Some Antimalarial Drugs:

Natural and Synthetic

By AURORA C. REYES
Chemist, Bureau of Forestry

Malaria is probably the worst of all human scourges. Not only does it kill 3,000,000 people a year, but 300,000,000 fresh victims are infected every twelve months. The medical literature abounds with drugs both natural and synthetic so that reports are rather conflicting as to their dosage and efficacy. Since malaria is a disease characterized by many stages, to effect a radical cure, the drug must have to eradicate all the forms of blood stages of the parasite. So far, no ideal antimalarial drug has been found to-date. The ideal drug must possess the following properties: (1) It must destroy the gametocytes or the sexual parasites of malaria in such a way that they become devitalized and non-infective to mosquitoes and thus, prevent the spread of the disease. The effect is said to be prophylactic. (2) It must be effective against the asexual forms which provoke the familiar signs and symptoms of the disease. The effect is said to be suppressive, and thus prevent relapses. (3) It must be effective against the different species of *Plasmodium* producing malaria in man. There are three different species, but only two are important, namely, *Plasmodium vivax* which has low mortality but great tendency to relapse and the *Plasmodium falciparum* which has high death incidence but less tendency to relapse. As to the preventive effect which drugs may have against malaria in man, very little is known.

Cinchona alkaloids have been the favorite "stand-bys" in the treatment of malaria of all forms. It is the oldest drug as an antimalarial and was used as the standard prior to World War I. Totaquina is the standardized mixture of cinchona alkaloids. This galenical preparation uses more economically the active principles found in cinchona bark. The various cinchona alkaloids, cinchonine, cinchonidine, and quinidine each has an antimalarial activity which compares well with quinine. Quinine preparations have been known and used since the seventeenth century in the treatment of malaria. The pure crystalline alkaloid was isolated from cinchona bark for the first time by Joseph B. Caventou and Joseph Pelletier on September 11, 1820. Pasteur in 1853 established the relations of the isomers quinine and quinidine, cinchonine and cinchonidine. The correct structure of quinine was proposed in 1908 and was synthesized by R. B. Woodward and W. E. Doering in 1944. Because of the complexity in the structure of the molecule, it took some time before the drug could be synthesized.

Quinine, however, has its limitations in malarial therapy. It has a selective effect on the different stages of the malarial parasite because it affects only the blood stages and does not influence the relapse rate. For this reason, several antimalarials are being synthesized to overcome the shortcomings of quinine.

The cinchona alkaloids, however, remained the only effective means of treating malaria until 1926, when plasmoquine or pamaquin was introduced by Muhlens. Pamaquin was first synthesized by three German scientists, Schuleman, Schonhofen, and

Wingler. This drug was first demonstrated by the British investigators in India before World War II. Because its effectivity lies in its administration in large doses which would be considered toxic, the Germans were led to continue investigating, and in 1933, "atabrine" was developed by Mause and Mietzsch. Other synonyms of atabrine are quinacrine, atebrin, and mepacrine.

As early as 1934, chloroquine had been synthesized by the Germans. It is available in the market in the form of diphosphate under the trade name "Aralen". It is interesting to note that chloroquine was first extensively used in Korea and was found to eliminate successfully the threat of malaria. Several drugs of this type have been developed, namely, oxychloroquine camoquin, santochin, and paludrine. Paludrine (also called chlorguanide and guanatol) is an English preparation. The French put it under the name Nivaquine.

The rapid pace in the production of these synthetic drugs was motivated by the exigencies of the conditions in 1941. Shortly after the bombing of Pearl Harbor, the United States, having been cut off from the main sources of supply of quinine bark by the Japanese and realizing the importance of antimalarial drugs in winning the global war, especially in malaria-infected areas, took active steps in the large scale production of synthesized anti-malarials. Because of military expediency, this loss of natural quinine, therefore, led to the development and further studies of anti-malarials that are more effective and powerful to all types of malarial infection. In the course of the investigation, some of the compounds developed like pentaquine and isopentaquine were clinically tested and were found to be an improvement over its predecessors.

