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The Secretary of the Expert Committee on Malaria
has the honour to communicate the following note:

THE ROLE AND IMPORTANCE
OF THE NEW SYNTHETIC ANTIMALARIAL DRUGS
IN THE PREVENTION OF MALARIA

by

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The history, still a recent one, of the synthetic antimalarials can already be divided into two periods:

I. 1926-1942, i.e. the period between the discovery of the first synthetic antimalarial drug and the impetus given to the search for new compounds by the necessity of replacing quinine.

II. The present period, which commenced in 1943 with the thorough study of existing synthetic antimalarials (encouraged by the presence of non-immune military personnel in the endemic zone) and continued until the end of the war, and thereafter, with the successive appearance of different new compounds.

I. The first synthetic antimalarial - pamaquine - dates from 1926. Its toxicity in prophylactic and schizontocidal doses as well as that of its substitutes [rhodoquine (French 1931), certuna (German 1935)] limited the application of these initial 8-amino-quinolines to their gametocidal and sporogonic action (BARBER and KOMP 1927), which largely restricted their use.

Indeed, at that period, supervised communities in the endemic areas where any attention was paid to this aspect of collective prophylaxis were still very rare.

The treatment of acute attacks and their clinical prophylaxis represented the main interest and, from this dual viewpoint, quinine remained the drug of choice.

In the case of certain favoured patients, an 8-amino-quinoline preparation was sometimes prescribed at the end of curative treatment with quinine. This medication was supposed to retard the appearance of relapses, concerning which it was already known, however, that they are not caused by parthenogenesis of the female gametes. At this period, furthermore, little was said of the part played by exo-erythrocytic forms and in any case in the doses prescribed the drug was without effect on such forms (P. vivax).

Quinacrine (mepacrine) made its appearance in 1930. Its activity in the treatment of acute attacks rapidly bore comparison with that of quinine and the first experiments in chemoprophylaxis also received favourable notice. (Malaya - FIELD 1937, Algeria - PARROT 1937, Sardinia - MOSNA and CANALIS 1937, USSR - FREIDE 1937).

Nevertheless, although on the eve of the war quinacrine was commencing to be widely prescribed, it could be said that the pre-eminence of quinine still remained unthreatened.

The first two years of the war (1939 - 1941) did not change this position.

II. In 1941 the presence of numerous troops in Malaya and India clearly showed (as had already been proved by the Macedonian campaign of the first world war) the need for clinical prophylaxis to keep the personnel up to strength. However, quinine was already considered by English authors as being of low activity and quinacrine was lacking.

In 1942, when the Anglo-American forces landed in North Africa, Indonesia was in the hands of the enemy. The health authorities no longer had a free choice of drug and so quinacrine was prescribed in an endeavour to prevent malaria in

spring 1943. (Nevertheless, on 30 May 1940 the Allied General Staff had been informed by French doctors of the therapeutic and prophylactic importance of a 4-amino-quinoline compound synthesized in Germany, namely Sontochin which was studied in Tunisia from 1941 onwards.)

It can be said that the "era of the synthetic antimalarials" dates from that time. There were hundreds of thousands of non-immune individuals to be protected and cared for; there was a fear that quinine could not be obtained, or again, it was underestimated; in short, it became essential to make a more thorough study of existing synthetic compounds and to search for others.

The initial stages of chemoprophylaxis with quinacrine were, moreover, difficult and unconvincing: indefinite posology, digestive upsets, lack of interest on the part of those in command and lack of discipline - these were the features in this respect of the North African and Sicilian campaigns, during which recourse had again to be had to quinine.

It was only in 1945, on the Italian mainland, that satisfactory results were obtained, thanks to enforced measures. At the same period Hamilton FAIRLEY, at Cairns, made a scientific study of the action of Quinacrine and then of Paludrine (proguanil).

Among the other synthetic compounds tried out, 4-amino-quinolines, new 8-amino-quinolines and a diaminopyrimidine compound appeared in succession and are now used for the prevention and treatment of human malaria.

As a result of extensive work bearing on tens of thousands of preparations, the objective was attained so that henceforth quinine can be done without under almost all circumstances (intramuscular mepacrine replacing quinine in emergency cases).

If research work on synthetic antimalarials had given only this result one could still say that it has been crowned with success.

Can these drugs play any other part? Do they represent a new acquisition as compared with quinine? In principle, yes. However, the conditions for their

application remain such that those benefiting from new indications for their use represent only a very small minority of individuals exposed to or suffering from malaria.

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1. Prophylactic properties of the synthetic antimalarials

(a) No synthetic anti-malarial brings about causal prophylaxis of P. vivax.

As concerns P. falciparum, causal prophylaxis has been obtained by H. FAIRLEY (1946) with proguanil, for New Guinea strains.

But this property has been shown to be too limited and its practical importance largely decreased by subsequent findings, indicating the existence in several different geographical areas of P. falciparum strains which are resistant from the outset, or may acquire such resistance to proguanil.

