History of Malaria Chemotherapy

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(with additions by Nicholas J. White)

Malaria historically has had two unique attributers: 1. Based on its characteristically intermittent fever patterns it had among the myriad of "fevers" the clearest definition. Even before the use of thermometers, a disease in which the patient became obviously feverish every third day was likely to be malaria. This is the reason that the disease often was called "intermittents." 2. It was the one disease for which a medicinal therapy potentially could actually be effective. "Peruvian (or Jesuits') bark," or colloquially, "the bark", was introduced into Spain from its Peruvian colony in 1639. The name "cinchona" for the tree whose bark was medicinal probably derived from the native Peruvian "quina-quina" and not from the name of the Countess of Chinchon (1). Treatment of malaria can be divided into the first 300 years of waxing and waning use of the bark, with production of synthetic anti-malarial drugs beginning in the 1920s.

According to Thomas Sydenham (1624-1689), "The Peruvian bark, has been famous in London for the cure of intermittent fevers for upwards of five and twenty years. .." (2a). Sydenham speculated that the disease was caused by an "atmospheric diathesis" which had caused an epidemic of it in London in 1678. "The Peruvian bark became my sheet-anchor; concerning which, in spite of the prejudices of many learned men. . . I may safely affirm that I have neither seen nor suspected any evil effects. . . ." (2b). The greatest therapeutic handicap, which Sydenham recognized, was that relapses were occurring two weeks after cessation of treatment. "The relapse. . . seemed to me to arise from the blood not being sufficiently saturate with the febrifuge, which, efficient as it was, could not exterminate the disease at once." (2c). Therefore treatment must be continued for some time after apparent recovery. He found that therapeutic response is more rapid in a quartan fever (every 4th day) than when fever was occurring every other day (tertian) or daily (quotidian) (2d). It was a long-standing belief, held into the nineteenth century, that to cure a disease its cause and effects must be physically removed, either via the gastrointestinal tract and/or by bleeding. Cinchona was confusing because it was beneficial without causing any excess evacuations. Sydenham stated: "The cure by the bark neither requires purging nor bears it; since the bark by itself, single-handed, relieves the fits, and relieves the dyscrasy of the system as well. . . . All evacuations, therefore, should be avoided. . ." (2c). He also employed smaller doses of bark in cases of "hysteria and hypochondriasis," but, "Still it must be owned, that bark in hysteria is less of a remedy than bark in ague. Here it works wonders. . ." (3).

Hermann Boerhaave (1668-1738) one of the most influential physicians of his time, still recommended cinchona bark as powder or decoction without additional ingredients "for intermittents" (4). By the nineteenth century bark or quinine was being prescribed in all possible formulations, administered orally or rectally and for all sorts of symptoms. An American formulary from 1849 contains 20 prescriptions containing cinchona and 10 containing quinine. In a "febrifuge bolus" cinchona powder was

accompanied by tartar emetic (antimonial), ammonium chloride and carbonate (5a). A prescription for "bilious intermittent or remittent fever" contained calomel (mercurous chloride), quinine and aloes (purgative) (5b).

The cinchona bark, being imported, was expensive and therefore frequently adulterated or completely faked. This probably was the leading factor in its inconsistent efficacy when the diagnosis was correct. An example of the drug's diminished regard was shown in 1837 by John Mackintosh. "The discovery of such a remedy has always been a great desideratum; and although no one remedy has yet been found out, I believe that bleeding, in the cold stage, conjoined with laxatives, and the occasional use of the sulphate of quinine, to be as certain a mode of treating intermittents, as any other set of remedies can be said to be certain in the treatment of any other class of diseases." (6). In the 10 months during 1848-'49 34,000 lbs. of barks were rejected at the port of New York as being fraudulent (7)! In 1830, according to Jonathan Pereira (1804-1853), England imported 556,290 lbs. of cinchona bark of which 90% processed as medication, was exported. Already in 1836 he expressed concern about the exhaustion of its only source: "When we take into consideration the immense consumption of Cinchona bark, that the trees yielding it are confined to one part of the world, and that no care is taken of their preservation; it is not improbable that in a few years this valuable drug may totally disappear from commerce." (8) This potential loss was addressed by the Dutch East India Company by establishing cinchona plantations of the high yielding Cinchona ledgeriana in the Dutch East Indies (Indonesia), with unforeseeable consequences in the twentieth century.

