THE CHEMOPROPHYLAXIS OF MALARIA.

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INTRODUCTION.

MALARIA is one of the major problems which face the worker in Preventive Medicine in tropical and sub-tropical areas. The geographical distribution is widespread. The economic aspects have been emphasized by many authors. In India, it is estimated that 100 million persons are affected annually, with 1,300,000 deaths. Dramatic epidemics occur such as that in Ceylon in 1935 when 80,000 deaths occurred in seven months. "No accurate estimate can be made of the actual number of deaths from malaria but it is certain that for every person who dies from an actual attack of the disease several others succumb to pneumonia or dysentery against which their resisting powers have been lowered by malaria. Ross suggested that some ancient civilizations such as those of Greece and Ceylon were destroyed by malaria" (Rogers and Megaw, 1935).

The recent war involved the employment of troops in many highly malarious areas and in consequence much large scale work in malaria prevention was carried out. There were two notable advances, one was the use of DDT in mosquito control and the other the large scale use of chemoprophylaxis.

It is proposed, therefore, to discuss chemoprophylaxis with special reference to experience in the recent war. It must, of course, be recognized that this is but one of the weapons at the disposal of the tropical health worker when attacking the problem of the prevention of malaria.

A brief review will be given of the prophylactic use of quinine and plasmoquin. This will be followed by some account of the information available about mepacrine prior to 1939. An account will then be given of some experiences with mepacrine in various theatres of operations during the war.

This will be followed by a brief note on paludrine. Finally an attempt will be made to summarize the lessons of wartime experience, to apply these lessons to possible large scale prophylaxis of civilian populations and to evaluate the place of chemoprophylaxis in the control of malaria.

Quinine.—Cinchona bark was used as a prophylactic by ship's surgeons and in the Colonies in the eighteenth century. Following the isolation of the pure alkaloid in 1831 it began to be used extensively but in a rather haphazard fashion by residents in malarious areas.

There is evidence to show that quinine suppression has produced good results in many areas and enabled Europeans to lead tolerable lives in highly malarious districts. None of this evidence is particularly conclusive. It was used quite extensively on the Macedonian and other fronts in the 1914–1918 War. Opinions as to its value are variable and the Medical History of the

War sums the matter up as follows :—" . . . quinine was extensively used as a prophylactic but there appears to have been no consensus of opinion as to its value. The evidence generally, however, was against the practicability of its use as a prophylactic. . . . "

Hamilton Fairley (1945) showed that quinine sulphate grains 10 daily failed to prevent overt attacks of M.T. malaria and that grains 5 quinine sulphate daily will not prevent overt attacks of B.T. malaria. With grains 10 daily complete suppression of B.T. malaria was afforded in some cases but not in others. This was with New Guinea strains of malaria and it is possible that other strains were more effectively suppressed. Sinton considers that of the population in areas which in the past have depended on quinine suppression, the majority had had attacks of malaria and as a result had developed a varying degree of immunity to the clinical effects of malaria infection.

Unsystematic suppressive and active treatment with quinine has been considered to be one of the causes predisposing to blackwater fever.

Difficulties in any really extensive scheme of quinine suppression would arise from the costs and the limitation of the amount produced, a state of affairs which has been aggravated as a result of the war in the Far East.

Plasmoquin.—This drug has been described as a true causal prophylactic but only in doses which are toxic. It cannot therefore be used as a suppressive.

Sulphonamides.—Certain of this group suppressed M.T. malaria in a high proportion of cases in a dosage of 1·0 gramme daily but failed to suppress B.T. infections.

Mepacrine (Synonyms : Atebrin ; Atabrine ; Quinacrine).—This drug was discovered by Kikuth in 1930.[1]

Mepacrine is an acridine derivative, the dihydrochloride of 2-methoxy-6-chloro-9-diethylamine-pentylamino-acridine.

The work of many observers soon showed that an important advance in the therapeutics of malaria had been made. The value of mepacrine in prophylaxis was then explored in a series of investigations carried out under the auspices of the League of Nations Health Organization.

Field (1937) carried out large scale field trials on coolies at tea and rubber plantations in Malaya. There were three groups. The first had prophylactic mepacrine 0·4 gramme weekly (0·2 gramme on two successive days), the second had 0·4 gramme quinine hydrochloride daily, the third group had an inert yellow tablet. The effects of the prophylactics were summarized as follows :—

" (*a*) Prophylactic treatment both with mepacrine and quinine effected a marked reduction in the number of malaria attacks which, from the incidence in the control group, would otherwise have been expected ; this reduction for the last six months of the experiment amounted almost to elimination.