None of the other drugs employed brings about causal prophylaxis of P. falciparum.

(b) On the other hand, the advantages of the synthetic antimalarials are more generally recognized as concerns clinical or suppressive prophylaxis.

Unless daily doses not below 0.40 g are prescribed, parasitaemia is not always prevented by quinine administered for preventive purposes.

Only the fact that the parasitaemia remains below the pyrogenetic threshold prevents acute attacks. Such attacks are indeed not always avoided, but they are reduced to a minimum.

In 1945 FAIRLEY demonstrated the value of suppressive prophylaxis produced by mepacrine. This product has already been practically given up however. Perhaps undue importance has been paid to the drawbacks of a digestive nature and the yellowish colouration imparted to the skin and certainly the importance and frequency of the cutaneous and psychic accidents associated with the continued administration of mepacrine have been exaggerated.

Failures in the use of proguanil due to the resistance of P. vivax and P. falciparum would perhaps have led to a reconsideration of the value of mepacrine. However, Nivaquine (chloroquine) has not these drawbacks and the results it gives are comparable, if not better.

Finally, the chances of curing the P. falciparum infection and the delay in the appearance of P. vivax are much greater after the preventive administration of mepacrine and chloroquine than after that of quinine.

In collective prophylaxis and among partially immune populations, the administration of bi-weekly, weekly (mepacrine, chloroquine, amodiaquine) or more widely spaced doses (Premaline, Premaline N) renders signal service.

As regards pyrimethamine, it has not yet been tried out on a preventive basis.

2. Practical importance of the synthetic antimalarials

(a) It is possible that proguanil can ensure causal prophylaxis for certain strains of P. falciparum.

None the less, failures are so frequent that in many territories no attempt is even made to bring about suppressive prophylaxis with proguanil.

Finally, the search for causal prophylaxis can only interest non-immune persons making a limited stay in an endemic zone. Success in this respect makes it possible for the person concerned to cease taking preventive doses as soon as he returns to a healthy zone. But failure is of no great importance since clinically obvious attacks can easily be cured. Adequate prolongation of preventive doses of a clinical prophylactic, moreover, usually prevents the appearance of malaria and offers the same advantages as causal prophylaxis.

(b) The clinical prophylaxis ensured by the synthetic antimalarials makes possible travelling, staying or working in the endemic regions with results equal or even superior to those given by quinine. To this should also be added, perhaps, a decrease in the incidence of blackwater fever, although the prevention of the latter would appear to be rather an advantage of regular prophylaxis than the result of special medication.

However, during the quinine era also, people lived and worked in the malarial zone. The better protection ensured by the synthetic drugs is only a question of degree. What is above all important, is to extend this protection and not to limit it to non-immune, non-indigenous persons or to those working for them.

Among the indigenous population the children are those who are non-immune. It is certain that so far few children have benefited from preventive medication. The price paid by the community for this lack of chemoprophylaxis in the young child is still an open question. However, it is regrettable that it cannot be administered except in a few limited regions, usually those affected by seasonal malaria.

Although the era of synthetic antimalarials has arrived, the social position has not greatly changed. Of course, interest in malaria has greatly increased and a larger number of schoolchildren undergo clinical prophylaxis. But the bulk of the children who have not reached school age, i.e. those most vulnerable and likely to fall victim to the disease, are still not protected, above all in the holo and hyper-endemic zones.

It is not certain that the appearance of synthetic drugs prescribed in spaced doses (Premaline, chloroquine, amodiaquine) has rendered easier the solution of the distribution problem. The problems of organization, of personnel (and credits) once solved, it is no more difficult to distribute one tablet per day, so that it is perhaps advisable to consider the matter thoroughly before giving up quinine which, at the expense of a few possible mild attacks, best ensures the development of the premunition desirable for this child population in such territories.

On the other hand, for the bigger children of school age, for semi-immune adults and for all those subject to inspection or who are already more "developed" the new synthetic drugs represent a distinct advance. In weak and spaced doses they successfully ward off any possible failure in immunity or attacks of heterologous reinfection.

CONCLUSIONS

The development of synthetic antimalarials represents the fruit of brilliant work. This work was spurred on ten years ago by the need to make up for the lack of quinine and has in large measure reached its initial aim, namely to make it possible to live and work in an endemic zone (prophylaxis) and to treat attacks of malaria (therapy) successfully without quinine.

The ideal drug endowed with properties which quinine does not possess (the ensuring of causal prophylaxis and radical cure for the three species of haematozoa) has not yet been found despite advances in this direction. However, it is still possible that it will be discovered.

Even then, if present conditions as concerns anophelism and the reservoir of the causal agent are not greatly changed and if economic development is not accelerated, only temporary and non-indigenous residents will greatly benefit from the advances made.

Any valid chemotherapeutic solution of the malaria problem must take the form of a product capable of breaking the man-anopheles cycle, by bringing about the prolonged disappearance of the gametocytes on taking a single dose of the drug.