During the war, because of the alarming death toll due to the spread of malaria, the United States under the circumstances found it necessary to prove further into the usefulness of synthetic antimalarials. Up to the present, the race for superior drugs is going on unabated.

The latest synthetic antimalarial is Daraprim which is twelve times more powerful than chloroquine, the standard antimalarial in wise use as a suppressant in recent years. The scientific name for Daraprim is *pyrimethamine*. It was made by Dr. H. Hitchings and was first announced in April, 1950.

So far, there had been 15,000 drugs tested for their therapeutic effect since 1941. Over 150 compounds have shown evidence of merit in the cure for malaria. All of them either prevent the spread of malaria, cure it, or mask the symptoms.

The Philippines, however, is not yet in a position to manufacture these synthetic antimalarials which is rather a complicated process and requires a complex plant. Nevertheless, we need not worry about synthesis, as the Philippines, unlike other countries, is more fortunate in that she has grown successfully several cinchona species. Thanks to our Bureau of Forestry which pioneered in the cultivation of cinchona. The success, however, is only on one phase—that of cinchona culture; the neglected phase —that of chemical manufacture and utilization. The foresters have done their share, now this is a challenge to our local chemists and chemical engineers. The importance has been repeatedly stressed and need not be over-emphasized. It is high time, therefore, that more serious attention be focused towards this direction.

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BIOGRAPHY OF . . .

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danao. In various other ways he has demonstrated a positive interest in the welfare of the local boyhood through volunteer service in Scouting. A real Scouter and leader."

On the occasion of the Golden Anniversary of the Bureau of Forestry on April 14, 1950, Agapito L. Cenabre was a recipient of service award diploma and special gift from Secretary Placido Mapa of the Department of Agriculture and Natural Resources. The service award was in recognition of continuous, faithful and meritorious service rendered to the Bureau for not less than 25 years, while the special gift was for attaining 42 years of service in the same Bureau.

"Tito" had twice made a vow with the seventh sacrament; however, in both cases he was not blessed with any child.

Tito had applied for retirement effective on August 18, 1953, but his services was indefinitely extended by the President of the Philippines in accordance with the decision of the Cabinet. He finally got retired on February 28, 1954.

But this biographer has only narrated so much of what he and other people know about and think of Cenabre. The following extract from a letter of Tito on his retirement, will give a direct insight of the man on his sense of duty and relation with his co-employees.

"* * * I am now retired since February 28, 1954. Of course the reality of such severance is poignant indeed minimized only by the thought that I always did my best in the interest of our country and the forestry profession.

"I cease to be an employee of our bureau, but my love for forestry will always remain, as well as the warm association I had with you. Above all, of course, I wish to thank you and those who have worked with me directly during all these years for their cooperation, and those other co-workers in the Bureau with whom I have come in contact, for all the help, courtesy and understanding extended to me.

"This severance is, however, not the parting of my ways from yours. I find my mind and body still responsive to our work and I believe I can still be of service to forest users in a private way. * * *"

Tito will stay in Manila for a while to work his way privately helping forest users as mentioned in the last quoted paragraph above. He will open his office as Consulting Forester at Capitol Theater Building, R-205, 31 Escolta, P.O. Box 1836, Manila.

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need of a forest. It is perhaps only in this way that we can enlist the support of almost everybody, the rich and the poor, the men and the women, and probably even going to the extent of winning the sympathy of our legislators, who are empowered to formulate our laws and to appropriate our revenues and taxes for such projects deemed necessary for public improvements. Once public sentiment on the preservation of our forests is created, the continuous existence of the Philippine Forests is assured.

Conclusion

In the furtherance of forestry in the Islands, an individual can cooperate with the government in many ways without the expense of his personal money, yet the help he has made for the cause of forest conservation finds no equal in money value.

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