian malaria. A radical break with former plans of treatment was made with respect to the length of medication for the acute attack and the prevention of relapses. The aim of the treatment should consist in helping the patient to acquire as much immunity as possible without interfering with his defense mechanism. Too large doses or medication over a long period might just have the latter effect.

Clinical cure of the attack and the treatment for prevention of relapses should not be combined. The Malaria Commission, therefore, made the following suggestions: The treatment of an attack in the acute stage should not exceed 7 days. In malignant tertian malaria, 3 tablets of atabrine of 0.1 gm. each might be given by mouth daily over a period of 5 or 7 days. In benign tertian malaria, the choice was left open between 1-1.2 gm. of quinine dihydrochloride or quinine hydrochloride daily for 5 days or 0.3 gm. atabrine daily over the same period. Regarding acute attacks of quartan malaria, the Malaria Commission was even less decided. Whatever the type of malaria might be and whatever the drug used for the primary attack, medication should, if possible, stop after the attack had subsided. The most favored plan for the treatment of relapses was this: "One waits until the first recrudescence and then uses the specific remedies in such a way that they will assist, rather than hinder, the development of the patients' natural defensive forces." It was expected that the same procedure repeated even more cautiously in further recrudescences would help the patient to become sufficiently premunised against further clinical manifestation of the disease. In cases of malignant tertian malaria, an endeavor to destroy the parasites during the first recrudescence was considered justifiable. For this purpose a second therapeutic course of equal duration, but with the drug not used before, was suggested. It is noteworthy that the use of plasmochin for curative purposes, either alone or in combination with the other drugs did not find encouragement in this report. Plasmochin came into

its own in the attempt to prevent the spread of malignant tertian malaria, where it "should be given twice a week during the period when crescents are present in the peripheral blood."

This report of the Malaria Commission was most effective in its negative criticism of former views and practices. Thus it stressed again the non-existence of a true prophylactic treatment, and the impossibility of a "therapia magna sterilisans" destroying the parasites once and for all and thereby preventing relapses. Although not without opposition, the report succeeded in converting the old prolonged standard treatment of the clinically existing disease into a more simplified scheme of taking care of the attacks whenever they occurred. On the other hand, the report was not very explicit in the evaluation of the synthetic drugs and their comparison with quinine. This was the main subject of the fourth report,¹³ issued about two years before the outbreak of the present war in Europe.

This report¹³ was largely based on experiments on a total of 12,288 persons carried out during 1935-36 by well known malarialogists in the following countries: Algeria,²³¹ Sardinia,²³² Federated Malay States,⁵⁹ Rumania,⁹⁴ and U.S.S.R.¹³ Since in all the countries covered by the report malaria is endemic, it is understandable that the results obtained were somewhat influenced by the nature of the population and the need of giving mass protection and mass treatment to people living permanently in malarious districts. The data collected referred mainly to infections with P. vivax and P. falciparum, since these two species were considered of prime importance in the epidemiology of malaria.

The negative opinion as to the possibility of a true causal prophylaxis was reaffirmed with some slight qualifications. In the main, however, the fourth report confined itself to the preventive and therapeutic efficacy of synthetic drugs as compared with quinine.



The prestige of the Malaria Commission, the wide scope of its experimental work, and the fact that the report included a discussion of the literature published since 1933 on the therapeutics and collective drug prophylaxis of malaria, gave great weight to this report as a summary of opinion on the action and use of antimalarial drugs. It can, therefore, be taken as a starting point for the development during the following years.

III. Clinical and Laboratory Experience with Antimalarial Drugs

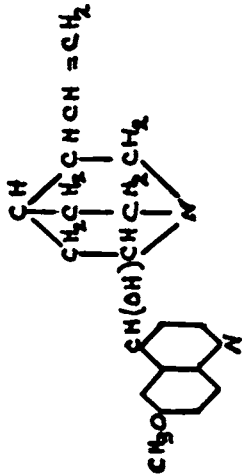
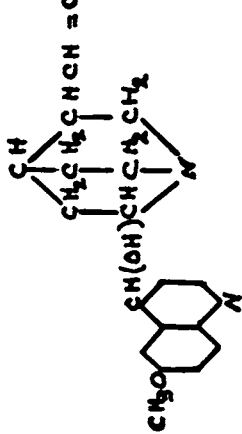
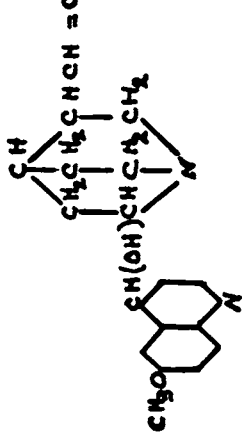
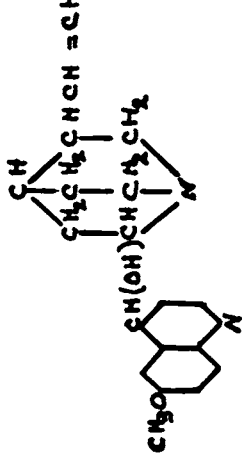
General Considerations. The clinical problems which the Malaria Commission of the League of Nations and subsequent investigators faced were the following: Which of the antimalarial drugs were most efficient in the prophylaxis and the treatment of the various stages of malaria? What was the relative value of these drugs with regard to the different species of plasmodia? What was the proper dosage in which the different drugs should be administered and what combinations of drugs--if any--were advisable?

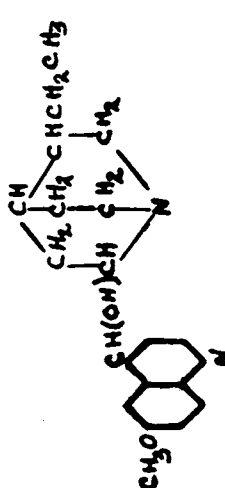
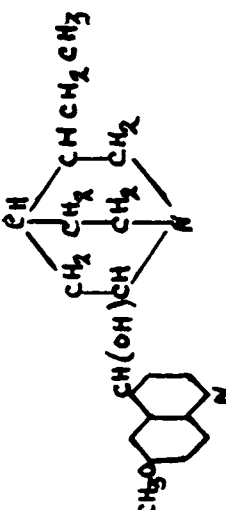
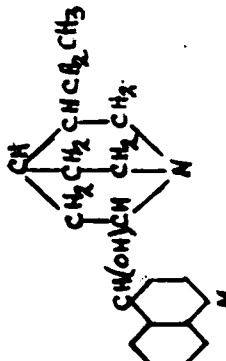
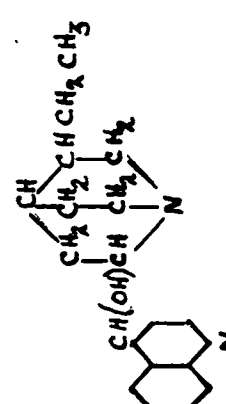
From the preceding paragraphs it will have become clear that tentative answers to these questions were given by experiments on animals and observations in artificially induced malaria in man. Nevertheless, the direct clinical experience in naturally acquired malaria had to be considered as the supreme test. On the other hand, clinical experience was not independent of pharmacological investigation. The usefulness of a drug depends on its toxicity as much as on its antimalarial effect, and the study of toxicity, again, implies an analysis of the pathological effects and investigation of the absorption and elimination of the drug. In other words, clinical, pathological and pharmacological observations could not be strictly separated and it will, therefore, not be possible here to draw a clear cut line between these aspects.

It seems advisable, in the following, to discuss the more important drugs from the point of view of toxicity and dosage, to record some of the tests for their detection and, finally to review briefly their expected antimalarial action. Such a discussion should facilitate the understanding of the development of the various treatment plans, especially those worked out under war conditions.

Before entering upon a detailed discussion of the more commonly used drugs, it may prove expedient to give a list of the drugs, the action of which on birds, monkeys and men, has been discussed in the literature of the past twenty years. This literature has been analysed by Curd¹¹⁵ who in a recent article tabulated the influence of drugs on the various species of animal as well as human plasmodia. In the following chart (simplified after Curd¹¹⁵ with some additions) no attempt is made to evaluate the literature on any given drug quantitatively. The sign  means only that some successful trial of the drug in the given host has been reported. The sign  indicates that the drug has been tried without success. Trials in humans have been broken down with respect to the type of infection studied:

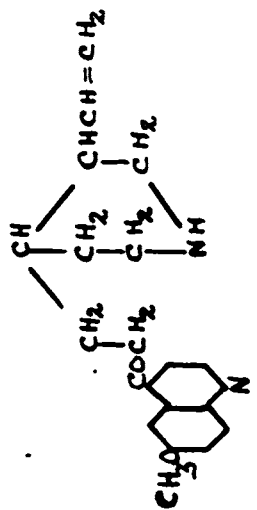
- V = vivax (benign tertian)
- M = malariae (quartan)
- F = falciparum (malignant tertian)
- I = induced malaria of paretics (no differentiation between blood-borne and mosquito-borne has been made, since this distinction is not always clear in the literature)

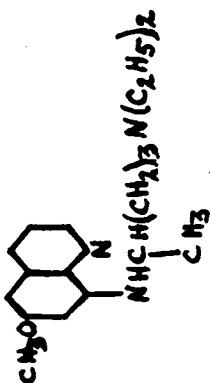
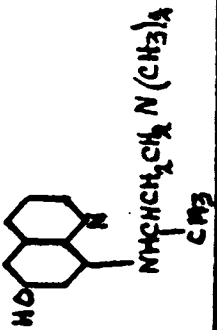
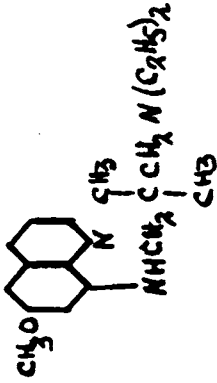
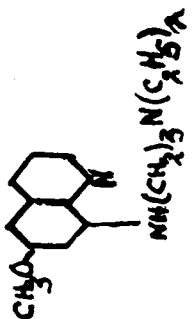
<p style="text-align: center;"><u>FORMULA</u></p>	<p style="text-align: center;"><u>NAMES</u></p>	<p style="text-align: center;"><u>AVIAN</u></p>	<p style="text-align: center;"><u>SINIAN</u></p>	<p style="text-align: center;"><u>V</u></p>	<p style="text-align: center;"><u>M</u></p>	<p style="text-align: center;"><u>F</u></p>	<p style="text-align: center;"><u>I</u></p>
<u>QUININE AND RELATED COMPOUNDS</u>							
	<p>Quinine</p>	<p>—</p>	<p>—</p>	<p>—</p>	<p>—</p>	<p>—</p>	
	<p>Quinidine</p>	<p>—</p>	<p>—</p>	<p>—</p>	<p>—</p>	<p>—</p>	
	<p>Cinchonidine</p>	<p>—</p>	<p>—</p>	<p>—</p>	<p>—</p>	<p>—</p>	
	<p>Cinchonine</p>	<p>—</p>	<p>—</p>	<p>—</p>	<p>—</p>	<p>—</p>	

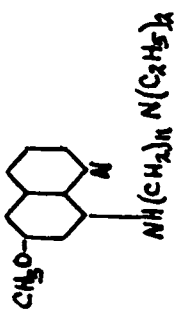
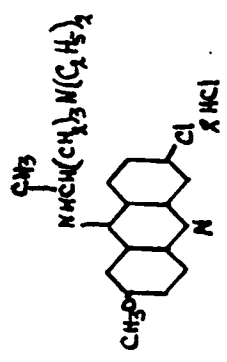
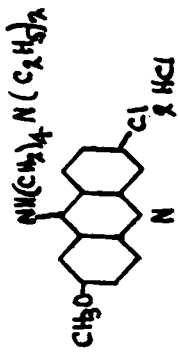
<u>FORMULA</u>	<u>NAMES</u>	<u>AVIAN</u>	<u>SIMIAN</u>	<u>HUMAN</u>			
				<u>V</u>	<u>M</u>	<u>F</u>	<u>I</u>
	Dihydroquinine	—					
	Dihydroquinidine	—					
	Dihydrocinchonidine	—					
	Didydrocinchonine	—					


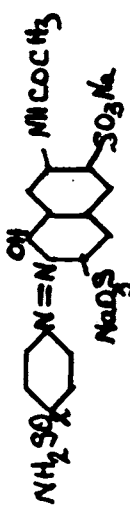


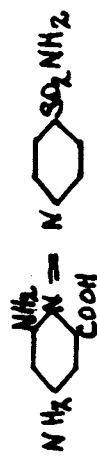

FORMULA	NAMES	AVIAN	SIMIAN	HUMAN			
				V	M	F	I
	Cupreine	—					
	Ethyloupreine	—					
	Quinethylene	—					
	Quinpropylene	—					
	Ethylhydrocupreine	—					
	Optochin	—					

FORMULA	NAMES	AVIAN	SIMIAN	HUMAN			
				V	M	F	I
	Isopropylhydrocupreine	—					
	Isoamylhydrocupreine Eukupin	—					
<p>Sodium salt of a complex copper derivative of hydroxyquinoline disulphononic acid.</p>	Cuprochin (Paludex)	X	X				
	Quitenine	X					X


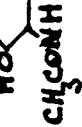


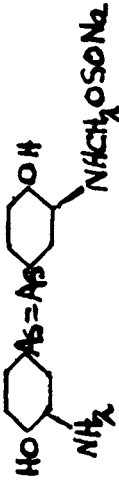


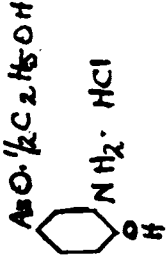
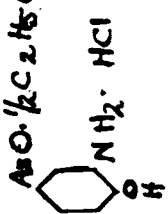
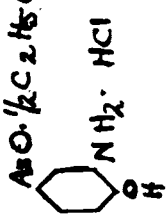
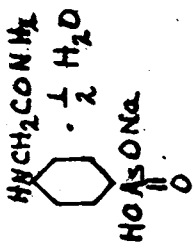
<u>FORMULA</u>	<u>NAMES</u>	<u>AVIAN</u>	<u>SIMIAN</u>	<u>HUMAN</u>			
				V	M	F	I
	<p>Quinotoxin (Quinicine)</p>	<p>—</p>		<p>X</p>			