[1]Kikuth survived the 1939–45 War. He was at the laboratories of I. G. Farben, Elberfeld, in that part of Germany with which the writer was concerned in the early days of the occupation. The writer had many discussions with him. He was still working on synthetic anti-malaria drugs and the exo-erythrocytic cycle of development of the malaria parasite.

(*b*) The effect of the prophylactic mepacrine on the malarial incidence and on parasite rates was somewhat more potent than that of the prophylactic quinine.

(*c*) There was a rapid return of the clinical evidences of malaria when the administration of the drug was suspended. . . . "

The quininized coolies suffered from deafness and tinnitus. The mepacrine group developed yellow staining of the conjunctivæ after some months but there were no other toxic effects which were, at that time, clearly attributed to mepacrine. Other authors had, however, described nausea, vomiting, diarrhœa, delirium and psychosis during mepacrine prophylaxis. L. Parrot (1937), carried out similar experiments on the natives of Algeria using quinine and quinacrine (the French sythesis of atebrin with a slightly different structural formula). In the quinine prophylaxis area 0·4 gramme was given daily, in the mepacrine area 0·05 gramme daily. The conclusions reached were that quinine " greatly reduced the splenic and splenometric rates, brought down the parasite and gametocyte rates to zero or thereabouts. . . . " That quinacrine ". . . brought about a very marked fall in the various endemic indices, in particular the splenometric and splenic rates. However, it did not bring the parasite and gametocyte rates regularly down to zero."

In summing up, the authors consider that the less satisfactory results for quinacrine were due to inadequate doses and recommend that the dose should be doubled when, they consider, the two products would be equally effective. They make no mention of any toxic effects.

Mosna and Canalis (1937) carried out experiments in Sardinia. There were no quinine controls. They gave 0·05 gramme mepacrine daily or 0·2 gramme twice weekly and reported no serious toxic effects and a marked reduction in malaria. They thought that 0·2 gramme twice weekly gave a better result than the daily dose.

Freide (1937), from U.S.S.R. reported " fairly good " prophylaxis from mepacrine, recommended increased dosage (i.e. above 0·05 gramme daily) and that the drug should be given within forty-eight hours each week to provide a high blood concentration for a short period. Occasional toxic symptoms, giddiness, nausea, vomiting and diarrhœa are mentioned.

Studies of the mode of action of mepacrine demonstrated that, like quinine, it is not a true causal prophylactic, i.e. it will not destroy the sporozoites in the body before they begin their asexual cycle of development.

It was thought probable, although not proved, that the parasite, on first entering the body underwent an exo-erythrocytic stage of development during which it was not susceptible to mepacrine or quinine.

In general, the above outline serves to show the information available about mepacrine prophylaxis up to the outbreak of the 1939-1945 War.

Early Experiences in the War in the Far East.

In 1941 numbers of British and Indian troops were dispersed through Malaya. Anti-malarial control was carried out in the vicinity of their camps

by the Malayan Medical Service. Drug prophylaxis was not generally used and the overall malaria rate was about 120 per 1,000 per annum.

In the case of two small detachments in hyperendemic areas mepacrine 0·2 gramme twice weekly was given with excellent results.

Later an Australian Force of some 10,000 men was located in Johore in a highly malarious area. The rate of incidence rose to 12 per 1,000 per week. Quinine prophylaxis grains 6 per day was given, the malaria rate dropped for the first week and then returned to the previous level. The dosage was later increased to grains 10 with little improvement. Subsequently, a travelling team carried out urine tests which showed that only 50 per cent of the force were actually taking quinine.

In late 1941 the forces in North Malaya had a high incidence of malaria. The Malaria Field Laboratory in this area included officers of the Malayan Medical Research Centre. Largely on their advice an agreement was reached to give these troops suppressive mepacrine but insufficient supplies were available. The withdrawal commenced shortly afterwards. Special arrangements were made to collect all mepacrine from rubber, etc., estates before they fell into enemy hands. Plans were made to give all personnel 0·2 gramme twice weekly but Singapore fell before this policy could be put into effect.

The North African Campaign.

