## Magic Bullets to Conquer Malaria

Since the dawn of time, malaria has been one of the most widespread, unremitting, and deadly diseases, and man has used natural remedies to try to contain the scourge. After quinine was isolated from the bark of *Cinchona* by Pelletier and Caventou in 1820, the first synthetic anti-malarial drugs came unexpectedly from the synthetic dyestuffs industry in the middle of the 19th century. In the last two decades of that century, the identification of the parasite and knowledge about the cause and transmission of malaria led to the first bases for chemotherapy. In that time, many efforts have been devoted to controlling the production and trade in quinine, and also to searching for synthetic drugs to circumvent the restrictions of the supply of quinine and of its shortage during World War II. This is the framework of a story that stretches over several centuries and all five continents, with obvious medical and scientific goals, but also intermingled with geographical, historical, financial, and political facets, which were—and still are—of crucial importance.

Irwin Sherman tells this story as an adventure, which is sometimes difficult to follow because many scientists in many different places and times were involved. He gives a lively description of the atmosphere of the events, with details of the lives of the people involved, and of collaborations as well as controversies and conflicts. Genius, curiosity, and work—a lot of work and diligence—characterize the advances in research against malaria, which were recognized by the award of several Nobel Prizes.

After a first chapter describing the progressive discovery and increasing knowledge of the malarial parasite between about 1880 and 1980, the second one is devoted to the history of Cinchona and quinine. The following chapters review the discovery of the main synthetic drug groups, including breakthroughs and setbacks, successes and reversals of fortune, toxicity of drugs, and the development of resistance by the parasite.

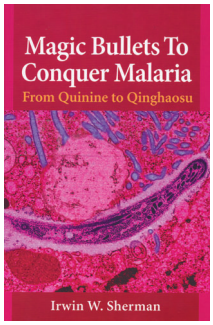
The first synthetic anti-malarial, the 9-aminoacridine derivative Atabrine, was introduced to the market by its German manufacturers in 1932, and was used throughout the world as a substitute for quinine, especially by the American Army during the Pacific War. Among efforts to develop drugs with fewer undesired side-effects, German chemists synthesized chloroquine (a 4-aminoquinoline initially named Resochin) in 1934. Incredible as it may seem now, they discarded it on the basis of deceptive results on bird malaria. Consequently, the lack of a suitable animal model delayed the development of chloroquine, until it was tested by the French and re-discovered by the Americans in 1943. Chloroquine was introduced into clinical practice in 1947, and has remained the drug of choice throughout the world for 25 years (Chapter 3). Chapter 4 is devoted to the use against malaria of anti-microbial inhibitors of the tetrahydrofolate pathways, sulfonamide and pyrimethamine. Chapter 6 deals with the discovery, rise, and fall of mefloquine, which, like quinine, is a 4-quinoline alcohol. The inhibitors of the liver stage of the disease (8-aminoquinolines) are reviewed in Chapter 5.

In several cases, very useful drugs were synthesized, tested, and widely used long before their putative target and mechanism of action were known. The vital need to contain the disease, particularly to protect troops, led to new drugs being used on a large scale only a few years after their discovery.

Antibiotics have played an auxiliary role in malaria therapy since the 1970s. That justified a foray into the field of the discovery of antibiotics during World War II (Chapter 9). In that case too, only three years were spent on research between the first trial of penicillin in mice and its production in sufficient quantities for military purposes, for patients infected by staphylococci and streptococci. Antibiotics tested in the 1950s had no practical value for therapeutic management of acute attacks of malaria. However, since the mid-1970s, the resistance of Plasmodium to chloroquine, and a better knowledge of the biology of the parasite, encouraged the search for antibiotics effective as anti-malarials.

Chapter 8 is devoted to the discovery of artemisinin and to artemisinin combination therapies that are now recommended. However, the author emphasizes the role of the World Health Organization and difficulties of collaboration with the Chinese, but downplays the fact that artemisinin had already been successfully used in Asia to treat millions people since the 1970s, long before the WHO became officially interested in it. The erratic supply and uneven cost of artemisinin are also noted.

Chapter 10 deals with the control of the disease, a "reasonable dream" since eradication is clearly out of reach. The first strategy to block the transmission of malaria is to kill mosquitoes, and to use long-lasting insecticide-impregnated bed nets. An alternative is to suppress human infectivity towards mosquitoes by developing a transmission-blocking vaccine to limit the transmission of human malarial infections to mosquitoes. Although hope remains for a protective vaccine, the goal is still elusive (Chapter 11). Sherman notes that "*medicines may offer the best practical and economic way*

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*to effectively control the disease*" (p. 246, Chapter 12). In this context, the omission of all the synthetic analogues of artemisinin (trioxolanes, tetraoxanes, trioxaquines) and of ferroquine, despite the fact that several of them are currently undergoing clinical trials, is regrettable.

One might regret that many of the schemes of chemical structures are redundant, and in some cases the stereochemistry is incorrect (pp. 172–173). Aniline is not an amide (p. 55). There are also some historical inaccuracies. The construction of the Panama Canal did not begin in 1907 (p. 41). And the bibliography consists mainly of reviews instead of original reports, even where these are easily available, a practice that will please neither scientists nor historians.

Having said that, it is not an exhaustive textbook for chemists or parasitologists, but a story for all curious readers. It should open the minds of scientists to topics other than their own disciplines, and make everybody aware of how chemistry can have an important role in decisive events for mankind.

Irwin Sherman cites Wallace Peters, author of about 350 papers related to malaria chemotherapy and drug resistance. Peters noted about "*young investigators*" that "*few of them have the remotest idea or interest in what has gone before them. It is an unfortunate fact of life that the younger you are the less you want to understand what has gone before you, internet or no internet!*". This book should help to change that.

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