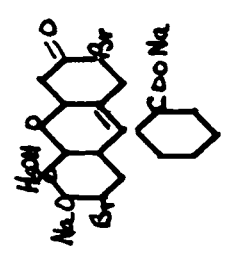
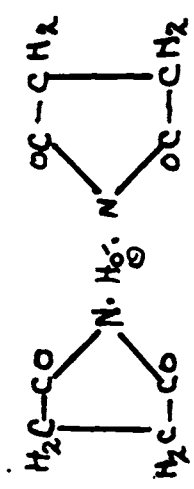
<u>FORMULA</u>	<u>NAMES</u>	<u>AVIAN</u>	<u>SIMIAN</u>	<u>HUMAN</u>			
				<u>V</u>	<u>M</u>	<u>F</u>	<u>I</u>
<u>PLASMOCHIN AND ATABRINE GROUP</u>							
	Plasmochin Plasmoquine Pamaquin Praequine	—	—	—	—	—	—
	Certuna Cillional	—	.	—	—	—	—
	Fourneau 664	—	—	—	—	—	—
	Plasmocide Rhodoquine Fourneau 710	—	—	—	—	—	—

<u>FORMULA</u>	<u>NAMES</u>	<u>AVIAN</u>	<u>SIMIAN</u>	<u>HUMAN</u>			
				<u>V</u>	<u>M</u>	<u>F</u>	<u>I</u>
	Fourneau 852	—					
	Atabrine Mepacrine hydrochloride Quinacrine Acriflavine	—	—				
	Acricidin 8	—					

<u>FORMULA</u>	<u>NAMES</u>	<u>AVIAN</u>	<u>SIMIAN</u>	<u>HUMAN</u>				
				<u>V</u>	<u>M</u>	<u>F</u>	<u>I</u>	
<u>SULFONAMIDE COMPOUNDS</u>								
	Prontosil red	X	—	—	—	—	—	—
	Prontosil 8 (soluble) Neo-Prontosil Azo-Sulfamide Prontosil	—	—	—	—	—	—	X
	Sulfanilamide Prontosil album Septoplax Prontylin	—	—	—	—	—	—	—
	Rodilone	—	—	—	—	—	—	—
	Rubiazole	X	—	—	—	—	—	—
	Proseptasine Septasine	X	—	—	—	—	—	—

FORMULA	NAMES	AVIAN	SIMIAN	HUMAN			
				V	M	F	I
<chem>NC1CCCCC1CNC2CCCC2S(=O)(=O)N</chem>	Soluseptasine		—	—	—	—	—
<chem>NaO3S[C@@H](C1CCCCC1)N[C@@H](C2CCCC2)C(O)C(O)O</chem>	Promin Diamino diphenyl- sulphone-N:N-di- dextrose sul- phonate	X	—	—	—	—	—
<chem>NC1CCCCC1S(=O)(=O)N2C=NC=C2</chem>	Sulfathiazole M & B 760	—	—	—	—	—	—
<chem>NC1CCCCC1S(=O)(=O)N2CCCC2</chem>	Sulfapyridine M & B 693	—	—	—	—	—	—
<chem>NC1CCCCC1S(=O)(=O)N2C=NC=CC2</chem>	Sulfadiazine	—	—	—	—	—	—
<chem>NC1CCCCC1S(=O)(=O)N2CCCC2</chem>	Sulfanilyl-Sul- fanillic Acid (sodium salt)	X	—	—	—	—	—

FORMULA	NAMES	AVIAN	SIMIAN	HUMAN				
				V	M	F	I	
<u>BISMUTH AND ARSENIC COMPOUNDS</u>								
$\text{Bi}(\text{SCH}_2\text{CO}_2\text{Na})_3$	Trio-bismol							
	Stovarsol (sodium)	—						
	Acetarsol							
	Spirooid							
	Salvarsan	X						
	Arsphenamine	X						
	Neo-salvarsan							
	Neo-Arsphenamine							
	Novarsenobillon							
	Mapharsen							
	Mapharside							
	Tryparsamide							X

<u>FORMULA</u>	<u>NAMES</u>	<u>AVIAN</u>	<u>SIMIAN</u>	<u>V</u>	<u>M</u>	<u>F</u>	<u>I</u>
$\text{KOOCH(OH)CH(OH)COO(SbO)} \frac{1}{2} \text{H}_2\text{O}$	Tartar Emetic	—		—	X	—	—
$(\text{SO}_2\text{O Na})_2 \text{C}_6\text{H}_2\text{O}_2 \cdot \text{SbO} (\text{ONa})_2 \text{H}(\text{SO}_2\text{ONa})$	Fuadin						—
	Merurochrome	—		—	X	—	—
$\text{NaOOCCH}_2\text{CONHCH}_2\text{CH(OcH}_3\text{)CH}_2\text{HgOM}$	Salyrgan Mersalyl						X
	Mercuric succinimide						X

ANTIMONY AND MERCURY COMPOUNDS

<u>FORMULA</u>	<u>NAMES</u>	<u>AVIAN</u>	<u>SIMIAN</u>	<u>V</u>	<u>M</u>	<u>F</u>	<u>HUMAN</u>
<u>MISCELLANEOUS DRUGS</u>							
	Methylene blue	—	X	—	—	—	—
	Giemsa G.77	—	—	—	—	—	—
	4:4 diamidino stilbene	X	—	—	—	X	—
	4:4 diamidino diphenoxy pentane	—	—	—	—	—	—
	Undecane-1:11-diamidine	X	—	—	—	—	—

A. Cinchona Alkaloids

1. Quinine

Little need be said here about the toxic effects of quinine, since the main features of cinchonism have been known for a long time and are well described in the standard textbooks of tropical medicine and of pharmacology. The same is true of the various preparations in which quinine can be used and the respective dosages for oral and intravenous administration. For more exact data, it will suffice here to refer to the standard texts and to the data given further below under the heading of treatment plans under present war conditions.

Absorption and Elimination. The fate of quinine in the body is usually described as follows:²⁸ If given orally, the drug is absorbed in the small intestine. After its appearance in the blood, the larger part (from 60-90 per cent) is removed by reticulo-endothelial cells⁴⁸ to the liver and is either destroyed here or fixed in such organs as kidneys, liver, lungs, heart and brain. In the blood, quinine is concentrated in the plasma as well as in the blood corpuscles, the relative proportion of distribution being either equal or smaller in the corpuscles. The concentration level in the blood varies with the dosage; an oral dose of 0.5 gm. of quinine dihydrochloride in man reaching a maximum of about 1.0 mg. per 100 cc. which in the course of 24 hours falls to 0.15 mg. A dose of 1-2 gm. per diem keeps the concentration constant between

0.3 to 1.0 mg. during this period. Intravenous injection seems to cause an immediate blood concentration somewhat higher (1.2 mg.). This, however, falls more rapidly than with oral dosage. If injected intramuscularly, 0.5 gm. of quinine dihydrochloride give a maximum blood concentration after about 2 hours, the figures being approximately the same as with the oral dose. Quite recently Kelsey, Oldham and Geiling⁴⁷ have shown that Leghorn roosters do not accumulate quinine in their tissues, whence it has disappeared 24 hours after the last dose even in long protracted medication. According to the same authors, intravenous injections effect a higher concentration of the drug in the leucocytes than in either plasma or erythrocytes. In the erythrocytes the concentration is greater at first than in the blood plasma, but a reversed ratio occurs in the course of 1 hour.

Quinine is eliminated from the body in the urine, the feces and some other secretions. The urine, apparently, receives the major share and the drug can be found here a few minutes after its administration, reaching a maximum after circa 4 hours and almost disappearing after 24 hours.⁴⁸ Because of the possibility that the antimalarial action of quinine may be due to some metabolic product, Kelsey and Oldham¹¹⁷ made quantitative studies of the quinine oxidase in the tissues of various animals. They found the largest amount of this enzyme in the rabbit, the liver being especially rich. During late pregnancy and the early postpartum period, a considerably reduced amount was found in the rabbit liver.¹¹⁸ These findings

0.30 to 0.40 gm. Kingsbury¹³ had had an incidence of 12 cases of psychosis among thousands of Malaysians treated with atabrine. In these 12, the psychosis was of short duration in 8, while 4 serious cases had to be sent to mental hospitals. Hoops,¹³ among 1,207 cases "treated in the usual way for from 5 to 7 days by atabrine," had only one case of mental excitement and 2 cases of serious colic. Seven other patients who also suffered from colic had been given plasmochin in addition to atabrine. More dangerous incidents were noted during the Ceylon epidemic of 1934. In one district, according to Briercliffe,¹³ not less than 15 cases of delirium developed among some hundred persons treated with atabrine per os and its use was discontinued. The summary of Fernando and Sandarasagara's experience as given in the League of Nations' report¹³ is worth quoting. These authors "after treating 299 cases in a Ceylon hospital with 0.3 gm. of atabrine for 5 days came to the conclusion that the drug was more toxic than quinine, and even than plasmoquine administered in 0.02 gm. doses for 5 days. They observed symptoms of poisoning in 3.3 per cent of their patients; in 2 cases, collapse occurred after 3 days' treatment; 1 case proved fatal, and death was attributed to atabrine of which the patient had been given only 6 tablets."

Considering the fact that these reports of toxic reactions were but few, if compared with the experiences of others who had not noted any untoward incidents, it is understandable that the League's Report arrived at the above mentioned favorable verdict. Bispham⁶⁰ arrived at a very similar conclusion on the basis of his material and a

perusal of the literature. It can be said that the general impression prevailing at the outbreak of the war was that atabrine given to adults in oral doses of 0.1 gm. 3 times a day over a period of 5 days might occasionally lead to negligible abdominal disturbances and psychotic episodes. The latter were considered of relatively greater importance and continued to receive some attention in the literature. Field⁸⁸ in 1938, estimated the occurrence of atabrine psychosis as less than one-tenth per cent of cases treated and described the clinical picture as beginning toward the end, or a few days after the usual treatment. The patients showed signs of excitement, confusion or even mania and the symptoms gradually subsided, after having lasted for approximately one week. The Journal of the American Medical Association⁶² drew attention to this article in an editorial of March 6, 1943. This editorial also stated that mental reactions following administration of atabrine in the Western Hemisphere appeared to be at least as rare as in the Far East and added that there had been no reports of mental symptoms as a result of the administration of atabrine in prophylactic dosage.

Present war conditions and the research stimulated by them have led to a better acquaintance with the possible toxic reactions during prophylactic (suppressive) treatment with atabrine. As stated by the Chairman of the Division of Medical Sciences of the National Research Council,¹⁸⁵ "Pharmacological and clinical investigations have revealed temporary gastro-intestinal disturbances in a variable percentage of persons receiving atabrine in the suppressive (prophylactic) treatment

of malaria." The dosage regimes of atabrine for suppressive treatment in use by the Armed Forces are 0.1 gm. once daily 6 days each week, or, as an alternative, 0.05 gm. once daily 6 days each week and 0.1 gm. on the 7th day.^{126,127,128} With such regimes, the untoward effects that might be encountered have usually been described as consisting of "nausea, abdominal cramps, or occasionally headache, vomiting and diarrhea. These symptoms may be prevented in most cases by giving sodium bicarbonate or sweetened drinks with the atabrine. They are never serious and almost invariably soon disappear if the drug is continued."¹²⁶

In contrast to the occurrence of toxic reactions sometimes reported with "usual" prophylactic and therapeutic doses, there exist observations of a remarkably good tolerance with much higher doses. Not only have doses up to 10 or 15 times the normal been given accidentally with relatively slight symptoms of poisoning,¹³ but larger dosage has been recommended as more efficient and safe. In order to control pyrexia more quickly, Stephenson⁶⁴ advised 0.3 gm. as a first dose followed by another 0.3 gm. 6 hours afterwards, 0.2 gm. on the mornings and evenings of the second and third days, and finally 0.1 gm. 3 times a day on the fourth, fifth and sixth days. He tried the higher dosage on himself and later used it in "many hundreds of cases" without having seen any toxic effect. Observations like these are important because of the recent recommendation of relatively high therapeutic doses of atabrine for the American armed forces which will be discussed in a subsequent paragraph.

The question as to the toxicity of atabrine appears, however, more controversial with respect to parenteral administration and proper dosage for children. Atabrine has been injected in the form of atabrine dihydrochloride or of atabrine musonate. Atabrine musonate was extensively employed in Ceylon during the malaria epidemic of 1935, when it was administered in 2 intramuscular injections of 0.375 gm. each on 2 successive days. During this and the following years a great many observations were published among which the critical study of Field, Niven and Guest⁶⁵ deserves mention. They studied the comparative response to quinine dihydrochloride and atabrine musonate in 555 acute cases of malaria. Local reactions were found to be relatively slight, urobilinuria did not seem to be more marked than in the cases treated with quinine, yet 3 cases of "severe nervous disturbance" were recorded after atabrine musonate. The authors arrived at the conclusion "that, although atabrine musonate efficiently controls an acute attack of malaria; its routine administration is not advisable. Oral therapy is the method of choice in the majority of cases and the alarming nervous sequelae occasionally occurring after atabrine musonate injections are a serious objection to its general use."

The experiences gathered by the League of Nations substantially agreed with the conclusions of Field and his coworkers. Most of the severe toxic reactions referred to in the fourth report¹³ had occurred after injections of atabrine musonate. The Commission, therefore, took the stand "that the injection of musonate of atabrine should be regarded

as unsuitable for mass treatment."¹³ Other observations refer to the parenteral use of atabrine musonate as well as atabrine dihydrochloride. Van Heukelom and Overbeek⁶⁶ stated that intoxication occurred more frequently after intramuscular injection of atabrine (dihydrochloride ?) than after its oral administration. Bryant,⁶⁷ on the other hand, from his long experience in the Sudan with severe P. falciparum infections not only recommended higher doses of atabrine than usual (even 0.6 or 0.9 gm. of atabrine were tolerated, if given with sugar in hot tea or otherwise) but also advised a combination of atabrine orally and atabrine musonate intramuscularly. Hill,¹³⁴ reported extremely good results with the intravenous injection of soluble atabrine in doses of 0.3 gm. in severe cases of subtertian malaria.¹⁰⁶ While Manson-Bahr¹³⁵ expressed a predilection for parenteral quinine over the intravenous or intramuscular administration of atabrine musonate, Dove,¹³⁶ on the other hand, allowed intramuscular injections of atabrine (dihydrochloride ?) only. He disapproved of atabrine and quinine for intravenous use and rejected quinine intramuscularly too because it might lead to sterile abscesses in spite of all possible care.¹⁰⁶ Hawking¹²⁹ recently reviewed the literature regarding the local effects caused by intramuscular injection of atabrine (dihydrochloride or musonate) and found that it was "generally considered that the intramuscular injection of atabrine is as a rule innocuous, but pain and swelling occur in some patients, and, rarely, abscesses may result." The same author injected atabrine musonate intramuscularly and subcutaneously into rabbits and rats and ascertained that microscopic

examination "always showed a certain amount of necrosis at the site of injection," although the damage caused was probably less than one-third as extensive as with injections of quinine.

