

## NEW RESEARCHES AND EXPERIENCES IN THE TREATMENT OF MALARIA

*By*

*Dr. Rudolf Hofbauer*

---

When I spoke about "Occurrence and Appearances of Malaria in South Thailand" in 1942 (cf. B.T.R.S. Vol. XIV No. 1, April 1944), the newest remedies against this terrible sickness, which is one of humanity's main scourges, were Atebrine, Mepacrine and Plasmoquine. When being taken in the beginning of a malaria attack, Atebrine cuts off the attack and frees the sick ones very quickly from their troubles; not only from the chills but also from the fever. This fact could not be observed in the same way by taking Mepacrine, where the fever did not disappear so quickly. It is known anyhow, that the parasites of all types of malaria disappear from the blood after about three to four days by the effect of Atebrine resp. Mepacrine. These two remedies are of nearly the same chemical structure and their essential and most effective substance is the dye-stuff Acridine with its typical yellow colour. The only exception where these two remedies are not effective are the subtertian gametocytes, which can be destroyed only by Plasmoquine, resp. by Quino-Plasmoquine, which, as the name says, is containing Quinine too.

The experiences have shown that the two Acridine dye-stuff preparations caused sometimes troubles and disturbances which should not be underestimated. First of all, all patients who take these remedies become yellow all over the body and besides that stomach troubles and vomiting have been observed very often. Also loss of appetite and the decrease of weight in some cases 12 kilos, have been observed. Furthermore, and this is only a subjective fact, the bitter taste — far more bitter than Quinine — prevented people very often to take these remedies.

In 1940 Siam's population was approximately 16,000,000 people and 2,000,000 of them were affected by Malaria, i.e. 12 1/2%. From these 12 1/2% about 40,000 people died, i.e. 2%. These few figures show better than any words can do, how thoroughly the fight against this dreadful sickness must be carried out in this country by all those who are in the position to do so !

I have, during the several years of my experiences with the treatment of malaria and the researches about this sickness, found that people, after having gone through an Atebrine treatment of 1.5 gms. (15 tablets 0.1 gm. each) have sometimes got relapses. So, to prevent these relapses it has become a general rule to take for 3-4 months nine tablets (on the first nine days of the month). It has been observed that those people generally remained free from relapses resp. new attacks, but there were also several who got relapses. But such treatment, of course, cannot go on indefinitely and besides that, the yellow coloration and the different stomach troubles, as already mentioned, appear newly, resp. do not disappear completely.

I like to render prominent that Atebrine and Mepacrine have not failed to help in the great fight against Malaria. Especially in India, Burma, Malaya and in the Dutch East-Indies Atebrine and Mepacrine has helped to keep the allied armies fit during the last war and when I spoke about the by-effects I do not like to provoke the impression that Atebrine resp. Mepacrine are not good anymore; the discovery of these remedies: Atebrine, Mepacrine, Plasmoquine are belonging to the greatest deeds, science has achieved. I am on account of my experiences, fully convinced that these remedies are far far more effective than Quinine and the view that, only on account of the loss of 95 per cent of the Quinine producing areas to the Japanese during the last war, the above three mentioned remedies have been used to that great extent, is absolutely absurd. Against malignant tertian malaria Atebrine and Mepacrine are of little value as preventives, but the actual fever can be controlled by a suitable dose of the drug.

It was natural of course then, that research-workers, after having got knowledge of the by-effects of these remedies, carried out new researches to get a still more effective drug. A team of British research-workers succeeded in 1945 to find a new drug which they called Paludrine which is said to be 10 times more powerful than Quinine, and much more effective than any anti-malarial drug known so far. This new drug is being produced in form of tablets, each containing 0.1 gm. of Paludrine. The tablets are of white colour, an advantage which is subjectively very important for those who have to take this drug, as there cannot be any yellow coloration. It has been said, that Paludrine does not taste bitter at all; I like to state already here by my own experience: this is completely true. As a matter of fact, Paludrine tablets are nearly tasteless. The three research-workers Drs. Curd, Rose and Davy have tried many compounds, which had to be worked out, tested and rejected, before compound No. 4888 was found and the name Paludrine was given to it.

Paludrine has been found to give complete protection against malignant tertian malaria, the parasites being destroyed entirely before they could become established in the blood stream.