In November 1942, an Allied Force of considerable size landed in North Africa. In the Spring of 1943, steps were taken to meet the forthcoming malaria season. It was decided to give mass mepacrine prophylaxis for the first time to a Force of such a large size. The dosage was 0·2 gramme twice weekly. This began in April 1943. After the administration of the third dose, something approaching a disaster occurred. Thirty per cent of the Force, including in some units up to 50 per cent of personnel, were incapacitated by nausea and diarrhœa. The percentage of personnel with these toxic reactions was very variable between units. It was at first thought that certain brands or batches of mepacrine might be responsible but no clear evidence of this was obtained. Another theory advanced at the time was that the troops were operating in conditions likely to lead to chloride deficiency and that this, in association with the mepacrine, caused the reactions. In the end, no very satisfactory explanation of any sort was achieved. A decision was made to continue the mepacrine, varying the dose to 0·1 gramme four times weekly, or to take ½ tablet (0·05 gramme) or any other variant which appeared suitable to the medical officer of each unit. With perseverance most men overcame their intolerance but a certain number of permanent mepacrine susceptibles was reported.

It was estimated at this time that only 20 to 30 per cent of men were taking mepacrine regularly. Furthermore, malaria discipline as a whole was bad and there was neglect on the one hand of personal precautions such as the use of proper clothing, nets, and repellents, and on the other, of the advice of the medical branch in the selection of sites.

The result was an alarming rise in the incidence of malaria in July 1943 when there were 7,200 cases with between 4,000 and 5,000 constantly in hospital.

This intial mass reaction was of great importance to the history of mepacrine prophylaxis in the Mediterranean theatre of operations. The circumstances became known to many Formation Commanders and Administrative Staff Officers. This resulted in lack of confidence in the drug and weakness of executive and disciplinary action to enforce the taking of it. This lack of interest was evident in the Sicilian landings and it was not until the lessons of the Sicilian Campaign had been driven home by the high incidence of malaria that the active support of Formation Commanders and Administrative Staff was obtained.

The Sicilian Campaign.

In July 1943 began the first assault on Europe when an Allied Force with components sailing from the British Isles, North Africa and the Middle East landed in Sicily during the malarious season.

It was planned that the forces would be mepacrinized for fourteen days before the assault. For security reasons and administrative difficulties this was not achieved in the case of certain troops sailing direct from the British Isles.

The dosage was 0·2 gramme twice weekly. Just after the landing it was altered to 0·1 gramme four days a week. About a month later it was increased to 0·1 gramme six days a week. Although individual cases of intolerance were reported there were no mass reactions to the drug. The advisers would have increased the dosage at an early date but for two facts, firstly, there were some difficulties in the supply of the drug and secondly, because they were concerned lest large scale intolerance should develop.

A factor in the reduction in the number of reactions was that the tablet was now ordered to be taken in the evening and followed by a large drink, usually tea.

There is little doubt that the administration of mepacrine in the early days in Sicily was highly unsatisfactory. Unit and sub-Unit Commanders had not been made to realize the importance of the drug and the taking of it was not enforced in many units. The incidence of malaria rose alarmingly during August. The average incidence during the worst six weeks of active operations (July 23 to September 3) was equivalent to 275 per 1,000 per annum. This seems high, but in Macedonia in 1918 the incidence for the whole year was almost 460 per 1,000 (Thompson, 1946).

Certain formations which fought in the highly malarious plain before Catania had a very high incidence rising in some units to 30 per cent to 40 per cent of strength on a weekly basis.

It was decided to give these troops quinine by a method which was called " blanket therapy." It was the intention to give every man on the same day 20 grains of quinine in the twenty-four hours. Difficulties in the supply of

the necessary amounts of quinine resulted in this " blanket " being given unit by unit over a period of three weeks. This tended to obscure the results of the treatment in these formations.

The results were difficult to assess but it was observed that the incidence of malaria stopped rising at the former rapid rate but did not fall.

A legacy of Sicilian infection was shown by the fact that in the first weeks of the operations on the Italian mainland 15,000 cases of malaria occurred of which over 8,000 were attributed to infection in Sicily.

The Sicilian infections were almost entirely B.T. with less than 1 per cent of M.T.