As previously stated, the fourth report of the League of Nations' Commission¹³ did not arrive at any definite result regarding the dosage of atabrine for children. This uncertainty prevailed both as to prophylactic and therapeutic treatment. In most of the countries, except the Malay States, the following prophylactic dosage was given:

0-2 yrs	0.025 gm. every other day
3-8 yrs.	0.025 gm. daily
9-12 yrs.	0.05 gm. daily

In the Malay States and one Posada group, atabrine was administered in bi-weekly doses as follows:

Posada			Malay States	
Up to 2 yrs.	0.05 gm.	Twice	Up to 2 yrs.	0.025 gm.
3-4 yrs.	0.10 gm.	a week	3-4 yrs.	0.05 gm.
5-8 yrs.	0.15 gm.	with an	5-6 yrs.	0.075 gm.
		interval	7-8 yrs.	0.10 gm.
		of two	9-10 yrs.	0.125 gm.
9 yrs. and over	0.20 gm.	days	11-12 yrs.	0.15 gm.
			13-16 yrs.	0.175 gm.

In the treatment of malaria, three different modes of dosage for children were recorded. In the Malay States, the drug was administered for 7 days to children of:

1-2 yrs.	0.05 gm. daily
3-4 yrs.	0.075 gm. daily
5-8 yrs.	0.10 gm. daily
9-12 yrs.	0.20 gm. daily
12-15 yrs.	0.25 gm. daily

Children over 15 years received the same dose as adults (0.3 gm. daily). In all other countries studies (except Oprisenti in Rumania),

the treatment also extended over 7 days but with a different dosage:

0-4 yrs.	0.10 gm. daily
5-8 yrs.	0.20 gm. daily

Children from 9 years on received the usual adult dose. At Opriseni (Rumania) the treatment lasted only 5 days and the amounts given were:

0-5 yrs.	0.10 gm. daily
5-12 yrs.	0.20 gm. daily
12 yrs. and over	0.30 gm. daily

Summarizing all these experiences with reference to toxicity, the report stated: "Relatively larger doses (than for adults) of atabrin are required during infancy, and it is often the custom to administer adult doses to children over 15 or even 12 years of age. In this case, however, the effective doses of synthetic drugs are already slightly toxic. This is due to 2 reasons: (a) because the dose is larger in proportion to weight, and (b) because the child organism is more sensitive to the drug."¹³

Apart from possible toxic effects, another difficulty in administering atabrine to small children up to 5 years was found in the fact that the drug was often regurgitated immediately after having been taken and, therefore, not properly ingested.¹³

It seems that the League was somewhat more cautious with regard to atabrine administration to children than were those observers who claimed good tolerance in general. Thus Cannistraci⁶⁸ believed that children as well as adults tolerated a prophylactic dose of 0.3 gm. one or two days a week.

Absorption and Elimination. The literature on the subject of absorption, elimination and organic effect of atabrine was abstracted by Molitor⁶⁹ in 1941. His review forms the main basis of the following sketch to which have been appended significant recent findings.

After oral administration, atabrine was rapidly absorbed so that it was found evenly distributed over the body tissues a few minutes afterwards. Two and one-half hours later, however, concentration appeared relatively greater in the liver, gall-bladder and intestines. After 5 days it could still be detected in the gall bladder and the upper portion of the gastro-intestinal tract. It took 7 to 8 days until it had disappeared from all organs. Excretion in the urine and feces in partly unchanged chemical form was very slow. In patients who had undergone a course of treatment, traces of the drug were found up to 9 weeks after the end of the treatment. This pointed at once to the slow excretion and the cumulative effect of atabrine. Further evidence of this was supplied by the fact that, whereas, a single dose of 0.3 gm. per kg. body weight proved fatal to dogs, the same lethal effect was reached, if a daily dose of 0.1 gm. per kg. was given over 15-27 days.

In cats, dogs and rabbits where the distribution in organs and tissues was studied after prolonged oral and intravenous administration, remarkable differences were found between these two modes. After 10 days of daily oral doses of 0.5 gm. atabrine per kg. to dogs, the distribution was as follows:

Spleen	2.75 mg. (per gram)
Kidney	2.5 mg. (per gram)
Liver	2.0 mg. (per gram)
Skin	0.11 mg. (per gram)
Muscle	0.07 mg. (per gram)
Brain	0.035 mg. (per gram)

On the other hand, three weeks after intravenous injections on 5 successive days, the distribution was:

Lungs	0.08 mg. (per gram)
Liver	0.01 mg. (per gram)
Kidney	0.004 mg. (per gram)
Spleen	0.0025 mg. (per gram)

These findings agreed with some other experimental data regarding the toxicity of atabrine. Generally speaking, the toxicity of atabrine seemed to vary, depending upon the species of experimental animal used. In cats and mice, 200 mg. of atabrine per kg. proved toxic, but in rabbits 500 mg. per kg. With regard to parenteral administration, it was ascertained that the lethal intravenous dose was 20 to 40 times smaller than the lethal oral dose and, moreover, largely dependent upon the mode of injection. Thus, for instance, 21 per cent of the dogs died, if 5 mg. of atabrine per kg. were injected over 30 to 60 seconds, while only 4.8 per cent succumbed to the higher intravenous dose of 7.5 mg. per kg., if injection took 60-90 seconds. The above mentioned data on the distribution of atabrine in various tissues also conformed to the general features of atabrine poisoning. Hyperemia and central injury of the liver and fatty degeneration of the renal tubules were the main findings in atabrine poisoning, and these two organs showed relatively high concentrations after prolonged administration.

The effect of atabrine on the blood, the cardiovascular system and on the uterus deserves special mention. In the blood, after oral or parenteral administration of widely varying doses, a level of approximately 1:300,000 was quickly reached and maintained for some hours.⁷⁰ Atabrine could not be completely extracted from the blood even with alcohol, an experience that pointed to its being selectively absorbed by erythrocytes (and possibly parasites).⁶⁹ Neither hemolysis nor methemoglobin formation seemed to result from it. Atabrine tended to lower the blood pressure and effected general vasodilatation, including dilatation of the coronary vessels as observed in the isolated heart of the monkey.⁶⁹ Small doses caused inconsiderable rhythmic disturbances, while large doses might lead to heart bloc, ventricular flutter and fibrillation.⁶⁹ Because of the cardiac and vasodilatory action of atabrine, an addition of 0.5 cc. of 1:1000 solution of adrenalin to each cubic centimeter of a 3 per cent solution of atabrine was suggested, if the latter was to be injected intravenously.⁶⁹ Several years ago, Ascoli recommended a treatment of malaria with adrenalin, expecting that the latter by its vasoconstrictor effect upon the spleen would activate the parasites accumulated in this organ. The combination of atabrine with adrenalin might, therefore, be interpreted as a combination of atabrine and Ascoli treatment.

In the isolated uterus of pigs, rabbits and cats, concentrations as low as 1:200,000 had a stimulating effect upon muscular tone and frequency of contraction; whereas, higher concentrations of 1:20,000 had the opposite result. If a pregnant cat was given 1 to 4 mg. per

kg. intravenously, a transitory increase of uterine contractions was observed. Because of the fact that this dose was much higher than that given in the treatment of malaria, the use of atabrine in pregnancy was not believed to be contraindicated.⁶⁹

Atabrine was not considered a general protoplasmic poison, since it did not decrease the oxygen consumption of isolated brain and testicular tissue. It had, however, an antipyretic effect, 0.1 gm. per kg. lowering the temperature by about 1/2 to 1° C. in a cat with experimental fever provoked by B. coli injection.⁶⁹

The general picture as sketched here can be considered as the experimental and theoretical background of the clinical study of atabrine toxicity. Recent experimental studies, however deviate in some essential points from this overall picture. Dearborn and coworkers⁷¹ determined in dogs "the amount of atabrine excreted in the urine and feces and the amount of accumulation in the tissues after small daily oral doses, comparable to those used in suppressive treatment of malaria." During a period of 4 weeks of daily administration of atabrine, its daily excretion in urine and feces soon reached a level of less than 4 per cent of the daily dose. Moreover, in a series of experiments, dogs were given small daily doses of atabrine over periods of varying length and the distribution of the drug in the tissues was studied 48 hours after the last dose. In most tissues maximum concentrations proved to be attained within 2 weeks. The tissue levels differed with the size of the dose, 50 mg. per kg. resulting in about 10 times the tissue levels reached with 5 mg. per

kg. In addition the same authors⁷¹ referred to unpublished data from their laboratory which showed "that there is no histologically detectable damage to the liver after 8 weeks and no apparent effect on the liver function (by bromsulphalein test) or the general health of the dogs, after 32 weeks during which they received 30 mgm. per kgm. per week."

Annegers et al.,⁷² impressed by the similarity of liver damage caused by cinchophen to that sometimes observed with atabrine, "undertook to study the excretion of atabrine in the bile and the effect of the drug on the liver as reflected by changes in the bile." Previous studies by Clark et al. had obtained no evidence of liver damage in dogs with 8 times the doses given to man, nor had the non-protein nitrogen content of the blood or the urea clearance tests indicated renal damage.⁷² Using rats and dogs for their experiments, Annegers et al. found that in these animals the drug was "rapidly destroyed or chemically modified," that storage in the liver, spleen and muscles was insignificant and that within 10 days the drug had largely disappeared from the body. Regarding urinary excretion of atabrine in dogs, the findings of these authors were very similar to those of Dearborn⁷¹ and coworkers. In some dogs, the cholic acid output was impaired, a fact pointing to the possible hepatotoxic action of atabrine. Although the biliary excretion of unmodified atabrine did not surpass a fraction of the dose, Annegers and coworkers did not believe that the drug was metabolized so as to lead to the excretion of toxic products in the bile and their reabsorption in the intestine.

Scudi and coworkers^{235,236} gave the results of their experiments on atabrine toxicity in animals under special dietary conditions. Fasting increased the toxic effect of a high single dose of atabrine in rats; the animals exhibiting severe irritation of the gastrointestinal tract and liver necrosis.²³⁵ With a diet high in proteins but low in fats, rats seemed to resist toxic effects of daily administrations of atabrine upon the liver. In dogs, daily administration of large doses of atabrine (25-50 mg. per kg.) produced an inanition within 3 to 6 weeks; but doses of 5-10 mg. per kg. did not show this effect even 3 to 5 months after administration of the drug had been started.²³⁶

Tests. Its distinct yellow color and fluorescence even in very high dilutions form the basis for various methods of testing for the presence of atabrine in excretions, blood and tissues. A very simple test for detection of atabrine in urine was given by Peter. The urine is made alkaline and the atabrine extracted with ether. After the ether has been evaporated the residue is dissolved in concentrated sulphuric acid, whereupon a yellow coloration and fluorescence will mark the presence of atabrine.²²

Another method was made known by Wats and Ghosh and modified by Field and Niven. Ten cc. of urine are made alkaline with a few drops of NaOH, then 0.25 cc. of amyl alcohol are added. After this mixture has been well shaken, the atabrine will be contained in the amyl alcohol which separates as an upper layer. Relatively large quantities can be detected by their yellow color when the test tube is viewed

against a dark background through transmitted light. Traces up to 1:2,500,000 will be recognizable by fluorescence in ultra-violet light. This method can also be used for a quantitative estimate by colorimetric comparison with standard solutions.²² Another method of colorimetric estimation was elaborated by Tropp and Weise.²²

Dearborn and coworkers⁷¹ estimated the concentration of atabrine in blood of dogs by buffering the laked whole blood to pH 8.5, extracting the atabrine directly with iso-amyl alcohol and determining the fluorescence of the alcohol extract. A more complicated method which allowed an accurate determination was used by these authors⁷¹ for tissue and excretion studies; this method, however, could not be applied to low blood concentrations.

Brodie and Udenfriend¹³⁰ worked out 2 methods "for the estimation of atabrine in biological fluids and tissues through the measurement of its fluorescence in an acid environment," partly based on the previous findings of Craig. Craig had studied the fluorescent material extractable by ethylene dichloride from blood and urine during atabrine therapy. The extracts included material the "combined solubility fluorescent characteristics" of which were different from those of pure atabrine solutions. But this material (degradation products of atabrine) was soluble in strong alkali and could be quantitatively removed by washing the extracts with a strong NaOH solution. The remaining fluorescent material had solubility characteristics identical with those of atabrine.¹³⁰ Brodie and Udenfriend based the specificity of their methods on the exclusion of such fluorescent degradation products

of atabrine as well as of naturally occurring fluorescent components of the biological fluids and tissues themselves. The first of their methods is a "double extraction procedure" and "is wholly satisfactory for the precise estimation of the concentration of atabrine in the plasma, whole blood, tissue, and urine of patients on the usual regimes of suppressive or definitive atabrine therapy." The principle of this method is as follows: "Atabrine is isolated from the biological material by an extraction of the free base with ethylene dichloride at a pH of about 8. The ethylene dichloride extract is then washed free of degradation products with 2.5 N sodium hydroxide and the atabrine is returned as the salt to an aqueous phase of concentrated lactic acid. The estimation of atabrine concentration is then made by its fluorescence in the lactic acid."¹³⁰

The second method rests upon the measurement of fluorescence in the initial ethylene dichloride extract after addition of acetic acid. It is less sensitive than the double extraction method and is not recommended for ordinary use with plasma where the concentration of atabrine is usually low. On the other hand, the method is simple and speedy and it is, therefore, recommended by the authors for most tissue analyses.

