PRESENT POSITION OF ANTIMALARIAL DRUG THERAPY IN INDIA.

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In this paper I propose to deal briefly with the present position with regard to drug therapy in malaria. The antimalarial drugs may be divided into two main groups :—

I. The Cinchona derivatives.

II. Other antimalarial remedies. This group includes most of the synthetic drugs.

I. Cinchona Derivatives.

A. *Cinchona alkaloids.*

It is well known that as many as 20 alkaloids and probably more are present in the cinchona bark, all of which are chemically closely allied to each other. These alkaloids have been divided into (i) crystallizable alkaloids, and (ii) amorphous alkaloids. The former group only has antimalarial properties ; the amorphous alkaloids have been shown to be inactive in this respect. Of the crystallizable alkaloids present, four occur in large quantities ; these are quinine, quinidine, cinchonine and cinchonidine. Till recent years these alkaloids were the only drugs available which had specific action on the malarial parasites. If given in suitable doses and under proper conditions their action in controlling malarial paroxysms is certain. Of the four alkaloids quinine still holds the foremost position in the treatment of malaria though the antimalarial value of the other three alkaloids has been fully established. From the data now available there is no room for doubt that quinidine, cinchonine and cinchonidine, in similar doses to quinine, are equally or very nearly as effective in the treatment of malaria. In considering the relative therapeutic value of different alkaloids, it is of importance to take into account their effect in causing harm or inconvenience to the patient. It may be said in favour of quinine, that it can as a rule be given in sufficient doses and for sufficiently long periods without danger to the patient. Cinchonine is more nauseating than quinine and is liable to produce blurring of vision. Quinidine is also more nauseating and has a powerful depressant action on the heart. Cinchonidine is neither toxic nor irritant but is distinctly the weakest of the four alkaloids.

The importance of the fact that all alkaloids have marked antimalarial properties is very great to India where the economic condition of the people is low and purified quinine preparations, on account of their high price, are beyond the means of ordinary people. The reasons why quinine is more expensive than the total alkaloids of the bark are: (i) That its proportion in the bark usually is a little more than half of the total alkaloids. *Cinchona succirubra* and *Cinchona officinalis* barks, for example, contain about 5 to 6 per cent of the total alkaloids of which only 3 per cent is quinine. *Cinchona ledgeriana* contains somewhat higher proportions. (ii) The cost of its separation from other alkaloids and purification further adds to its price. It would follow, therefore, that if the total alkaloids are used they will be cheaper than if only quinine by itself is used. It was for this reason that 'cinchona febrifuge' has been used in India and the League of Nations have introduced *totaquina* which contains 70 per cent of the total alkaloids of which 15 per cent must be quinine. By this means it is hoped that the treatment could be made less expensive and extended among the masses.

Some of the other alkaloids of the cinchona bark which occur in smaller quantities than the four alkaloids stated above, for example cupreine and cupreidine compounds, have also antimalarial properties. Cupreine sulphate in doses of 1 gm. was found by Giemsa and Werner to be a good substitute for quinine in human malaria, but it is much more expensive and toxic. These observers also obtained good results with quin-ethyline and quin-propyline in doses of 0·3 to 0·4 gm. in human malaria and with these compounds and quinamyline in bird malaria. Ethyl-hydrocupreine or optochin has been tried in malaria but it is a toxic compound.

The hydro-alkaloids are said by some to be more effective than ordinary salts. Giemsa and Werner, Baerman, MacGilchrist, Morgenroth, Goodson and many others have proved that hydroquinine as regards both its tolerability by the human subject and its parasiticidal action is superior to quinine. Rabe and his co-workers have been successful in preparing hydroquinine synthetically, but the process is so costly that there is no likelihood of possible competition between the artificial and natural products.

The disadvantages of the cinchona alkaloids are:—

(1) They have no action on the sporozoites injected by the mosquitoes and therefore they cannot have any really prophylactic action in this disease. This was demonstrated by Yorke and Macfie (1924) who showed that 18 grains of quinine for 5 days before and 7 days after the mosquito bite failed to avert an attack of malaria, but if the drug was continued for 10 days, the disease did not develop. This shows that these alkaloids have little effect on the injected sporozoites but act on the asexual forms liberated from the infected red blood corpuscles.