The malaria plan for Sicily did not, of course, rely entirely on suppressive mepacrine. It may be said, however, that owing to ignorance, apathy, inexperience and the shortage of materials inherent in an assault landing the other methods of control, i.e. protective clothing, nets, protective creams, mosquito control and larvicidal methods, were ineffective.

The Italian Campaign.

The lessons of Sicily were studied and applied. Mepacrine was given at a dosage of 0·1 gramme weekly and its administration was backed by intensive propaganda and disciplinary measures. There was a steady fall in the incidence of malaria which by 1945 had fallen to 38·85 per 1,000 per annum.

A graphic illustration is shown by the fact that in the third quarter of 1943 in Italy there were two malaria casualties to each battle casualty, by 1945 there was only one malaria casualty to ten battle casualties.

It would, of course, be wrong to attribute this improvement entirely to mepacrine prophylaxis. There was a great interest in malaria in the whole force, beginning with a committee of all branches at Army Headquarters with corresponding committees at lower formations. A special staff officer—Deputy Assistant Adjutant General for Malaria—was appointed to the H.Q.s of Divisions to deal with malaria and particularly mepacrine discipline.

Malaria Field Laboratories followed close on fighting troops and collected and disseminated information about infected areas. The advent of DDT provided an excellent method for killing adult mosquitoes by residual spraying of accommodation.

Large schemes of larvicidal control were undertaken in base areas by specially organized anti-malaria control units. Extensive use was also made of DDT and paris green sprayed by aircraft.

In August 1944, the Germans in their retreat extensively damaged the bonification works in, among other places, the village of Maccarese, north of Ostia. The civilian inhabitants were given mepacrine prophylaxis at the instigation of military government officials.

Considerable care was taken over the administration of the drug. It was given in doses of 0·3 gramme twice weekly, taken under the supervision of a nurse and the dose recorded in a book carried by the individual. Of 3,850 who had full prophylaxis 2 contracted malaria, of 231 who refused 25 contracted malaria.

The Cairns Experiments.

It was felt, particularly in the Far East, that there was need for a comprehensive series of experiments which would demonstrate convincingly the efficacy of mepacrine prophylaxis in such form that it would appeal to Force Commanders and thus form a basis for an intensive campaign of propaganda backed by disciplinary action to enforce the regular taking of mepacrine by troops in malarious areas.

The problem was the more urgent in that malaria casualties in the various South-West Pacific Campaigns were from five to thirty times as numerous as battle casualties.

The work was carried out by a Research Team working under Hamilton Fairley (1945). The experiments were on a very large scale and provide the first comprehensive scientific investigation of chemoprophylaxis.

The conclusions may be summarized as follows : The experiences of quinine prophylaxis have been described. Certain sulphonamides in a dosage of 1·0 gramme daily suppressed M.T. malaria in 20 out of 21 volunteers and cured 17 of them. The same dosage failed to suppress B.T. infections in 21 out of 24, the remaining 3 developing clinical malaria shortly after the administration of the drug had ceased. Mepacrine in a dosage of 0·1 gramme daily suppresses malignant tertian fever and if continued for the requisite period (four weeks) after the last exposure to infection cures the disease. Under similar circumstances mepacrine suppresses benign tertian malaria but overt malaria supervenes with great regularity a few weeks after suppressive mepacrine ceases.

Hamilton Fairley concluded from this that, granted infallible mepacrine discipline, a non-immune force could fight for many months in hyperendemic malaria areas with insignificant malaria casualties. The residual problem would be one of relapsing B.T. malaria.

He claims that application of these principles was one of the main factors in reducing the hospital admission rate in New Guinea from 740 per 1,000 per annum in December 1943 to 26 per 1,000 per annum in December 1944.

In the course of the experiments it was demonstrated that persons having 0·3 or 0·4 gramme of mepacrine weekly, while showing no overt malaria, were yet, in some cases, gametocyte carriers, a very important epidemiological observation which may explain some of the anomalous results observed in the past.

The fact that mepacrine is not a true causal prophylactic was demonstrated by early sub-inoculation tests when 200 c.c. of blood taken from M.T. infected volunteers on 0·6 or 0·7 gramme mepacrine weekly produced attacks of M.T. malaria in the inoculated individuals despite the fact that parasites were never found in thick blood smears. This indicates that mepacrine destroys the young asexual parasites as they enter the circulating blood from the seventh day onwards.