Another method for quantitatively estimating atabrine in blood and urine was described by Masen.¹³³ The test which is also based on fluorescence measurement is supposed to give accurate results for as little as 0.1 mg. of atabrine per liter of blood and can be performed on a 5 cc. sample. The identification of atabrine depends on comparing

fluorometer readings for solutions at pH 6 with readings from solutions at pH 12. "Atabrine shows 9 times as much fluorescence at pH 12 as at pH 6. Application of this test to human urine passed during 26 days after discontinuance of atabrine administration showed the 9:1 ratio for some days, but a lower ratio later, indicating probably decomposition products of atabrine."

Therapeutic Effect. Generally speaking, atabrine and quinine evince the same effect in the treatment of malarial infections, though not always in the same degree. It is, therefore, understandable that the evaluation of atabrine has usually been undertaken in comparison with the action of quinine. This comparative point of view is documented in the bulk of the literature to be studied here.

Höhne⁷³ was able to observe the destructive influence of atabrine upon young ring forms of P. falciparum in Giemsa-stained blood preparations. The cytoplasm as well as the chromatin were both severely altered in their morphological appearance. Degenerative processes were also noticed by Hewitt and Richardson¹³¹ in experiments with P. lophurae, but the effect of atabrine or plasmochin was not as rapid as that of quinine. Decourt⁷⁴ stressed the dysgonic action of atabrine (quinacrine), believing that the asexual reproduction and gamete formation of schizonts became almost entirely lost.

Whatever the pharmacodynamical mechanism may be, the effect of atabrine on the trophozoites seems to be well established from a clinical point of view. The fourth report of the Malaria Commission

of the League¹³ stated that the therapeutic daily dose of 0.30 gm. of atabrine acted somewhat more rapidly on the trophozoites of P. vivax than did quinine in the dose of 1 gm. The trophozoites were supposed to disappear after the second or third dose of atabrine, and the parasitocidal action was said to last longer after treatment with atabrine than with quinine. The same was believed to be true with regard to P. malariae and the trophozoites of P. falciparum, according to this report, disappeared from the peripheral blood after 4 doses of atabrine in most cases. However, the relative values of atabrine and quinine did not seem clearly established to the Commission. The latter expressed itself very cautiously regarding a possible slight superiority atabrine might have over quinine in the action on the gametocytes of P. vivax and P. malariae. As far as the gametocytes of P. falciparum were concerned, both quinine and atabrine were practically powerless.

In looking over the clinical investigations of atabrine published during the last 5 to 6 years the impression prevails that the main interest of the authors lay in the prophylactic action of the drug and its ability to prevent relapses rather than in its immediate effect upon the acute attack. The latter was hardly doubted and according to the League's report, "In benign tertian the fever nearly always falls after the first 3 therapeutic doses of atabrine—that is to say by the second attack. In malignant tertian the fever falls almost invariably by the third attack."¹³

Comparing the prophylactic effects of atabrine and quinine, the League's Commission¹³ believed a daily dose of 0.05 gm. atabrine

inferior to a daily dose of 0.40 gm. of quinine. It seemed that the weekly administration of 0.40 gm. atabrine, given in 2 installments of 0.20 gm. each on 2 successive days or with a 1-2 days' interval, was somewhat more effective than quinine given every day. Also, this dosage appeared to have a slightly stronger effect on the gametocytes of P. vivax. The discredited dose of about 0.05 gm. atabrine a day taken for a period up to 7 years, according to Junge,⁷⁵ gave excellent results in 20 Europeans in Liberia. According to Ejercito⁷⁶ 212 laborers in the Philippines who had not had malaria previously received 0.20 gm. atabrine prophylactically twice a week, while another group of 272 was not given any prophylactic treatment. Of the first group, 78 remained in the malarial area for about 41 days and 10 of them (13 per cent) developed malaria. Of the second group, 106 stayed at the place for an average length of 23 days and 38 (36 per cent) developed malaria. However, in a recent report from a South Pacific Base, Simpson et al.¹³⁷ recorded the occurrence of symptomatic malaria in nearly 50 per cent of cases who had taken 0.195 gm. (3.0 grains) of atabrine twice weekly; i.e., a dosage almost identical with that recommended by the League of Nations.

Most of the other reports published during recent years deal with populations in districts of endemic malaria, populations which either possess a certain degree of immunity or in which a pre-existing history of malaria cannot be excluded. Consequently, the problems presenting themselves were: Can an epidemic outbreak of malaria be suppressed? Can relapses be prevented? Can the population be kept in average good health?

Canet,⁷⁷ giving the results of 4 years' mass prophylaxis among many thousands of coolies on plantations in Cochin-China, had no doubts that synthetic remedies were superior to quinine. 0.30 gm. of atabrine daily for 3 to 5 days would very quickly suppress any serious outbreak of malaria. However, the treatment had to be continued with the same daily dose, usually given once a week. Without such after treatment, conditions would soon become as bad as they had been before.

Melik-Adamian⁷⁸ reported on 2,031 school children in the U.S.S.R. who had been suffering from malaria and who received atabrine in the spring of the following year. During the next 13 months only 11.5 per cent of these children had relapses. Fastovskaia and Chenderowitch⁷⁹ stated that in Pakrovskoie (U.S.S.R.) which had a stable population and where malaria (P. vivax and P. falciparum) was endemic, atabrine with or without plasmocide gave better relapse rates than did quinine with or without plasmocide. A review article by Hoare¹³² shows that a good many other Russian publications from 1940 to 1942, likewise reported satisfactory results with atabrine. Hill and Goodwin⁸⁰ worked among a population of 1,646 in the southern United States which had first been rendered free from malaria parasites by treatment. During the following year the population was divided into 3 groups and treated with the following results:

Group I	0.1 gm. (1.5 grains) atabrine 3 times a week	1.8% clin. cases
Group II	0.65 gm. (10.0 grains) quinine daily	5.6% clin. cases
Group III	Control (soda bicarbonate capsules)	31.7% clin. cases

During the second year when no quinine was given, the atabrine group

showed an incidence of 0.3 per cent of clinical cases and the control group 5.3 per cent. It should, however, be added that plasmochin-- 0.01 gm. (1/6 grain) 3 times a day for 7 days--was also given at the end of each season.

These examples of satisfactory experiences with atabrine may now be contrasted with the observations of others who expressed more or less grave doubts of its effectiveness in malarial countries.

In the Panama Canal Department of the U. S. Army with an average troop strength of 13,000, the annual malaria rate was estimated as 40 per thousand. The cases received treatment at various station hospitals as well as at the Gorgas and Colon Hospitals. The treatment was not uniform, but of all kinds of treatment Gentzkow and Callender⁸¹ found atabrine alone the least effective in the prevention of relapses. Large and prolonged doses of quinine were declared much more effective in the prevention of relapses in falciparum infections, and slightly more effective in infections with P. vivax. The result was different, if plasmochin was added, but the role of plasmochin in the prevention of relapses will be discussed in the following section. Instead, there has now to be considered a group of reports which are skeptical of the lasting benefit derived from prolonged medication with atabrine.

Lamprell,⁸² for instance, studied the relative effects of quinine and atabrine medication upon a population of 2,173 in a number of estates in Assam where malaria was hyperendemic. In the first series, a 5 day treatment with atabrine was followed by 0.2 gm. atabrine daily

to each adult once a week from the end of May until the middle of September. A second series was given quinine every third week on 5 consecutive days. A third series served as a control. As long as the administration of the drugs lasted, the incidence of malaria decreased in the atabrine as well as the quinine series. Afterwards there was higher incidence in these 2 groups, particularly in the atabrine group, than in the control series.

Similar results were obtained by other observers, particularly from the Malay States.^{83,84} What is the explanation for this phenomenon? Field and Niven⁸⁴ whose observations covered 2,500 immigrant Indian laborers who, after having received atabrine and quinine prophylactically, showed higher malaria incidence than the controls, made some tentative suggestions. Primary attacks might have been delayed during the prophylactic treatment, or the lack of acquired immunity might have resulted in an outbreak of clinical symptoms due to infection easily contracted in a hyperendemic region. At any rate, these observations tended to confirm the opinion of Clark and Kamp, expressed as early as 1935, that drug control of malaria in people living in a district situated in the midst of an endemic area was of doubtful benefit. Freed from clinical symptoms, these people did not develop their immune defenses. As soon as an infection occurred (possibly by importation from the neighborhood) the disease was apt to flare up more vehemently than before.¹³

C. Plasmochin

Dosage and Toxicity. Efforts to imitate or to improve the German product, plasmochin, have been made in various countries and have led to a number of more or less modified drugs. The French-manufactured "Praequine" is supposed to be identical with the German "Plasmochin," while another French compound "Rhodoquine" (= Fournau 710) lacks a $\text{CH} - \text{CH}_3$ group in the side chain.

Rhodoquine and praequine, mixed in equal parts, constitute a drug called "Rhodoprêquine"⁸⁵ which in the dosage of 0.03 gm. daily for 3 days is supposed to exert a gametocidal and schizontocidal action on P. vivax.⁸⁶ The Italians (S. A. Farmaceutici Italia) turned out a product "Gamefar" which, though perhaps not quite identical with plasmochin, seems to have a very similar antimalarial action.⁸⁷ The term "plasmocide" was given as a general name for plasmochin-like substances synthesized at the State Pharmacological Laboratories in Moscow.

The Imperial Chemical Industries have been manufacturing a product "pamaquin," and according to biological tests, pamaquin dihydrochloride is identical with the German plasmochin dihydrochloride.⁸⁹

The Germans themselves in 1938 announced a new product "certuna" (also called "cilional"), a 6-hydroxy-8-(γ -dimethylamino- α -methyl-butylamino) quinoline. This drug proved more potent than plasmochin in its action on the exflagellation of the male gametocytes of P.

catheimerium, and seemed to be less toxic than plasmochin in humans, though as efficient against the gametocytes in P. falciparum infections.¹⁵⁴ Chopra et al.¹⁴⁰ stated that a dosage of 0.35-0.4 gm. (0.03 gm. t.i.d.) was usually effective and well tolerated.

From the time of its invention, toxic reactions to plasmochin have been noticed. Both Sioli³³ and Mühlens³⁴ frequently observed cyanosis especially of the lips which Sioli considered a signal for stopping plasmochin medication. The latter had also had one case of plasmochin poisoning among the 40 cases of general paretics on whom he was trying the drug. The symptoms were the following: the patient suffered from abdominal pain, livid discoloration of the skin, cyanosis of the lips and general weakness. His blood was of a chocolate color and somewhat later the urine showed a gray sediment beneath a black surface. Upon rising from bed the patient collapsed and vomited. However, recovery took place after 4 days. This patient had received daily doses of plasmochin up to 0.25 gm. This picture combines most of the outstanding toxic reactions to plasmochin; the drug may form methemoglobin and in fatal cases hepatitis and fatty degeneration or necrosis of the liver have been observed.⁵⁷

The potential toxicity of plasmochin imposed restrictions on the scope of its employment as well as upon the dosage. It was suggested in the early thirties that plasmochin was a true prophylactic-- but even if correct, this would be of no practical consequence since the doses required would lie beyond the range of safety. The drug was considered a schizontocide for P. vivax and P. malariae. Nevertheless,

the threat of toxic reactions made it a questionable substitute for the other two schizontocidal drugs. It was, however, unique in its effect upon the gametes, especially of P. falciparum. Therefore, from an early date combinations of plasmochin with quinine and atabrine have been proposed in order to improve the relapse rate and to decrease the number of gametocyte carriers of malignant tertian malaria. This explains why plasmochin has been used almost exclusively in combination with or subsequent to other drugs. But this, in turn, has added another problem; viz., that of its compatibility with quinine and atabrine. The belief is now widely shared that quinine and plasmochin can be given together, while the simultaneous administration of atabrine and plasmochin is harmful. If used at all, plasmochin should be given after atabrine medication.

From these considerations it becomes understandable that the dosage of plasmochin has been gradually reduced from its original height. According to the fourth report of the League of Nations' Commission,¹³ large daily doses of 0.06-0.04 gm. and even such small doses as 0.02 gm. of plasmochin, if given for 10 days or more, caused dizziness, cyanosis and eventual icterus in an average of 3.5 per cent of cases. Prophylactic doses of 0.02 gm. twice a week seemed relatively safe. According to the same source, the therapeutic dose of plasmochin was 0.01-0.03 gm. daily for adults, "associated with quinine or atabrine, given either simultaneously or after certain lapse of time." The latter statement, however, received the qualification that "the association of quinine with plasmoquine is undoubtedly less toxic than that

of atebirin with plasmoquine."

In view of these facts and in order to avoid repetition, it seems advisable to discuss further observations on the toxicity and desirable dosage of plasmochin in a subsequent paragraph in connection with its therapeutic effects. It is, however, worth mentioning here that the Russian plasmocide is supposed to have a somewhat different toxic action.¹³ While it may cause pain and vomiting, it is believed not to lead to the formation of methemoglobin, one of the main dangers of plasmochin.