(2) Cinchona alkaloids have little effect on the sexual forms of malignant tertian parasites. They, however, impede the formation of the pre-gametocytes

of *P. falciparum* and may thus be regarded as directly schizonticidal and indirectly gamotocidal.

(3) They do not prevent relapses.

(4) These alkaloids do not act uniformly on all strains of malaria.

After the Great War there was a feeling against the use of cinchona alkaloids especially quinine and it was said that this drug was not effective against certain forms of malaria. Further investigation, however, showed that this was not due to any fault of the drug but due to their improper use.

It has been proved by hæmatological and other evidence that the best method of administration of these alkaloids is by the mouth. It is advisable to give them in the form of solution but owing to their bitter taste they may produce vomiting. They can be given in the form of tablets so long as these are easily disintegrable. Subcutaneous injection finds few advocates. Intramuscular injection should only be tried in those cases where administration by the mouth is not desirable or possible as it is liable to produce serious mutilation of parts. Intravenous method should only be used for severe and urgent cases. Parenteral method should not be used for routine administration of these drugs. Intravenous injections must only be employed where the patient is cómatose, or very gravely ill when an immediate response is necessary. Any evidence of impending cerebral malaria is an imperative indication for injection treatment.

On the appearance of acute symptoms of primary infection, quinine has a definite action from the third day onwards (second paroxysm of fever) in benign tertian malaria. Its action is less rapid according to the strains of malignant tertian concerned and symptoms may continue until the fifth dose (third or fourth paroxysm).

As regards the time of administration of these alkaloids by the oral route, it is advisable to give them 2½ to 3 hours after a meal when the gastric contents are acid, the digestion has been complete and the stomach is nearly empty. If given at this time they rapidly mix with the contents of the stomach and pass into the small intestine from where they are quickly absorbed into the circulation. There is less liability of their irritating the stomach if administered in this way.

Dosage.—Experience shows that in the case of Indian strains of malaria, a 5 to 7 days' course of treatment with 20 to 25 grains of the alkaloids daily is effective. Larger doses are not only wasted, but may do harm. According to the Fourth General Report of the League of Nations, 0·5 gm. of quinine hydrochloride sometime causes a temporary disappearance of trophozoites of benign tertian and quartan infection but a mean daily dosage of 1 gm. for 5 to 7 days is often necessary to cause the trophozoites to disappear and not to make their reappearance in the peripheral blood after a latent period of varying lengths, in the course of first relapse. In malignant tertian malaria 1·3 gm. produces analogous results. It is also agreed that definite advantage is obtained by combining them with alkalies.

B. *Preparations containing Cinchona Derivatives.*

During recent years a number of cinchona derivatives have been used in the form of proprietary remedies whose composition is secret. Various claims have been made for these, amongst others that they have destructive action on both the sexual and asexual forms of all forms of parasites, that they prevent relapses and that they have prophylactic value. A number of preparations are on the market and we have tested some of these. Our observations show that their action is practically the same as cinchona alkaloids, they have no action on the gametocytes of malignant tertian, they do not prevent relapses and have no effect on the trophozoites. Being proprietary remedies they are very much more expensive. The following are some of the preparations in use :—

Malarcan.—Malarcan is said to be a compound of a stereo-isomeric base of methyl-cupreine with methyl-acridinium chloride and hydrocholic acid. It is thus probably a derivative of quinine or quinidine.

Tebetren.—Tebetren is described as methyl hydro-cupreine-methyl-acridine-dihydrocholate, i.e. a compound in which quinine is combined with acridine (from which atebrin is derived).

Paludex.—Another synthetic drug which has been recently introduced is paludex. It is a complex organo-metallic preparation containing copper joined to an oxyquinoline group. Chemically paludex is cupro-oxyquinolin sodium sulphonate, and contains 8·37 per cent of metallic copper. It is a greenish amorphous powder, readily soluble in water, forming a solution which is neutral in reaction and stable under ordinary conditions.