Through my personal professional connections in England I approached the Imperial Chemical Industries and I succeeded to get one original tin containing 1000 Paludrine tablets with which I carried out my experiments and researches. I have mentioned already that the tablets are completely tasteless and the main point of my researches consisted in controlling the effect of the new drug on malignant tertian malaria here in Bangkok.

I like to render prominent that my hope was fulfilled completely. When one tablet Paludrine was taken daily, people who had been bitten by infected mosquitoes, did not get the slightest effect. In cases of benign tertian malaria 1 tablet a day was already completely sufficient to prevent any fever developing. Parasites could not be detected in the blood, and mosquitoes feeding

on the blood of 26 patients who had agreed to serve as "volunteers" for my researches, failed to transmit infection to others. I found furthermore that this new drug is able to control the actual fever of those who suffer from malaria. The necessary dose is extremely small compared with the former three remedies and very much smaller compared with Quinine.

For Atebrine and Mepacrine a course of at least 1.5 gms., i.e. 15 tablets was needed to fight the attack as effectively as possible and sometimes Plasmoquine had to be given too for killing the gametocytes in malignant tertian cases. I have found that not more than at last six tablets of Paludrine were necessary to fight an actual malaria fever. The microscopical blood control never showed any parasites from which type of malaria soever. My special aim to fight the malignant tertian form, the most terrible and most dangerous from the malaria, was successful. Nine cases, which I saw, were cured within 2 days without any by-or after-effects. There is another highly important point which must be mentioned here. In spite of all the effective drugs which we had before the Paludrine the general weakness of the patients after the malarial fever attacks was hampering them to do their work to its full extent. This had disappeared with Paludrine and workmen are able to take up their work again after - so to say - some hours.

The question of relapses cannot be answered definitely yet; from all the cases I have seen, altogether 35, I saw one relapse from the group of 26 people. This patient suffered from benign tertian malaria. We know that this form is not so dangerous, but it is persistent. The fever may be cured, but it can recur again and again through the years. The 9 patients with malignant tertian malaria so far (3 months) have not had any relapses.

We have seen that even 9 Atebrine resp. Mepacrine tablets being taken each month did not prevent always relapses. In case of Paludrine 1 tablet per week, that means 4 tablets per month, have proved to give a complete protection. Perhaps it may result by

further microscopical blood control that 4 tablets Paludrine monthly may be able to kill off the parasites in their entirety.

Some words about it's chemistry. Paludrine, according to the "Annals of Tropical Medicine and Parasitology, February 1946," has the chemical formula : N-1-p-chlorophenyl N-5-isopropylbiguanide.

Reading this chemical compound one is apt to think that this must be a very complicated drug. The fact is quite contrary; this compound is very simple, much more simple in fact than any anti-malarial drug known up to now. Paludrine has proved to be absolutely nontoxic, it has not even one of the objections associated with Atebrine or Mepacrine-treatment and, as I have been informed, the cost price will be lower than all the anti-malarial drugs known hitherto, including Quinine.

The greatest importance of all is the fact that the mosquitoes are unable to transmit malaria parasites from the blood of a person who is taking Paludrine. It can therefore be stated that the cycle of infection from one person to another by way of the mosquitoes has finally been broken.

We have seen that in many cases where 9 Atebrine-or Mepacrine-tablets were taken prophylactically, relapses occurred and with 4 tablets Paludrine monthly nearly no relapses occurred. It has been stated that Paludrine is about 3-5 times more effective than Atebrine or Mepacrine, and 10 times more effective than Quinine. Paludrine has been called "the wonder drug". It seems nearly that the drug is entitled to this name. 300,000,000 people are suffering from malaria and about 3,000,000 people die yearly from this dread disease. If it becomes true in the long run that Paludrine keeps all its promises, those 3,000,000 lives might be saved, or at least a very high percentage of them and Paludrine will then be very near to the ideal of the anti-malarial drug, scientists have been working for.

The terrible effects of the tropical and sub-tropical (malignant tertian) malaria are known all over the world. In the past, malaria has killed more men than wars have done. Today malaria causes more death and suffering than any disease whatsoever known to medical science. If Paludrine will continue to prove its wonderful and marvellous effects – and the symptoms seem to be extremely good – this terrible scourge of today may well be obliterated tomorrow and it is most likely that Siam, with the benefit of Paludrine, may become more or less completely free from Malaria.

---