Absorption and Elimination.* Quickly absorbed in the gastrointestinal tract, plasmochin begins to appear in the urine within 20 minutes following its administration. However, it seems that a small portion only is excreted, the bulk being destroyed in the tissues.⁶⁹ Using Bancroft differential manometers, Nandi⁹⁰ measured the oxygen uptake of various tissues of the guinea pig in the presence of plasmochin. In the blood where stimulation was most marked, the coefficient of stimulation was 41 per cent with a concentration of plasmochin as low as 1:300,000 (the level usually reached in therapy). According to this author the phenomenon was an enzymatic (thermolabile) reaction, the decomposition of plasmochin taking place mainly through thermostable systems present in the tissues.⁹⁰

Just as in the case of atabrine, the toxicity of plasmochin was found to be different in various species of animal.⁶⁹ Rabbits and

* Here again, Molitor's⁶⁹ summary of 1941 has been used freely.

canaries showed a preponderately acute type of reaction with nervous, circulatory and respiratory disturbances soon following upon the administration of plasmochin. In mice, cats and dogs, however, symptoms of a more delayed action consisting in cyanosis, methemoglobinemia and possible respiratory failure were more pronounced. Taking the toxicity of an oral dose as a relative standard, subcutaneous injection was 5 to 6 times as toxic in the rabbit, and intravenous injection 60 to 70 times. It would appear, however, that the rabbit formed an exception, other species of animal not showing any marked difference between oral, subcutaneous and intravenous administration as far as toxicity was concerned.⁶⁹

Regarding pathological findings due to plasmochin, two sets of toxic effects stood out.⁶⁹ First and foremost was the formation of methemoglobin which was observed in man as well as in horses, cows, sheep, pigs, cats and dogs. In the latter 2 species of animal, a blood concentration of 1:12,500 seemed sufficient to form methemoglobin. In rabbits and mice, on the other hand, methemoglobinemia took place only after the blood had been hemolyzed. If administration of plasmochin was discontinued, signs of methemoglobinemia disappeared, and negative bilirubin and urobilin tests tended to prove that the formation of methemoglobinemia was not connected with the destruction of erythrocytes or damage to the liver. Yet hemolysis could be observed in vitro, if the concentration of plasmochin exceeded 1:5,000.⁶⁹

The other set of toxic effects of plasmochin observed in man as well as in all species of animal investigated related to the cardiovascular

system. A comparison of plasmochin, quinine and atabrine showed all 3 drugs to be negative chronotropic as well as negative dromotropic in the electrocardiogram of man and dog. In the isolated monkey heart, they caused irregular beat and diastolic standstill. In heart-lung preparations of frogs and rabbits the minimal concentrations for bringing about diastolic standstill were given as 1:2,000 for plasmochin, 1:500 for atabrine and 1:300 for quinine. In the isolated heart of these animals, concentrations of 1:100,000 sufficed to cause irreversible diastolic standstill. In submaximal doses, plasmochin (and atabrine too) decreased the minute volume and had an adverse effect upon the function of the vasomotor centers. In small concentrations, plasmochin caused vasoconstriction; whereas, vasodilatation was observed with large concentrations.⁶⁹

Tests. A test for the detection of plasmochin in urine said to show the presence of the drug in a dilution up to 1:200,000 was recommended by Schuleman, Schönhöfer and Wingler and may be quoted here after Field.⁸⁸

- "1. Mix 200-300 cc. of urine with 20 cc. of 50 per cent caustic potash and stir.
2. Shake 3 times with 30 cc. of pure ether. The ether layer is separated. (If an emulsion forms, clear by the addition of a few drops of alcohol.)
3. Pool the ethereal extracts, filter, and shake twice with 10 cc. of water to which 2 drops of N/caustic soda has been added.
4. Separate the ether from the water and shake up again with 6 cc. of 2 per cent acetic acid.
5. Separate the acetic acid solution and heat over a water bath to remove any residues of ether.
6. Add 3 cc. of pure glacial acetic acid and about 0.05 gramme of chloranil. Heat over a flame in a test tube for about 1½ minutes. A blue colour develops, or in weak solutions a blue green, if plasmochin is present."

Tchitchibabine and Hoffmann⁹¹ used iodic acid (HIO_3) instead of chloranil and worked out a test sensitive to a dilution of plasmochin in urine of about 1: ten million. The test has been described as follows:⁹¹

"200 cc. of urine are made alkaline by addition of 50 cc. of a 30 per cent solution of caustic soda. This is then extracted thrice, in a separating funnel, with ether, 25 cc. each time. The ethereal solution, 75 cc., is shaken with a few grammes of anhydrous potassium carbonate and then filtered into a 250 cc. separating funnel. Five cc. of 10 per cent sulphuric acid are added: after shaking, the lower layer is decanted into an ordinary test tube. The contents of the tube are gently boiled for 30 seconds to drive off the ether. After complete cooling under running water 2 cc. of a 10 per cent watery solution of iodic acid are added; the tube is then shaken and left to settle.

If plasmochin is present in the urine a violet colour develops in 2 or 3 minutes: this darkens somewhat and lasts for nearly half an hour. By this method it is possible to identify plasmochin in quantity as small as a tenth of a milligramme per liter of urine. Rhodoquin and plasmocid also give colour reactions with this test. With plasmocid the colour only appears after a delay of 15 to 20 minutes, as compared with 2 or 3 minutes with plasmochin. If appreciable quantities are present, plasmochin gives a violet blue colour, plasmocid violet red. With plasmochin the colour persists for about half an hour, with plasmocid it begins to fade after a quarter of an hour."

Nandi and Dikshit⁹² described a test which allows the detection and quantitative estimation of plasmochin in tissues, but cannot be used in urine. A few drops of Folin's phenol reagent are added to an aqueous acid solution of plasmochin. The mixture is made strongly alkaline with Na_2CO_3 and a blue colour then develops reaching its greatest intensity in approximately half an hour. Plasmochin in a dilution of 1:1,000,000 can thus be detected and can be estimated quantitatively in dilutions up to 1:200,000. However, the test is

not specific, a number of substances of a phenolic character in the tissues also responding to it. But if the tissues are treated with an excess of NaOH and then extracted with ether, the test is applicable.

Therapeutic Effect. As with quinine and atabrine, so with plasmochin, the exact action of the drug on the various phases of the malaria parasites has not been established with any degree of finality. According to Boyd and Dunn,⁹³ its effect on P. cathemerium in canaries is similar to that of quinine; i.e., mainly reducing the rate of reproduction. Hewitt and Richardson¹³¹ claim a direct plasmodicidal effect on P. lophurae. Whether the drug given in high doses of 0.06-0.08 gm. to paralytics bitten by infected mosquitoes really destroys the sporozoites or whether it acts on forms developing from the sporozoites, thereby preventing the appearance of trophozoites at the end of the incubation period, is a matter for debate. Also debatable is the degree of its effect upon the trophozoites of P. vivax and P. malariae.^{13,88} Its gametocidal action on P. falciparum, however, is beyond doubt. In practice, plasmochin has been mainly used in combination with other drugs, either to diminish the number of gametocyte carriers or to prevent relapses. The fourth report of the League of Nations' Commission¹³ definitely stated: "In minimum doses of 0.02 grm., plasmochin devitalises the gametocytes of P. falciparum, and at the same time diminishes their numbers." It also stated that in association with quinine or atabrine, plasmochin was markedly effective in preventing relapses in benign tertian and quartan malaria "and appears similarly to reduce the frequency of malignant tertian relapses."

In the literature subsequent to this report, these views are found to be partly supported and partly doubted. It is, moreover, permissible to say that in more recent times, the doubts have increased.

A group of Rumanian investigators headed by Ciuca⁹⁴ reported in 1938 that among the 4 schizontocides, quinine, aristoquine (= aristochin = diquinine carbonic ester) atabrine and acriquine, atabrine was the most efficient in preventing relapses of quartan and malignant tertian malaria, particularly if followed by plasmochin. For this purpose, they believed, a single dose of 0.02 gm. of plasmochin repeated if necessary every 5 days in those rare cases where crescents persisted was sufficient to devitalize the gametocytes. Livadas⁹⁵ and associates treated 112 cases in a mountain village in the Peloponnesus whom they kept under long continuous observation. They divided their patients into 7 groups. Groups 1 to 3 received quinine for 7, 10 or 20 days respectively; group 4 received atabrine, group 5 plasmochin. Group 6 was given atabrine followed by plasmochin, and group 7, quinoplasmin. The latter combination appeared the most effective in preventing relapses. Barbosa²³⁷ found atabrine associated with plasmochin much more effective in preventing relapses of P. vivax infections (175 with primary infections, 139 with reinfections) than quinine and atabrine. He also obtained excellent results with P. falciparum infections with a treatment of atabrine for 5 days followed by plasmochin for 4 days.

Gentzkow and Callender⁸¹ who had been doubtful of the value of atabrine alone for the prevention of relapses among the malaria patients of the Panama Canal Department of the U. S. Army, (see p. 65), nevertheless,

witnessed a pronounced effect upon the incidence of relapses, if plasmochin was administered concurrently with atabrine or following it. This effect, although evident in all types of malaria, was especially marked in P. vivax infections.

To this list may be added a number of experiences with slightly different preparations. Raskine⁹⁶ combined acriquine (Russian) with a preparation designated as "quinoline no. 31" by giving the former drug in the dosage of 0.01 gm. 3 times a day and 0.03 gm. of quinoline 31 twice daily for 5 days. In both benign and malignant tertian malaria, the fever disappeared in about 3 days and the schizonts in about 4 days, while the gametocytes of malignant tertian malaria disappeared by the sixth day. However, slight abdominal pain of 2 to 3 days duration was observed in some of the cases so treated. Dupoux⁹⁷ and coworkers used premaline in mass treatment as well as in prophylaxis in the Cape Bon area of Tunisia in 1937 and 1938. The parasite index and the splenic index decreased remarkably; no relapses were reported after treatment and subsequent bimonthly administration of the drug, nor were toxic reactions observed. Similar experiences with weekly administrations of premaline were noted by Genevray⁹⁸ et al. in Tonkin. Messerlin,¹³⁸ however, from experiences with exceptionally severe malaria prevalent in Morocco in 1941, stated that the prophylactic administration of premaline did not show the same striking results as in previous years. Since premaline represents a combination of quinacrine and rhodoprèquine,⁹⁹ its administration can be considered as somewhat equivalent to the simultaneous use of atabrine and plasmochin. In this connection,

it is noteworthy that some observers have not only failed to object to the simultaneous use of the latter 2 drugs, but have even recommended it. Thus MacMahon¹⁰⁰ treated his acute cases (mainly malignant tertian) with large doses of quinine and small doses of plasmochin-compound. After the symptoms had disappeared and the patient was feeling well he was given 0.1 gm. atabrine and 1 tablet of plasmochin compound (0.01 gm. plasmochin and 0.125 gm. quinine) 3 times a day. With this treatment MacMahon reported toxic symptoms in less than 10 per cent of his patients and recurrences in less than 25 per cent. Ayala and Bravo,¹⁰¹ on the other hand, reported 4 cases of severe mental disturbance during or immediately after treatment with "atapè" tablets (each of which contains 0.1 gm. atabrine and 0.005 gm. plasmochin).

It will have been noticed that the reports of an alleged beneficial influence of plasmochin on the relapse rate of malaria rested largely on an empirical basis, above all on experiences in India among British and Indian troops.¹³⁵ From the theoretical and experimental point of view, plasmochin as a gametocide could only be expected to decrease the number of infectious gametocyte carriers and thereby help to eradicate the disease where it is endemic or prevent further spread of malaria. The early hopes for malaria eradication by the combined use of quinine (or atabrine) and plasmochin have, however, not materialized. To give but one example, Clark¹⁰² and his associates in Panama in 1937-1938 treated all parasite carriers who were discovered at monthly surveys. One group was given 0.1 gm. of atabrine 3 times a day for 5 days and 0.01 gm. plasmochin twice daily during the subsequent 5 days. A second

group received 1.0 gm. (15 grains) of quinine sulfate daily instead of the atabrine, the treatment otherwise being the same as in the first group. There was little difference in the efficiency of the 2 methods, both led to an all but complete clinical disappearance of the disease—but not to its eradication. Since similar results had been obtained with quinine or atabrine alone, it is not surprising that Clark¹⁰³ and his group arrived at the conclusion that plasmochin had contributed relatively little to the good symptomatic effect. Similar doubts relative to the prophylactic value of gametocides in controlling malaria in endemic areas have also been expressed by others.¹⁰⁴ Logically, it might be assumed that these negative findings would also have a bearing on the wisdom of adding plasmochin to quinine or atabrine in order to decrease the number of relapses in individual cases. Since the effect of plasmochin on the schizonts of P. falciparum is practically nil, there is no theoretical reason to expect any additional gains from the drug in this type of malaria infection at least. Experiences during the present war have indeed confirmed this suspicion and the routine use of plasmochin in the treatment of acute malaria has lately been discarded by the armed forces.¹⁰⁵

D. Treatment Plans of Malaria Under Present War Conditions

In the preceding section the main emphasis was placed on the evaluation of one drug or the other, rather than on regular treatment schemes. Furthermore, the bulk of the experience related to mass treatment and mass prophylaxis of stable populations in regions of endemic malaria. In as far as peace-time observations and recommendations

were concerned, it was assumed that, theoretically at least, quinine, atabrine and plasmochin were equally available. The war has caused fundamental changes in many respects. The acute shortage of quinine has imposed definite restrictions on its use and has made the employment of substitutes imperative. Main attention has shifted from stable and premunised populations to American and European soldiers exposed for the first time to malarial infection and expected to retain their fighting strength under conditions of both mental and physical stress. It has, therefore, become necessary to draw up standardized plans for the prophylaxis and treatment of malaria, plans which at one and the same time should be based on the best scientific and clinical judgment available. This task would have been facilitated, if there had been common agreement on the theoretical and clinical factors involved. This, unfortunately, was hardly the case. Summarizing some recent papers on the subject, White,¹⁰⁶ in December 1942, wrote: "The majority of papers dealing with the treatment of malaria have certain features in common; their authors all know how malaria can best be treated. There is a praiseworthy dogmatism about their pronouncements, but there is anything but uniformity of dogma. There is not even uniformity of opinion regarding the manner in which quinine, the oldest and best tried remedy of all, should be administered. There is still less uniformity of opinion regarding the merits and demerits of the different remedies, the indications for their use, and the doses which can be safely administered in the treatment of the acute attack of malaria and in clinical prophylaxis. In great part the diversity

of views is explained by the very different malarial conditions prevailing in the countries in which practical experience has been gained, by differences in strains of malaria parasites, by differences in the manner in which different races of mankind react to infection and to some of the specific remedies, and by differing degrees of malarial endemicity."

White¹⁰⁶ also summarized the main points on which some agreement had been reached before the war: (1) preference for short courses of treatment, particularly in endemic regions where reinfections were likely to occur and the building up of a state of resistance seemed advisable. (2) Sparing use of specific drugs in hyperendemic regions by restriction of the drug to children mainly, until they had acquired the degree of solid immunity against local strains possessed by the adult population. (3) Regular administration of specific remedies in prophylactic doses for susceptible sojourners in such hyperendemic areas. But, White added, "such considerations are applicable for the most part only to civilian populations engaged in peace-time pursuits. In war other considerations predominate."