Plasmodex is a similar compound, containing copper in a larger proportion.

Esanofeles.—This is a proprietary preparation containing 0·1 gm. of quinine bisulphate, 0·001 gm. of arsenious acid, 0·3 gm. of iron citrate and some bitter principles. If given in the prescribed form, it contains too little of quinine to be of any therapeutic value, specially against malignant tertian infection.

II. Other Antimalarial Remedies which include Synthetic Antimalarial Drugs.

These compounds can be divided into two groups : (1) Those which have action like the cinchona alkaloids on the asexual cycle, e.g. atebrin, and (2) those whose main action is on the sexual cycle particularly of the malignant tertian variety, e.g. plasmochin.

Neither of these compounds act on the trophozoites injected by the mosquitoes and therefore have no true prophylactic value. They do not prevent relapses though their action in this respect is said to be more powerful than that of cinchona alkaloids.

Their dosage as compared with the cinchona alkaloids is much smaller, but they are more toxic.

(1) *Plasmochin.*—The shortage of quinine supply during the war led to experiments at Bayer-Meister-Lucius Research Laboratory at Elberfeld with the object of finding a synthetic drug which could be used in its place. Schulemann and his colleagues chose methylene blue for investigation ; they prepared a large number of compounds which were tested on canaries infected with *Plasmodium relictum*. Among these compounds they found one which was particularly effective and this was an amino-quinoline derivative in which a basic aliphatic radicle was united to a quinoline nucleus by a connecting link of nitrogen. This compound was modified in many ways, and eventually the compound, first known as ' beprochin ' and afterwards as *plasmoquin* or *plasmochin* was produced. It was at first thought to have a definite curative effect in the treatment of all forms of malaria, but later experience showed that, while it was effective in adequate doses (which often produce toxic effects) in curing the benign tertian and quartan malaria by itself, in sub-tertian malaria it was of no therapeutic value because it had no action on the schizonts and some observers went so far as to say it had a provocative action. It, however, possesses the remarkable and unique property of destroying the crescents in the peripheral blood.

On account of this peculiar property of damaging the gametocytes it renders them non-infectious to mosquitoes. Even such doses as 0·01 or 0·02 gm. of plasmoquin daily are effective in this respect. This remarkable effect against the more resistant form of the parasites is the greatest virtue of the drug but unfortunately it has little or no effect on the asexual form of malignant tertian parasites.

It should be fully appreciated that plasmoquin is a drug which is likely to give rise to toxic effects and it should not be used for routine treatment of malaria. It is combined with quinine, and it is claimed that this combination when continued for 2 to 3 weeks is more effective than quinine and the number of relapses is decreased. Prolonged administration of this combination in therapeutic doses is likely to produce toxic effects but these are not so marked as a combination of plasmochin with atebrin. Plasmoquin by itself thus holds a minor place in the symptomatic treatment of malaria.

Cilional.—The toxic effects produced by plasmoquin have been fully appreciated by the workers of Bayer's Scientific Laboratories and they have been busy in producing less toxic compounds. Cilional is one of these compounds which has been recently introduced and which according to preliminary experiments was not only more effective than plasmoquin but was considerably less toxic. Trials on human beings show that this compound is certainly less toxic than plasmoquin but it is not so effective unless larger doses are given. The work in the School of Tropical Medicine has shown that this certainly is the case with the gametocytes from Indian species of *P. falciparum*.

Atebrin.—The work of Schulemann and his colleagues at Elberfeld, which culminated in the synthesis of plasmoquin, was continued by Mietzsch and

Maus. More than 1,200 compounds were prepared and eventually the drug originally called 'erion' and now known as atebrin was produced. Chemically it is the dihydrochloride of an alkylamino-acridine derivative and is a yellow powder with a bitter taste. Its solubility in water is 1 in 14 and it forms a neutral fluorescent solution. The action of atebrin is very similar to quinine, but according to some workers it is more effective than quinine in reducing the number of relapses. None of these drugs by itself nor any combination thereof, such as atebrin and plasmoquin or quino-plasmochin, represents a *therapia magna-sterilisan*.