Bang and others (1946) investigated the efficacy of mepacrine suppression in American and Australian troops by a study of the concentration of mepacrine in the blood plasma. They found that the variation of drug level obtained

with a standard dose is so great that, granting that concentration is related to protection, a small percentage would be unprotected by the standard dosage of 0·7 gramme of mepacrine per week.

Reid (1945), working at the Royal Army Medical College, Millbank, showed that the blood mecaprine level is clearly related to the development or prevention of M.T. malaria. He found that in a significant proportion of men taking 0·1 gramme mepacrine daily for three months, the blood mepacrine level may tend to fall even if the administration of the drug is continued regularly.

Further doubts on the "infallibility" of mepacrine suppression suggested in the original Cairns experiments are demonstrated in a recent paper by Hamilton Fairley (1946).

He found that, over a period, the incidence of malaria in troops in New Guinea was low as a result of mepacrine prophylaxis except in one particular area where one formation suffered a severe outbreak of malaria, chiefly M.T. This outbreak was investigated in some detail and it was finally concluded that there existed in this particular area certain strains of *P. falciparum* which were relatively mepacrine resistant.

Paludrine.

The ideal chemoprophylactic agent must obviously be a true causal prophylactic. In 1945 Curd, Davey and Rose synthesized two biguanide compounds M.4330 and M.4880 which were causal prophylactics in bird malaria. M.4880 was the more effective and was called paludrine. The value of the drug in malaria therapy was demonstrated by Adams, Townsend and King (1945). The prophylactic properties were investigated by Hamilton Fairley (1946) in experiments analogous with his previous work on mepacrine. He concluded that in M.T. malaria, paludrine acts as a true causal prophylactic, i.e. the malaria was completely suppressed and sub-inoculation tests were negative with doses varying from 100 mg. daily to as little as 25 mg. daily. In B.T. malaria, the drug in similar doses acted as a partial causal prophylactic. No volunteers developed overt malaria or demonstrable parasites whilst having suppression. Sub-inoculations on the 9th and 14th days after exposure were negative. After paludrine administration had ceased all four volunteers of a group who had taken 100 mg. daily developed overt malaria between the 37th and 117th days after the last dose.

Of a group taking 300 mg. daily one developed overt malaria 19 days after the last dose, the remaining 5 had not developed malaria in from 70 to 118 days.

These results were confirmed by experiments of a field type in which volunteers were also subjected to stresses and strains similar to those likely to be encountered on active service.

The schizenticidal action of paludrine was also investigated and it was found that a single dose of as low as 0·1 gramme would resolve but not, of course, cure overt attacks of M.T. and B.T. malaria in non-immune individuals.

This opens up possibilities in the control of outbreaks in large populations by a weekly one dose régime. It is important, however, to remember that these results refer only to New Guinea strains of malaria.

There was an absence of any toxic effects unless administration was increased to 1·0 gramme daily, a dose which is far in excess of that required either for prophylaxis or therapy.

Discussion.

In discussing the value of chemoprophylaxis it is necessary to decide how far extensive prophylaxis can in itself control malaria and to what extent it is still necessary to rely on extensive schemes of malaria control chiefly aimed at larvicidal methods and on the other methods of personal prevention such as the use of proper clothing, mosquito nets and repellent creams.

In so far as military forces are concerned, chemoprophylaxis with mepacrine has clearly proved its worth. It has been demonstrated that with effective chemoprophylaxis, forces can operate in highly endemic areas where other methods of control are impracticable. The crux of the matter is effective administration and this must be achieved by good propaganda and a high standard of mepacrine discipline in the force, without this, chemoprophylaxis cannot succeed.

Paludrine was discovered too late to allow of large scale trials under conditions of actual warfare but it seems clear that it would give even better results than mepacrine with the advantages of reduced dosage, negligible toxicity and absence of yellow staining of the skin.

In mobile warfare in forward areas most of the normal methods of malaria control are impracticable and to a large extent chemoprophylaxis must be the main line of defence. The time has not yet arrived, however, when the well tried other methods of control can be abandoned in line of communication and base areas. Schemes are still necessary for the control of adult mosquitoes, for larvicidal methods and for the other adjuncts of personal protection.

Presumably the complete causal prophylactic will one day be discovered and it may be possible to rely more complete on chemoprophylaxis. Until then, the problem of the B.T. relapse remains to be solved with both mepacrine and paludrine although the advent of paludrine has simplified treatment of these relapses.