Intensive and continuing experimental and clinical work on the treatment of malaria, as well as mounting experiences in war zones, has led to a gradual development of war-time measures and recommendations. Circular Letter No. 56, issued by the Office of the Surgeon General¹⁰⁷ on June 9, 1941, may be taken as a starting point. The value of chemical prophylaxis was considered limited to special situations when troops had to be kept fit in endemic areas. The choice was left

open between atabrine 0.2 gm. every 3. or 4 days, or quinine sulfate in the dose of 0.3 gm. daily. Regarding the treatment of clinical malaria, a difference was made between field forces and hospital patients. Oral therapy for the former envisaged the use of quinine or atabrine with the possible addition of plasmochin to either drug. Quinine was to be given for 7 days before meals, in 3 daily doses of 0.6-1.0 gm., and 0.02 gm. plasmochin might be given once a day after meals during the same period. If atabrine was preferred, 3 doses of 0.1 gm. each were given after meals for 5 to 7 days. In this case, however, plasmochin, if used, had to be added after completion of the course, 0.02 gm. being given daily for 3 days. In hospital patients, the above oral medication of quinine in the form of quinine sulfate capsules or quinine bisulfate tablets might be replaced by the "Sinton treatment" in the following form: The patient was purged and then given 30 cc. doses of "mixture A" at intervals of 1 hour. "Mixture A" has the formula:

Sodium bicarbonate	92.0 gm.
Sodium citrate	60.0 gm.
Calcium carbonate	4.6 gm.
Water to make 690 cc.	

After 3 doses of this mixture were given and half an hour had passed, 30 cc. of "mixture Q" of the following composition were administered:

Quinine sulfate	14.0 gm.
Citric acid	42.0 gm.
Magnesium sulfate	84.0 gm.
Water to make 630 cc.	

During the subsequent 7 days, 30 cc. of "mixture A," followed half

an hour later by 30 cc. of "mixture Q," were given 3 times daily. In addition, plasmochin, 0.02 gm., once daily was administered for 7 days.

Parenteral therapy as an emergency measure by intramuscular injection of 1.5 gm. of quinine (hydrochloride or dihydrochloride) or 0.2 gm. of atabrine dihydrochloride was mentioned for forces in the field. The injection might be repeated after 12 hours. In the case of hospital patients, parenteral therapy might be indicated not only if the patient was comatose or unable to retain oral medication, but also if tests showed that the drugs had not been absorbed. The choice then lay between quinine or atabrine given intravenously and quinine injected intramuscularly. Whatever parenteral administration was chosen, it should be replaced as soon as feasible by oral medication.

Viewed as a whole, these recommendations were in line with the treatment plans suggested by the League of Nations' Commission and many subsequent authors. The relatively slight emphasis placed on drug prophylaxis was influenced by the realization that the drug did not prevent infection but only suppressed manifestations of the disease. All treatments proposed were "short-term" treatments; the choice left open between quinine and atabrine reflected prevailing opinion and so did the possible addition of plasmochin.

If these recommendations are compared with the treatment of malaria as practiced at the same time in the British army,¹⁰⁸ some differences are worth noting. Although quinine and atabrine were regarded as practically alternative by the British also, quinine was

believed to have a more rapid antipyretic action than atabrine. Plasmochin was viewed as antiinfective and antirelapse and, therefore, suitable for treatment after the acute attack. Accordingly, the British standard army treatment consisted of the use of all three drugs, quinine, atabrine and plasmochin in the following order:

<u>Days</u>	<u>Drug</u>	<u>Dose</u>
1-2	Quinine (bisulfate or hydrochloride)	0.65 gm. (10 grains) t.i.d.
3,4,5,6,7	Atabrine	0.1 gm. t.i.d. after meals
8-9	None	None
10,11,12,13,14	Plasmochin	0.01 gm. t.i.d. after meals

This "combined quinine-atabrine-plasmochin (QAP) treatment" went back, in principle at least, to suggestions made by Amy and Boyd¹⁰⁹ in 1936, based on experiences with the British forces in India. These authors had recommended quinine during the initial febrile attack, followed by 0.3 gm. of atabrine daily for 7 days and 0.03 gm. plasmochin for 5 days afterwards.

After the entry of this country into the war, the "combined QAP treatment" as standardized in the British army was recommended by the Subcommittee on Tropical Diseases of the National Research Council¹⁸⁵ as the "method of choice," the main difference being that totaquine might be used instead of quinine sulfate. The place assigned to totaquine is understandable, since, in the meantime, the Japanese conquest of the Netherlands Indies had cut off the main sources of quinine supplies. This fact also explains why an alternative treatment combining atabrine and plasmochin was foreseen for "simple vivax

infections and in other infections where no totaquine or quinine is available." As a third possibility, in cases where atabrine was not available, a combination of totaquine or quinine-plasmochin was suggested. Regarding "suppressive treatment," atabrine was the only drug mentioned in these recommendations which may be quoted in extenso:¹⁸⁵

- "(1) Combined QAP Treatment (method of choice).
 - (a) Totaquine or Quinine sulfate 0.64 Gm. (10 grains) three times daily after meals for two or three days or until pyrexia is controlled. Then give
 - (b) Atabrine 0.1 Gm. ($1\frac{1}{2}$ grains) three times daily after meals for five days. Then after two days without antimalarial medication give
 - (c) Plasmochin 0.01 Gm. ($\frac{3}{20}$ grain) three times daily after meals for five days, except for the debilitated patient, who should receive only two doses daily. (Discontinue if toxic symptoms occur. Never give atabrine and plasmochin concurrently.)
- (2) Atabrine-Plasmochin Treatment (may be used for simple vivax infections and in other infections when no totaquine or quinine is available).
 - (a) Atabrine, as above for seven days. Then, after two days without antimalarial medication give plasmochin 0.01 Gm. three times daily for five days, as above.
- (3) Totaquine or Quinine-Plasmochin Treatment (method when no atabrine is available).
 - (a) Totaquine or quinine sulfate, as above, for seven days during the last five of which accompany each dose of totaquine or quinine with plasmochin 0.01 Gm. three times daily.
- (4) Suppressive Treatment.
 - (a) Atabrine. Give 0.1 Gm. ($1\frac{1}{2}$ grains) twice daily after meals on two days a week, allowing a two to three days interval between days of medication."

This outline of a suggested routine therapy was followed by a note of caution: "It was the consensus of this subcommittee that until we have had more experience with the use of atabrine it should be used only under the guidance of a physician or public health officer." The remark is interesting because it reflected some preoccupation with

the possible toxic effects of atabrine. German observers,¹¹⁰ on the other hand, who had had experience with malaria during 1941, were positive in stating that gastro-intestinal troubles occurred almost exclusively in cases where plasmochin had been combined with atabrine. Among the "great number of malaria patients of 1941 treated predominantly with atabrine" hardly any serious gastro-intestinal complaints which might influence prophylaxis or therapy had been encountered. "Even in cases of malaria combined with acute gastro-enteritis or dysentery, the troubles were not essential."

The combined QAP treatment as recommended by the National Research Council was given as the method of choice by the Surgeon General, U. S. Army, in the Circular Letter No. 135 of October 21, 1942,¹¹¹ with the exception that totaquine was not mentioned as an alternative to quinine sulfate. In addition, quinine (0.64 gm. daily after the evening meal) was noted as a substitute for atabrine in emergency suppressive treatment, if the latter drug was not available. Parenteral administration of quinine dihydrochloride or atabrine dihydrochloride was suggested in the following cases:

Malaria with coma-- 0.64 gm. of quinine dihydrochloride in not less than 200 cc. sterile normal saline, intravenously, very slowly every 8 hours until oral medication becomes possible.

Malaria with vomiting-- Either: 1.0 gm. of quinine dihydrochloride in 10 cc. sterile normal saline intramuscularly, repeated if necessary in 8 hours; or: 0.2 gm. of atabrine dihydrochloride in

5 cc. sterile normal saline injected intramuscularly, if quinine is not available.

Reports from American¹³⁷ and British¹³⁹ troops indicated satisfaction with the combined use of quinine and atabrine (similar to the recommended QAP treatment) but also a tendency to discard plasmochin in the routine treatment. Hill^{134,135} had demanded a daily dose of 0.1 gm. of atabrine as a standard prophylactic treatment for troops as far back as August, 1942. Experimental work, including investigations of the plasma concentration of the drug,¹²⁶ shed new light on the scientific basis of antimalarial therapy. Many considerations thus combined to necessitate the drafting of a new treatment plan which was outlined in Circular Letter No. 153 from the Office of the Surgeon General, August 19, 1943.¹¹² Fundamentally, the changes were based on these factors: (a) the necessity of saving quinine, (b) the conviction that the toxic effects of atabrine were not frequent or serious enough to limit its use either in suppressive or therapeutic doses, while plasmochin questionable as to its therapeutic results, allowed but a small margin between therapeutic and toxic effects, and (c) a realization that the efficiency of antimalarial drugs depended on their reaching an effective plasma level. The latter point is of particular significance. Since quinine is eliminated rapidly and atabrine retained in the tissues for some length of time, the QAP treatment led to a temporary gap during which neither quinine nor atabrine was present in the plasma in sufficient concentration. The QAP treatment was now given up and instead atabrine was given "in

relatively high initial doses, followed by smaller maintenance doses."

The recommended treatment of the acute attack of malaria is now the following. "Atabrine hydrochloride 0.2 Gm. (3 grains) and sodium bicarbonate 1 Gm. (15 grains) by mouth with 200 to 300 cc. of water (or an equal amount of sweetened tea or fruit juice) every six hours for five doses, followed by 0.1 Gm. ($1\frac{1}{2}$ grains) three times a day after meals for six days (total 2.8 Gm. in seven days)." Quinine sulfate 1 gm. (15 grains) orally after meals 3 times a day for 2 days and then 0.6 mg. (10 grains) 3 times a day for 5 more days (total 16 gm. in 7 days) is the alternative, if atabrine is not available. Plasmochin is no longer given as a routine measure, and only to hospitalized and closely watched patients. "The course consists of plasmochin 0.01 Gm. ($\frac{1}{6}$ grain) by mouth three times a day after meals for four days except for the debilitated patient, who should receive only two doses a day. Each dose of plasmochin should be accompanied by at least 1 Gm. (15 grains) of sodium bicarbonate. The fluid and sugar intake should be liberal during and for some days after the course." This course may either follow immediately upon the end of the atabrine therapy or may be initiated during the final days of treatment with quinine. In severe cases of malaria, or where the disease is complicated by serious disorders (including vomiting) or where oral medication is not feasible or of no avail, atabrine or quinine is given parenterally. The recommended parenteral methods are as follows:

"(a) Atabrine dihydrochloride 0.2 Gm. (3 grains) in 5 cc. of sterile distilled water injected intramuscularly with the usual precautions into each buttock (total 0.4 Gm. or

6 grains). If necessary, one or two additional doses of 0.2 Gm. (3 grains) may be given intramuscularly at intervals of six to eight hours. As soon as the patient can take and retain oral medication atabrine should be given by mouth in such doses as to give a total by both routes together of 1.0 Gm. in forty-eight hours, followed by 0.1 Gm. three times a day after meals for five days (total 2.8 Gm. in seven days).

(b) Quinine dihydrochloride 0.6 Gm. (10 grains) in sterile isotonic solution of sodium chloride 300 to 400 cc. (minimum 200 cc.) injected intravenously with the usual precautions, especially avoiding speed. If necessary, there should be no hesitation to cut down to the vein. This treatment may be repeated in six to eight hours, if the situation demands it. When the patient can take and retain oral medication give a complete course of atabrine (preferable) or quinine by mouth as described for uncomplicated cases in paragraph 5b."

Measures for the control of vomiting and the general care of the patient are stated in detail in the letter. Relapses are treated in the same manner as first attacks although "prolongation of maintenance doses of atabrine to a total period of two to three weeks may be tried." If, nevertheless, relapses occur repeatedly, the oral quinine treatment "may be used and continued with a daily dose of 0.6 Gm. (10 grains) to a total period of three or four weeks; but such instances must be kept to a minimum in order to conserve quinine."

The preservation of quinine also dominates the suppressive treatment of malaria where, with a few exceptions, atabrine alone is to be used. 0.1 gm. of atabrine is given at the evening meal on 6 days each week. As an alternative, 0.05 gm. of atabrine may be given at the evening meal, 6 days each week and then 0.1 gm. at the evening meal on the 7th day. Although a mere emergency measure, suppressive treatment, if indicated, should preferably be started

2 weeks in advance for the purpose of achieving a high plasma concentration at the time of actual exposure. Besides, since side reactions are more apt to accompany the use of initial doses, they would be overcome by the time the troops reached the danger zone.

It seems, however, as if opinion on the necessity of pre-treatment with atabrine were changing, in spite of the fact that "with the usual suppressive dosages the maximum plasma concentration of the drug is not attained until after three to six weeks."¹²⁶ With a dosage schedule of 0.6 gm. per week, a protective level is apparently reached, if suppressive treatment is started coincidentally with exposure.

In summing up, it may be said that the cinchona alkaloids and atabrine still stand out as the best antimalarial drugs available, but they do not constitute an ideal solution in every respect, particularly with regard to prevention of infection and relapses. Other drugs which have been tried with varying degrees of promise will be discussed in the following section.

E. Sulfonamide Compounds

Prontosil and Sulfanilamide. The use of prontosil and sulfanilamide in connection with studies on bird and monkey malaria has been briefly mentioned above (p. 21). Somewhat equivocal results were obtained in the therapy of avian malaria^{30,41} but Coggeshall and Maier⁴⁴ found that a single oral dose of sulfanilamide completely eradicated the highly fatal P. knowlesi infection of rhesus monkeys.

Further work on monkeys was performed by Das Gupta and Chopra¹⁵⁰ and by Rodhain¹⁵¹ in the same year, 1938. Using doses of 3 cc. of prontosil per day for 3 days, the former obtained complete cures but they felt the high dosage was out of the range possible for humans. Rodhain obtained cures with sulfanilamide in chimpanzees infected with "a falciparum-like organism" (P. reichenowi ?) and monkeys infected with P. knowlesi, but the drug did not appear to him to be as active as atabrine, since 0.3 gm. of it were necessary to achieve the same results effected by 0.05 gm. of atabrine.