Chopra and his co-workers (1933) carefully tested this drug on the Indian strains of malaria and have come to the following conclusions:—

(1) Atebrin is an effective drug in the treatment of Indian strains of malaria. Its destructive action on the asexual forms of benign tertian, malignant tertian and quartan types of malaria is about equal, the schizonts disappearing from the peripheral circulation after 0·6 to 0·9 gm. of the drug.

(2) The sexual forms or gametocytes are more slowly acted upon than the asexual forms. The gametocytes of the benign tertian and quartan types are readily destroyed. The gametocytes of the malignant tertian type are not affected at all.

(3) The drug is effective in doses of 0·1 gm. three times a day, the course lasting for five days, making a total of 1·5 gm. of the drug for the cure. The drug can be given intravenously in doses of 0·1 gm. to 0·3 gm. dissolved in 1 to 2 c.c. of distilled water when the number of parasites in the peripheral blood is large.

(4) In chronic types of malaria the drug is effective and produces a rapid reduction in the size of the spleen.

(5) Atebrin has earned a great reputation as a powerful remedy in preventing relapses in all species of human malaria. In view of clinical evidence, the drug would appear to be more powerful than quinine in curing malaria but so far as prevention of relapses is concerned this is not the experience with Indian strains of malaria.

Atebrin musonat.—This form of atebrin has come into prominence through trials made during the recent epidemic in Ceylon. It is simply an improved form of a soluble atebrin salt suitable for injection, 0·3 gm. of atebrin being contained in 0·375 of the salt. Hecht has shown that when atebrin is administered by mouth much of it is retained in the upper intestine, liver and bile, and only overflow goes to the peripheral circulation after these organs are saturated. This exceptionally high concentration of atebrin is responsible for the manifestation of toxic symptoms. By injections the drug gets into the circulation quicker and gives response earlier. Doses from 0·1 to 0·37 gm. are given and a single injection often produces remarkable effects on the clinical symptoms, but recrudescence usually occurs in a few days. Two similar injections on successive days, however, proved sufficient to control the temperature within 48 hours and in four days all forms of benign tertian

parasites and the ring forms of malignant tertian are destroyed. Crescents are not affected and must be destroyed by plasmoquin. The intravenous route can be used, but this method apparently produces no quicker response than does the intramuscular and by some is not considered free from risk. The drug though quickly absorbed is quickly excreted and relapses are said to be more frequent with intravenous injections.

It has been reported that some cases of malaria fail to respond to quinine and are controlled by atebrin and *vice versa*. This may be due to a number of factors which interfere with the proper absorption of these drugs. The parasiticidal effect of neither of these drugs is immediate and takes a certain time to manifest itself.

Toxic effects of atebrin.—Atebrin even in therapeutic doses produces yellow staining of the skin which may take weeks to disappear. It may also occasionally produce headache, abdominal discomfort or colic, but cyanosis frequently met with plasmoquin is not seen. There appears to be no doubt that cases of psychoses of various forms and other cerebral complications have been associated with its use.

Relapses and Prophylaxis.—Quite a large number of malarial patients get relapses occurring within a few weeks to a few months after treatment, whether quinine or atebrin is used. Relapses are said to be less common with synthetic drugs than with cinchona alkaloids but neither of these drugs completely eradicates the infection. Although they have remarkable parasiticidal power over the asexual forms which produce clinical manifestations of the disease, their action on the gametocytes is much feebler and on the sporozoites negligible. As regards sporozoites there is evidence to suggest in bird malaria that there may even be a further cycle in the vertebrate host, and that sporozoites may not all directly give rise to asexual forms in the blood but may undergo schizogonic cycle of their own in the cells of the reticulo-endothelial system. In this form unharmed by drugs they may exist as a reservoir from which the blood may get subsequently re-infected and produce clinical relapse. This has not yet been demonstrated in the case of human malaria.

A number of anti-relapse treatments are suggested, the best for this country is 7½ to 10 grains of quinine twice daily for two consecutive days in the week for two months following the original course, or 5 to 7½ grains may be taken daily for a like period. In the case of atebrin a 5 days' course of 0·1 gm. thrice daily repeated at intervals of a week or 10 days is suggested.