Having established the place of chemoprophylaxis in military practice, consideration must be given to its value under civilian conditions. Will it be of any value in dealing with the mass of mortality and morbidity which malaria causes throughout the world ?

Sinton (1939) in a study of immunity in malaria and its relation to drug therapy suggested the following general principles.

(i) When infections are contracted by individuals resident under conditions in which the chances of reinfection except at comparatively long intervals are slight the treatment of choice is one which produces a radical cure of the infection at the earliest possible moment.

(ii) When individuals are resident under conditions where they are exposed to frequent and constant risk of infection, reinfection and super-infection, the object of treatment should be the rapid production of clinical cure of each attack and not a radical cure of the infection. When practicable this should be combined with clinical prophylaxis so that the number of acute attacks is markedly diminished most especially if the population under consideration does not possess any great degree of natural or acquired immunity.

(iii) When individuals are exposed only temporarily to chances of frequent infection and super-infection then clinical prophylaxis of the disease with an appropriate drug is the treatment of choice.

Since the above was written, recent experiences have

(*a*) discredited quinine as a large scale prophylactic ;

(*b*) shown that mepacrine is only effective if given in adequate doses with meticulous attention to the details of administration;

(*c*) produced paludrine.

The objection to radical therapy in highly infected populations was that it abolished immunity and that it was only immunity which enabled such populations to avoid disastrous epidemics. Clinical prophylaxis as with quinine or mepacrine does not abolish immunity. It would seem that causal prophylaxis with paludrine may very well abolish it. This would be a subject for future field trials. If it does, it means that paludrine prophylaxis should not be started in a heavily infected population in an endemic area unless it can be continued indefinitely.

Economic factors must also be considered. Mass production of synthetic anti-malarials such as mepacrine and paludrine would in the end make them comparatively cheap. Widespread schemes of malarial control by other methods often have very high capital and maintenance costs.

In the case of malaria in rural Europe such as is seen in Sicily, Southern Italy and Macedonia with a limited and clear cut malarial season it would appear that the ideal approach would involve chemoprophylaxis during the malaria season associated with the usual schemes of mosquito control. Effective prophylaxis would eliminate the gametocyte carrier and this associated with mosquito control should, in time, eliminate malaria.

To consider tropical malaria, it seems clear that for Europeans living in endemic areas and for small mixed communities as in mines, plantations, &c., where physical conditions and expense make large scale control schemes impracticable, chemoprophylaxis will be of the greatest value, especially if associated with local control work. In such communities it should be possible to ensure that the administration of the prophylactic is carried out effectively.

On the other hand, in the case of a town or city in an endemic area with a large European and Native population it is not considered that chemoprophylaxis has any substantial contribution to make. With such a population, the problems of administration and distribution of drugs to ensure regular and adequate doses would be insuperable and in these circumstances nothing can replace the time-honoured methods of mosquito control, improved

as they will be in the future by the use of modern civil engineering machinery and by the use of DDT and other synthetic insecticides.

There remains the most difficult problem, the rural community in highly endemic tropical areas with a population which is heavily infected, impoverished and under nourished. Economic conditions and physical difficulties often make large scale mosquito control schemes impracticable. The institution of prophylaxis would raise problems of practicability of distribution; of prejudice, apathy and cost.

It is possible that mepacrine and paludrine may have toxic effects on under-nourished populations when given for long periods.

The administration of prophylactic drugs to such populations for indefinite periods can scarcely be visualized. There is no doubt, however, that chemoprophylaxis has a most valuable part to play in the control of epidemics. The experimental evidence suggests that doses of paludrine as low as 100 mg. twice per week would control an epidemic such as that in Ceylon, which was mentioned earlier in this paper. This alone is an enormous advance. For a long term policy, however, chemoprophylaxis will not be the universal panacea for tropical rural malaria.

The real solution lies in a comprehensive campaign directed to education, to improved nutrition, to effective treatment and to localized control schemes using inexpensive locally available materials. Schemes of this sort had had some success in Malaya until they were ruined by invasion.

SUMMARY.

The work on chemoprophylaxis prior to 1939 has been briefly reviewed.

An account has been given of experiences in prophylaxis on a large scale in various theatres of operations during the recent war.

An attempt has been made to apply some of the lessons of wartime experience to civilian conditions.

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