At about the same time the first trials of sulfonamides in human malaria were reported. Niven^{152,153} in the Malay States treated 80 natives, variously infected with P. falciparum, P. vivax and P. malariae, with prontosil album in a dosage of 3 gm. per day for 7 days. He found the drug less potent in effecting cures than quinine which he administered to 68 controls. Although he had no toxic reactions in his series, he considered prontosil potentially more dangerous than quinine and also pointed to its relatively high cost. A similar opinion was expressed in the Annual Report of the Institute for Medical Research of the Federated Malay States for the year 1938.¹⁵⁴ Yamamoto¹⁵⁶ used sulfanilamide for control of induced malaria in 14 cases. He obtained cure in 2 of them after a total administration of 15 to 17 gm. of the drug. In 5 cases no antimalarial effect was seen and in 7, varying degrees of slight improvement alone were noted. Faget et al.¹⁵⁵ considered both prontosil and sulfanilamide unsuitable for clinical use.

In the 4 cases of falciparum infection in which they tried them, both drugs failed to free the blood stream of parasites, although they did alleviate immediate clinical symptoms. This very fact constituted a danger in their opinion, since patients so treated might form unsuspected reservoirs of infection. Sorley and Currie's¹⁵⁷ evaluation of sulfonamide therapy was somewhat similar though they were more favorably impressed than Faget with the immediate clinical effects of the drugs. They treated 10 patients with P. vivax infection with 10 grains (0.65 gm.) of prontosil album 3 times a day for 4 days. More rapid improvement occurred than with other antimalarial drugs, but the improvement in the patients' condition was not paralleled by improvement in the parasite picture, so the authors advised following the prontosil with a 5 day course of atabrine to clear the blood stream. Chopra, Das Gupta, Sen and Hayter¹⁶⁶ gave 0.5-1.0 gm. of prontosil 5 times a day per os or intramuscularly to 19 humans. Both sexual and asexual forms of vivax and malariae parasites were destroyed but only the asexual forms of falciparum. There was no action upon crescents, a conclusion substantiated by Chopra and Basu¹⁶³ who fed laboratory bred A. stephensi upon crescent carriers to whom as many as 40 tablets of prontosil had been administered. The crescents were not devitalized but grew to sporozoites in many of the mosquitoes. Sulfanilamide was used intravenously by De Leon¹⁶⁴ in patients infected with P. falciparum. He found the drug exclusively schizonticidal, but considered it a useful substitute for atabrine where intravenous treatment is indicated.

Soluseptasine, Septisine, Proseptasine. Working with soluseptasine and septisine (derivatives of sulfanilamide), Farinaud and Eliche^{159,160} demonstrated "remarkable schizonticidal activity" of the drugs. In 3 to 5 hours there was total disappearance of schizonts from the peripheral blood. Gametes of P. vivax were also destroyed but not those of P. falciparum. Sinton et al.¹⁶¹ found proseptasine (the benzyl derivative of sulfanilamide) to be a true causal prophylactic in 5 out of 8 cases of induced P. falciparum infection, but they did not consider the results capable of practical application until further studies had been made.

Sulfapyridine, Sulfathiazole, Sulfadiazine. Despite certain encouraging leads provided by this early experimental work on sulfonamides, there prevailed a general sense of dissatisfaction with sulfanilamide itself as a therapeutic agent in human malaria,¹⁷¹ particularly in contrast to its activity in monkey malaria and in certain human infections other than malaria. Experimental work was accordingly undertaken with members of the sulfonamide group less closely allied with sulfanilamide. Coggeshall and Maier¹⁶⁹ used sulfadiazine, sulfathiazole and sulfapyridine in monkeys infected with P. knowlesi and found them all therapeutically effective in doses of 1.5 gm. per os for 2 to 3 days with, in the case of sulfathiazole, an additional 0.5 gm. intravenously for 2 days. Studies of their effect upon the respiration of plasmodia in vitro substantiated the opinion gained from therapeutic tests, although, as previously mentioned (see page 22), no direct correlation between host response and in vitro reactions was demonstrated.

Sulfapyridine (M & B 693) was given 8 monkeys infected with P. knowlesi by Singh and Singh.¹⁶⁷ Two 0.5 gm. tablets per day by mouth freed the blood of parasites and effected cure, but the authors commented that this was proportionately much in excess of the human dosage of the drug as it is used in other diseases. Chopra and Das Gupta,¹⁶² on the other hand, obtained cures in monkeys with 0.05 to 0.15 gm. of M & B 693 given daily intramuscularly. This dose they considered smaller than the proportionate dose for a monkey as compared with that for a man. In the light of this success, Chopra et al.¹⁶⁸ tried the drug in 12 human cases, administering 4.0 gm. daily by mouth for 5 days. The treatment controlled symptoms and drove both forms of P. vivax and the asexual form of P. falciparum from the blood. Recrudescence in 14 days occurred if smaller dosage was employed, as was demonstrated by the administration of 1.5 gm. for 5 days to certain of the patients who were infected with P. malariae. A second course of M & B 693 given these patients still failed to eradicate parasites from the blood entirely.

Dikshit et al.¹⁷⁰ used sulfathiazole for the treatment of monkeys with P. knowlesi malaria. Following a single oral dose of 0.1 gm., the parasites disappeared from the blood stream temporarily. Three grams of sulfathiazole given during 3 days resulted in radical cure at the end of the course. Coggeshall and Maier¹⁷¹ treated 17 human cases of naturally occurring vivax and falciparum infections with promin, using an average daily dose of 15 gm. for 3 days, and produced definite therapeutic effect in all. The vivax infection was somewhat more

resistant than the falciparum. Of 13 patients treated by these workers with sulfadiazine, 26 gm. total dosage by mouth in 6 days, 10 showed effect and 3 none, the drug thus appearing in their experience to be less effective than promin. Their conclusion upon the basis of this work was that "at present there is no reason for preferring these drugs to quinine or atabrine." Schwartz¹⁷³ and his coworkers drew similar conclusions on the basis of 14 cases treated with sulfathiazole in like manner. Johnson¹⁷² used sulfathiazole for control of paroxysms in 2 cases of induced malaria. His dosage schedule was 2 gm. every 4 hours for 24 hours, then 1.0 gm. every 4 hours for 2 days. Rapid improvement was effected by the drug with final clearance of the infection by quinine. A subsequent series of cases was given a smaller initial dose (1.5 gm.) with similar temporary control of fever. Johnson used sulfadiazine in 14 other cases administering 24 to 40 gm. over a period of 4 to 8 days to 10 of the patients, and 44 to 48 gm. during 19 days to the remainder. Among the 14 patients there was a relapse rate of 23 per cent, a second course of sulfadiazine in all instances controlling the relapse. Johnson's conclusions were that sulfathiazole had some antimalarial action but did not effect interruption of the course of the disease, while sulfadiazine was of such curative efficacy that he advised it for military use.

F. Thio-bismol

Bismuth combined with arsenic was used by Cignozzi¹⁷⁸ in 1925 in the treatment of about 100 cases of malaria. The drug employed, "metilarsinocitrobismutato sodico," was used as an adjuvant to quinine therapy in cases where quinine by itself was ineffective. Speranza¹⁷⁹ in 1927 first employed bismuth alone. His preparation, "Salbiolo," was a complex organic salt of bismuth in an oily suspension which he injected intramuscularly. Twelve cases were so treated and in all of them some antimalarial action of the drug was demonstrated, although the results were considered definitely inferior to those obtained with quinine. The author attributed the action to direct influence of bismuth upon the asexual forms of the parasites.

Schwartz¹⁸⁰ and Cole et al.¹⁸¹ first employed sodium bismuth thioglycollate (thio-bismol) in 1939 and 1940 in treating therapeutically induced malaria in paretics. The paroxysms occurring in these patients are often of alarming severity so that it is desirable to interrupt the rapid succession of attacks without stopping the malaria courses. For the production of such "rest periods" the ordinary anti-malarial drugs are not satisfactory since, if given in effective doses, they may terminate the course entirely. This Cole et al.¹⁸¹ demonstrated in the preliminary studies leading up to their choice of a bismuth compound for management of the course of therapeutic malaria. Single injections of the antimony compounds, fuadin, antimony and potassium tartrate and sodium antimony thioglycollate, for example, stopped the

clinical course completely or produced too long an afebrile period before resumption of the cycle. Similarly, arsphenamine, nearsphenamine and mapharsen, while possessing undoubted antimalarial effect, did not have the desired powers of temporary inhibition. Thio-bismol was selected¹⁸¹ as the most successful drug to achieve this purpose out of a series of bismuth compounds tried, including bismuth subsalicylate, sobisminol, biliposol, sodium bismuth tartrate, bithoxyl and iodobismitol. A single intramuscular injection of 0.2 gm. of thio-bismol brought about cessation of fever within 6 to 12 hours and produced a rest period of 2 days before resumption of the cycle. Subsequent paroxysms were unaffected unless repeated thio-bismol injections were given. In 263 patients treated by Cole and Schwartz, the mortality rate was 2.2 per cent, a figure comparing favorably with that for mortality in induced malaria in general (2.2-5.38 per cent).¹⁸⁵ Brunstig and Love¹⁸⁴ at the Mayo Clinic used thio-bismol on one or more occasions in 33 of 90 consecutive cases of therapeutic malaria and obtained results similar to those of Cole and Schwartz. They found single doses of 0.1 gm. sufficient for control of the succeeding paroxysm, while 0.2 gm. exerted a more lasting effect than was generally desired.

Whelen,¹⁸⁶ observing that "P. vivax, in spite of its name (benign tertian—simple three-day fever), gives rise to quotidian and not tertian fever in 80 per cent of primary cases," used 0.2 gm. of thio-bismol intramuscularly in 32 treated patients to control the fever. Consistent results were obtained depending upon the stage at which

the drug was administered. Given during the incubation period of the disease, before the first paroxysm, there was no effect either upon the time of onset or upon the type of fever. Given during the fully developed quotidian stage, a remission of 48 hours was produced, followed by regular tertian fever. The drug was thus observed to have a selective action upon alternate cycles. Mayne and Young¹⁸³ applied this same technique in induced malaria in their own practice, achieving similar results.

Combination of thio-bismol with quinine was tried in cases of induced malaria by Young et al.¹⁸² who demonstrated that the bismuth compound inhibited the next paroxysm while the quinine controlled the general infection so that quicker therapeutic response was obtained than with quinine alone.

The method of action of thio-bismol is as yet imperfectly understood. It appears, however, that only certain stages of the parasite are influenced. Whelen's¹⁸⁶ conversion of quotidian fever to tertian by means of thio-bismol seemed to him to indicate that semi-mature rather than very young parasites were damaged. Cole et al.¹⁸¹ showed that in tertian infection, if the injection was made within 10 hours of the expected onset of a paroxysm, that paroxysm would be effectively inhibited with a resultant two-day afebrile interval. If the injection was made more than 10 hours before the expected onset of the chill, no effect was observed. This negative result they considered dependent upon the relatively rapid rate of absorption and excretion of the drug which reduces blood stream concentration below the therapeutic level

before the parasite matures and commences its next asexual cycle.

At the same time, the two-day rest period between an effective injection of thio-bismol and resumption of the cycle of paroxysms indicated to their minds that the drug affects the half-grown parasites in the blood at the time of injection. An experimental study carried out by Young and coworkers¹⁸² confirmed this hypothesis. In quotidian fever occasioned by P. vivax infection, thio-bismol, 0.1 or 0.2 gms., inhibited the next expected paroxysm caused by a given brood of parasites, if it was injected 16-28 hours after the last paroxysm caused by that brood. Injections at other hours had no effect. Degeneration of the parasites could be demonstrated in stained films and their number was markedly decreased. In P. malariae infections no definite action of thio-bismol against any particular age group of parasites could be demonstrated in the experience of this group of workers, although therapeutic results were occasionally apparent. Against P. falciparum infection thio-bismol was practically without effect.

G. Arsenicals

The efficacy of arsenated benzene compounds as agents to control malarial paroxysms has been known for some time.^{190,191,192,193} Originally, these drugs were employed with partial success in the treatment of the naturally occurring disease. However, since the introduction of the malaria therapy of central nervous system syphilis and recognition of the desirability of giving patients undergoing this treatment occasional rest periods, the whole group of arsenicals has

been accorded greater recognition for the inhibitory type of action also displayed by bismuth compounds.

Arsphenamine. Experiments with arsphenamine (salvarsan) in malaria therapy were instituted not long after the introduction of the drug as an anti-syphilitic agent. Werner, as early as 1910,¹⁹² used single intramuscular doses of 0.6 gm. of the drug in treating cases of tertian and aestivo-autumnal malaria. In the former, the parasites had generally disappeared from the blood stream within 24 hours after the injection and no relapses occurred for several weeks. Only half of the aestivo-autumnal cases, however, showed any immediate response to the drug and most of those doing so had relapses within a period of a few weeks. A large body of subsequent work (for the copious literature on arsenated benzene compounds see Curd¹¹⁵ and Cole¹⁸¹) has dealt with refinements of this technique but the final conclusion of most authors has been substantially like Werner's.