The reason why daily doses of quinine is often suggested as a prophylactic when its action on the sporozoites is negligible is that, although quinine and atebrin may not be lethal to sporozoites, their presence in the blood tends to suppress the multiplication of asexual forms and so inhibits clinical manifestations. For prophylaxis, 5 grain doses of quinine daily or larger doses at correspondingly longer intervals have been used. Some use 0·3 gm. of atebrin weekly, but with this drug it is difficult to strike a balance with a dose which is effective and which is free from undesirable effects.

Both quinine and atebrin have been combined with plasmoquin in preventing relapses and as prophylaxis, but this is not considered desirable.

Atebrin and Plasmochin combination.—As atebrin only acts on the asexual forms of malignant tertian parasites it has been combined with plasmoquin. A comparative study of the action of atebrin and atebrin-plasmochin combination on Indian strains of malaria by Chopra and co-workers (1936) showed that, (1) in cases of benign tertian and quartan malaria the combination of the two drugs is not more effective than atebrin alone in so far as the time of disappearance of the parasites from the blood is concerned; (2) in the case of malignant tertian infection, however, the combination appears to be more effective and the parasites disappear more rapidly from the peripheral circulation; (3) with regard to the relationship between the number of parasites and their disappearance from the peripheral circulation, atebrin alone and atebrin-plasmochin combination behave in the same way; (4) the relapse rate is definitely lower in cases when the combination of the two drugs is used; (5) the combination of the two drugs is more toxic.

It is therefore recommended that in those cases where crescents are present, a 3 days' course of plasmoquin 0·01 gm. twice daily be given after the course of atebrin is completed. The toxic effects are thus eliminated.

Antimalarial Drugs in Ape-malaria.

A few words may be said about the action of these drugs on ape-malaria. It has been shown that *P. knowlesi* produces a very intense and virulent infection in *Silenus rhesus*, causing death of the animal if untreated. This plasmodium appears to be more closely related to that occurring in man than plasmodia occurring in birds which are usually used for testing antimalarial drugs. The results obtained should therefore be more readily applicable to man. Chopra and Das Gupta (1933) showed that the destructive action of atebrin on *P. knowlesi* was exceptionally powerful. Usually two doses of 0·025 gm. of the drug given intramuscularly or intravenously are sufficient to control a very heavy infection which may amount to a million parasites per c.mm. of blood. The drug affected equally the schizogony and the gametogony. Owing to its slow excretion, atebrin appears to exert a more prolonged action than quinine and atebrin is successful in checking a heavy infection whereas quinine may not. It was, however, shown that even after five days' intensive treatment with atebrin, the parasites invariably reappeared in the monkeys in 10 to 15 days and multiplied with the same rapidity as in the previous attack, causing death of the animal if prompt treatment was not given. The recrudescence can, however, be checked more easily, one dose sufficing to control the multiplication of the parasites. After this a low grade of infection persists for long periods, the parasites losing their virulence. In contra-distinction to the action of atebrin, quinine according to Chopra and Das Gupta (1934) has a much less powerful immediate effect on these parasites. When the parasite count is low, i.e. below

100,000 per c.mm., one dose (intramuscular or intravenous) may be effective in controlling the infection, but when the parasite count is higher, 2 or 3 injections are necessary to control the infection. Further, the first effect of injection may be an actual increase in the number of parasites. The advantage of quinine is that relapses rarely occur after the treatment of the primary infection, and even when they do occur, they are not often fatal. The action of quinine thus appears to be slower and if the treatment is started at a time when the infection is moderately heavy, the infection does not seem to be effected, in most cases, in 24 hours or even longer with quinine, whereas with atebrin even if treatment is started late, i.e. when the count exceeds half a million parasites per c.mm., this invariably falls to a negligible number.

Stimulated by the results of these experiments, further work has been carried out on the concentration attained by these drugs in the circulating blood at different intervals of time in relation to parasite count. With regard to quinine, Chopra, Ganguli and Roy (1935) have shown that there is no direct relationship between the concentration of quinine in the blood and the parasite count at any particular time. The highest concentration of the alkaloid attainable without producing toxic effects produced no apparent reduction in the number of parasites nor degenerative changes in them. The action of quinine thus appears to be synergistic to other defensive mechanisms set up in the body. In therapeutic doses quinine augments these processes or possibly it acts on the parasites in such a way as to render them more vulnerable or unable to propagate. Studies on the concentration of atebrin in the blood by Chopra, Ganguli and Roy (1936) show that the highest concentration of atebrin occurs between half an hour and six hours after the injection of atebrin. The number of parasites per c.mm. of blood distinctly diminishes in the majority of cases in the first 6 hours when the concentration of atebrin in the blood is highest. Within 24 hours the parasites are reduced to a negligible number even in spite of the concentration of atebrin rapidly falling off. It is, therefore, reasonable to state that atebrin, unlike quinine, has probably some direct lethal action on *Plasmodium knowlesi* in vivo. This has been further confirmed by Chopra, Das Gupta and Roy (1936) who showed that atebrin solution in a dilution of 1 in 50,000 *in vitro* is capable of destroying the parasites even when the infection is heavy. The smears of blood which were kept in contact with atebrin showed degenerative changes in the parasites. This work is being further elaborated.

Three important points which have come out of this work are :

(1) Atebrin has a more powerful and more rapid effect on *P. knowlesi*. Whereas quinine takes 24 hours to produce its effect, atebrin is effective in 6 hours and concentration of this drug runs parallel with the decrease in the number of parasites.

(2) Atebrin has some direct action on *P. knowlesi* (1 in 50,000 concentration), quinine has not. In fact the first effect of quinine administration may be an actual stimulation of growth of parasites.

(3) A fatal relapse is more common after atebrin than after quinine. The action of quinine, though less powerful and less rapid, appears to be more prolonged and lasting.

Whether all these are applicable to human malaria remains to be seen.

Cinchona Alkaloids *versus* Synthetic Antimalarial Drugs.

What is going to be the effect of the introduction of these powerful synthetic antimalarial drugs on the cinchona alkaloids? Are these old veterans going to be entirely replaced by the new-comers? The Malaria Commission of the League of Nations has rightly pointed out that neither of the two groups, however intensive the treatment may be, is *therapia magna sterilisans* and their effect in preventing relapses is not marked. They also have no true prophylactic action. The synthetic drugs, according to the Commission, are not to be regarded as 'substitutes for quinine but as additional weapons for use in particular circumstances and for special purposes'.

This, I have no doubt, is the correct point of view. The cinchona alkaloids have a very low degree of toxicity and can be used with impunity in the mass treatment of malaria and even self-medication by the patient without any danger of serious harm. The same cannot be said about the synthetic antimalarial drugs. They have a high degree of efficiency combined with toxicity and should always be used under proper medical supervision. Even under such conditions, toxic effects are frequently met with. Unless further researches produce less toxic drugs, and I may say that efforts are being made in this direction—cinchona alkaloid will hold the field for treatment of malaria generally.

During the last few years, it has been debated whether the cinchona plantations in this country should be extended. One of the arguments brought forward against their extension is that in view of the rapid development of synthetic antimalarial drugs there will be no further necessity for cinchona alkaloids. I personally feel no hesitation in saying that unless something extraordinary happens, for the next 15 to 20 years, we shall have to use the cinchona alkaloids in our struggle against malaria in India. The cinchona plantations take 7 to 8 years to mature and if we wish to extend the treatment of malaria among the masses, which is one of the chief methods of eliminating this disease, it is very desirable that cinchona plantations should be extended till such time as an effective and harmless synthetic drug is available which can be used for mass treatment of malaria without any special supervision.

In Formosa large areas have been put under cinchona plantations and in a few years' time Japan will be able to meet all her own requirements. In India large scale and economic production should be taken in hand now that information is available regarding the species of cinchona which yield the highest percentage of the alkaloids and the best soil for cultivation. It may be ten years before India, even if she starts work at once, can hope to produce all

the cinchona alkaloids her population needs, but in the meantime it should be possible to overhaul the existing resources. It is a health rather than a fiscal problem.

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