Neoarsphenamine. Arsphenamine has been largely supplanted by neoarsphenamine in malaria therapy. Shortly after the introduction of the latter drug, trials of its efficacy in malaria were carried out in Germany,^{216,217,218} Werner, who had done the initial malaria work with arsphenamine,¹⁹² establishing a dosage ratio of 1.0 arsphenamine: 1.5 neoarsphenamine and demonstrating identical activity upon "tertian" malaria. As with arsphenamine no effect upon "tropica" could be produced. The drug was believed to be most efficacious when given in a single intravenous dose of 0.8 gm. repeated at about 5-day intervals. Results with intramuscular dosage were less predictable

and not as long sustained.²¹⁶ Subsequent experience with neoarsphenamine in the hands of other German workers and a number of British investigators^{219,220,221,222,223,224} substantiated the prompt effect of the drug upon clinical course and parasitemia. This effect regularly occurred within 12 to 24 hours. By giving subsequent injections no less than 24 hours before the time of each anticipated relapse both clinical and hematological evidences of recrudescence could be avoided, but no long-time suppression was achieved. The British school,^{225,226,227} found smaller intravenous doses (0.45 gm.) equally as effective as larger ones. While agreeing upon the favorable effect produced in P. vivax malaria, they considered the drug most valuable when used as an adjuvant to quinine. The occasional appearance of parasites during treatment of latent malaria by neoarsphenamine which they and also Silvan²²⁸ noted, was the basis for the recommendation that a quinine course follow use of neoarsphenamine. Repeated attempts to influence infections with parasites other than vivax^{224,225,226} or to use the drug in avian malaria²²⁹ remained unsuccessful. None of the reports dealing with use of neoarsphenamine in malaria records toxic reactions of any significant degree; even mild gastro-intestinal disturbances were not associated with the low dosage and the wide intervals employed.

Neoarsphenamine is currently considered more valuable in induced than in spontaneous infection. Its successful use for many years by Amsterdam hospitals conducting malaria treatment (both blood and mosquito induced) of paretics has been described by Winckle.¹⁹⁰

P. vivax infections alone were controlled by the drug and various strains of vivax were found to be unequally sensitive to it. It was necessary, therefore, to determine the optimum dosage for each case individually. In general, however, intravenous injection of 0.05 to 0.15 gm., converted a double fever into a simple one or obtained for the patient a few afebrile days. To cut the fever short definitively, when use of quinine was not desirable, a series of injections of neoarsphenamine was given (0.15 gm. followed by 0.3, 0.45 and 0.6 gm.). In Goldman's¹⁹¹ experience also, a single intravenous injection of neoarsphenamine, without adjuvant quinine or atabrine, would not terminate therapeutic malaria.

Mapharsen. Mapharsen, the hemialcoholate of 3-amino-4-hydroxy phenylarsine oxide hydrochloride, which is thought to be the effective breakdown product of the arsphenamines in the body, was first used by Goldman¹⁹¹ in the treatment of P. vivax infections in 1938. His clinical material consisted of 20 patients undergoing malaria therapy and one patient with chronic recurring natural malaria. The dosage was the same as that used in the treatment of syphilis, i.e., an intravenous dose of 0.04-0.06 gm., depending upon the patient's body weight. In 90 per cent of the cases this single injection permanently terminated the malaria, but 3 to 4 more doses at weekly intervals were found to be advisable to insure against recurrences. At the end of 24 hours after the first injection, the blood stream was free of parasites and splenomegaly had begun to subside. It was necessary to make the injection 24 or more hours before the expected onset of a chill in order to

prevent its occurrence. Goldman described mapharsen as the "drug of choice in the treatment of malaria," and "immeasurably more effective than quinine, certainly as effective as atebrin." No trials of its efficacy in falciparum infection were made.

Niven¹⁹⁶ studied the effect of 2 intravenous injections of 0.04 and 0.06 gm. of mapharsen with a 5-7 day interval in 20 cases of falciparum, 9 of malariae and 20 of vivax infection (spontaneous infection?). In the latter, he evaluated the effect of the drug as more rapid than that of quinine given by mouth in daily doses of 1.0 gm. per 100 lb. body weight. Against P. falciparum and P. malariae, it proved useless, having no effect upon either schizonts or gametocytes. Young and McLendon¹⁹⁵ had similar results with a series of 10 patients suffering from P. malariae infection. Mapharsen (in conjunction with thio-bismol) relieved the clinical symptoms but failed to eradicate the parasites in any instance. Identical results were obtained with try-parsamide plus thio-bismol.

Malario. This drug, prepared by a Singapore firm, was said to contain 2 parts of arsenic per million. Its action in 47 cases of acute malaria was tested by J. C. Niven¹⁵⁴ who reported parasites still present in the blood of 25 out of 26 falciparum patients treated and in 17 out of 21 vivax patients. The action upon fever was slightly better, but Niven's general conclusion was: "'Malario' is of no value in the treatment of acute P. falciparum malaria and of very low efficiency in acute P. vivax malaria."

H. Antimonials

The literature dealing with the action of antimony preparations upon clinical malaria and upon malaria parasites was reviewed by Schmidt and Peter²⁰⁵ in 1938. They found that modern work in the field commenced with Rogers who, in 1917, reported disappearance of falciparum gametocytes from the blood stream following tartar emetic treatments. In succeeding years these results were both confirmed and contradicted by the experience of various investigators working upon other human malaria parasites as well as upon falciparum. Synthetic antimonials were also employed: stibenyl, stibosan, antimosan, alone and in combination with quinine. Opinions of the efficacy of these drugs were divergent, but there was general agreement upon the puzzling phenomenon of malarial activation in latent cases treated with antimony for other reasons. Thus Napier precipitated malaria attacks in kala-azar patients whom he treated for the latter disease with antimony and Peter had similar experience with bilharzia patients receiving antimosan. Fischer caused clinical attacks of malaria by use of stibenyl in several cases of chronic malaria which showed crescents in the peripheral blood; and in another case, previously rendered parasite-free by plasmochin, injections of antimony caused reappearance of clinical malaria.

De Nunno^{202,203} offered an explanation of this discrepancy between the therapeutic value of antimony reported by some authors and the generally accepted fact of its provocative effect upon latent

malaria. By administering a 1 per cent aqueous solution of tartar emetic to human patients in increasing doses of 1 to 14 cc. during 15 days, he produced typical clinical attacks with mobilization of parasites in the blood stream. Simultaneously, splenomegaly regressed and, following a total administration of 1.75-2.13 gm. in 2 series of treatments, 13 out of 14 cases of chronic ("estivo-autunnale") malaria were permanently cured.²⁰³ The mechanism of the cure appeared to be an early flushing out of parasites harbored in the spleen with subsequent activation of the protective forces of the reticulo-endothelial system. Forty subsequent cases of induced vivax malaria treated by De Nunno²⁰³ responded in similar fashion. Carra²⁰⁴ used De Nunno's method in 29 cases and found the drug highly satisfactory.

Fuadin, antimony and potassium tartrate and sodium antimony thioglycollate were investigated by Cole et al.¹⁸¹ in the course of their search for a suitable agent to control induced malaria paroxysms (see p. 95). Fuadin and the tartrates in the dosage employed stopped the clinical course entirely, the thioglycollate produced an afebrile interval of 4 to 5 days followed by resumption of the cycle.

I. Mercurials

Smalarina. Two synthetic drugs containing mercury have been prepared and successfully tested by Italian investigators. One, bearing the trade name, "Smalarina," was introduced by Professor Cremonese in 1925.²¹¹ The mercury is combined with antimony in this

preparation and tablets of the drug are administered on alternate days in arithmetic progression beginning with 1 tablet on the first day; 136 tablets in all being given in 31 days. Cremonese considered the action of the drug to be a stimulation of the defense forces of the body rather than a direct action upon the parasites and advised that it be combined with quinine for immediate effect upon the clinical symptoms of an acute attack. Two years' immunity to malaria were conferred by a full course of the drug in his experience. Peroni²¹⁰ reaffirmed the efficacy of smalarina, basing his opinion upon an extensive anti-malaria project in Stormara in 1925-1926. Chronic malaria treated with smalarina showed but 10.6 per cent failure, while in similar cases treated with quinine 73 per cent failed to respond. The failure rate in prophylaxis was zero with smalarina and 65 per cent with quinine in this study. Froilano de Mello²⁰⁹ and Bird,²¹¹ however, were unable to duplicate these results. In their hands the drug was almost completely ineffective, therapeutically and prophylactically.

M₃. M₃, a synthetic antimalarial composed of mercuric manganese iodide and concentrated extract of spleen¹⁹⁷ manufactured by the Biochemical Institute, Milan, was tried by several workers between 1938 and 1939. Fattovitch et al.¹⁹⁸ and Manca¹⁹⁹ reported favorable results, in both treatment and prophylaxis, which they attributed to the action of the drug upon the reticulo-endothelial system. No direct action upon sporozoites was demonstrated. Chopra and Basu et al.,^{197,201} on the other hand, found no prophylactic or therapeutic action on the part of the drug and concluded that it was without value in malaria.

Reports of an extensive study of the drug recently carried out in north eastern Brazil,²⁰⁰ a highly endemic area, indicate that the drug is there regarded as a valuable prophylactic and curative agent. In the report of the survey, the drug is said to stimulate the reticulo-endothelial system, to eliminate depots of parasites in the spleen and other viscera and to reduce splenomegaly. Its protective action may not become effective for some 2 months after the course of treatment is ended, but by that time resistance has been developed in most subjects. Those persons not entirely protected will at least develop a less severe type of malaria than controls,

Mercurochrome. The treatment of quinine-resistant or quinine-sensitive patients with mercurochrome was suggested by Ross.²¹²

These patients provide a serious enough problem that he considered trial of the drug worthwhile, even though in his own small series, it proved to be of temporary value only. He gave intravenous injections of 8-20 cc. of the 1 per cent solution, in 2-5 cc. doses, to each of 6 patients. In 5 of them the blood stream was promptly freed of parasites and clinical symptoms were alleviated, but in 3 cases parasites reappeared in 10 to 30 days. Liu²¹³ effected an apparently permanent cure with mercurochrome, 5 mg. per kg. body weight intravenously, in 1 quinine-resistant case.

Salyrgan and Mercuric Succinimide. Mercury in the form of salyrgan was given by Cole et al.¹⁸¹ to 3 patients, each receiving 3 injections of 2 cc. on alternate days. There was no change in the course of the fever and parasites were easily found in the blood

stream at all times. To another patient, Cole gave 0.01 gm. mercuric succinimide daily for 10 days and to still another 0.012 gm. of the drug every 6 hours for 5 injections. No change in clinical course or parasite picture occurred in either.

J. Miscellaneous Drugs

Alstonia Scholaris. The necessity for importing the raw materials of synthetic antimalarials into India has emphasized the desirability of finding, if possible, an effective antimalarial drug in the indigenous materia medica. To *alstonia scholaris*, "chhatim" in the Hindi and Bengali vernacular, has traditionally been ascribed high antimalarial value. The drug was accordingly assayed in 1942 by Mukerji, Ghosh and Siddons²⁰⁸ and an alkaloid, "ditamine," was found to be the active principle of the bark. A preparation of the drug tried in *P. knowlesi* malaria of monkeys and in naturally occurring human malaria had little or no demonstrable action and was not recommended as a substitute for quinine or other cinchona alkaloids.

Amidino Compounds. The work of Warrington Yorke¹⁸⁷ and of J. D. Fulton¹⁸⁸ has demonstrated the activity of amidino compounds in malaria as well as in the other protozoal infections in which they are successfully utilized. Stilbamidine (4:4-diamidino stilbene) and 4:4-diamidino diphenoxy pentane administered intravenously rendered *P. knowlesi* infections in rhesus monkeys non-fatal. The action was slightly slower than that of atabrine and relapses occurred in 7 of

8 subjects. Both drugs had an inhibiting action upon in vitro respiration of monkey parasites. In Human malaria, stilbamidine had a definite effect upon therapeutically induced P. vivax infections, but little or no action in natural P. falciparum infections.

Balsamina. Gonzalez Revilla²⁰⁶ treated 10 patients with falciparum and vivax, or mixed infection, with an infusion of balsam apple (momordica charantia). Infections with P. falciparum responded more satisfactorily than those with P. vivax. Six patients showed definite improvement. However, the active antimalarial principle was not isolated and the drug was not recommended for extensive clinical trial until pharmacological tests were performed.

Giemsa C. 77. Prepared by Giemsa and Schuleman,⁸⁸ this hydroquinine derivative is one of the series of synthetic compounds which culminated in the production of plasmochin. The addition of an extra quinoline ring to hydroquinine at the point 5 N represented an attempt to decrease toxicity without reducing activity. A small series of 21 cases treated with C. 77 by Green¹¹³ in Kuala Lumpur responded to it as they would have to quinine, but the effect was, in general, less pronounced. There were no symptoms of cinchonism.

Hydroxyethylapocupreine. Large doses of this drug (0.36 mg./gm. body weight) given either orally or parenterally were found by Hegner et al.²³⁰ to be more effective than quinine in the treatment of infections by P. lophurae in ducks, P. relictum in pigeons and P. cathemerium in canaries. Parasite counts were reduced, apparently by cutting down the number of merozoites produced by each schizont.

Iamar. This complex chemical of which the exact composition is not divulged is said to contain quinine, arsenic, methylene blue and other agents. Parise²⁰⁷ used it successfully in the treatment of 38 cases of malaria, most of which were relapses. The mode of its action is not discussed.

Italchina. This acridine derivative is said not to cause any pigmentation of the skin. Employed by Ballero²¹⁵ in a dosage of 0.3 gm. per day for 7 days, it was found to have a slower but more lasting effect upon the 150 patients in his series than either quinine or the standard synthetic preparations. The action was directly schizonticidal and indirectly gametocidal. Clinical symptoms were controlled, splenomegaly decreased and relapses reduced to 10-13 per cent.

Malarin. Malarin, a vegetable drug tried by Field,¹⁵⁴ destroyed the parasites in only 3 out of 17 cases of vivax and falciparum malaria. Six cases actually had more asexual forms in the peripheral blood after receiving malarin for 7 days than at the beginning of treatment, an occurrence which the author stated he had never seen with quinine treatment.

Undecane 1:11 diamidine. The action of undecane 1:11 diamidine, a member of a chemical group not previously used in malaria, was studied by Glyn-Hughes, Lourie and Yorke¹⁸⁹ in 1938 in 19 cases of induced vivax infection. Intravenous injections of 25 mg. twice a day were given or oral doses of 50 mg. twice a day. Slight anorexia and nausea occurred with the higher dosages, but no toxic reactions of greater significance

appeared. In all cases, the fever and parasitemia were abolished. Two further paroxysms generally occurred after institution of therapy. Asexual forms disappeared from the blood stream first with complete elimination of all parasites within 3 to 6 days. Relapses occurred in 3 cases at 4, 6 and 8 weeks. The remaining 16 cases had had no recurrences at the end of 6 months.

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