In 1820, P.J. Pelletier (1788-1842) and J.B. Caventou (1795-1877), French apothecaries, reported the extraction of quinine from cinchona bark. The production of quinine rapidly became a large enterprise. In 1826 two Paris laboratories produced 59,000 ounces of the drug. According to an English manufacturer, 100 lbs. of yellow cinchona bark would yield 25-50 ounces of quinine sulfate (7). Quinine was first extracted in the United States (Philadelphia) in 1823, and in 1845 between 40,000 and 50,000 ounces were produced there (9). Dunglison (1853): "Sulphate of quinia possessed almost all the medical virtues of cinchona. . . It has now taken the place of cinchona in all periodical diseases." (7)

Alphonse Laveran (1845-1922) discovered the malaria parasite in 1880 and Camillo Golgi (1844-1926) in 1889 differentiated Plasmodium vivax and falciparum. However, twenty years passed before the Plasmodium was generally accepted as the pathogen (10). Ronald Ross (1857-1932), a British army physician in 1897 demonstrated that the vector of this parasite is a mosquito (11) and MacCallum (1874-1944) in the same year observed fertilization in avian malaria. Henceforth the approach to malaria became two-fold: in addition to treatment of the infection, attempts to eradicated infectious mosquitoes and/or their breeding sites (12).

Guttmann and Ehrlich were the first to identify a synthetic antimalarial drug (methylene blue), but this was insufficiently effective to supplant quinine. World War I eliminated the Indonesian source of quinine from Europe and North America. Therefore, soon after the war German pharmacologists began to search for synthetic alternatives to quinine. Their chemical starting point was the quinoline (2 ring) nucleus. In 1925 an 8-amino-quinoline (Pamaquine) became the first synthetic drug with radical curative activity against vivaxmalaria, and the first of a long line of synthetic compounds based

around this structure. But it was quite toxic. In 1930 quinacrine (mepacrine, atabrine) was discovered. It was based on an acridine (3 ring) rather than a quinoline structure. Acridine is a yellow dye and the chronic ingestion of quinacrine caused a non-toxic but disagreeable, reversible staining of the skin. The Japanese entry into World War II again blocked the Indonesian source of quinine. Therefore, quinacrine became the standard suppressive and therapeutic anti-malarial of the Allied forces.

Nevertheless, a huge program of screening and clinical testing of potential anti-malarials was begun in the U.S. in 1941 and independently in Great Britain. This resulted in several drugs, the most useful of which was chloroquine (a 4-amino quinoline). In fact chloroquine had been already discovered by Andersag and colleagues working in the research laboratories of IG Farbenindustrie (subsequently Bayer) n Germany in 1934, but was shelved because of toxicity concerns. Instead methychloroquine (Sontoquine) was produced initially. But after World War II, chloroquine, which has the same side chain as quinacrine, but a quinoline nucleus, was developed. Beginning in 1946, its greater potency and safety gradually caused chloroquine to replace quinacrine (13). However, according to a 1958 edition of Harrison's Textbook of Medicine, ". . . both quinine and quinacrine will undoubtedly continue to be used for many years." (14) Meanwhile in the UK, scientists had developed a completely different antimalarial based on inhibition of folic acid synthesis. This was proguanil (chloroguanide). This was followed six years later by pyrimethamine, one of Elion and Hitchings Nobel prize winning synthetic purines. These antifols became widely used both in prophylaxis and treatment. A critical difference between malaria caused by P. falciparum and P. malariae and disease due to P. vivax and P. ovale is that the former two species do not form hypnozoites, or sleeping forms, which remain dormant in the liver may cause new attacks (relapses) weeks or monthsafter apparently effective treatment. Primaquine, a new and better tolerated 8-amino quinoline, was introduced in 1951. Field testing during the Korean War demonstrated that the combination of three days of chloroquine administration with two weeks of primaquine reliably prevented recurrences of vivax malaria, and to this day primaquine is the only available drug for the radical treatment of vivax and ovale malaria. The next episode in antimalarial drug discovery was the Vietnam war, which stimulated an enormous US Army program of drug discovery, and led to mefloquine and halofantrine. On the other side of the globe in the 1970s, Chinese scientists rediscovered the remarkable antimalarial activity of qinghaosu (artemisinin) derived from the ubiquitous shrub Artemisia annua. Indeed as we lose the first generation of synthetic antimalarial drugs to resistance, it is to Chinese scientists that we owe the discovery of the majority of new antimalarials either under development or deployed already (artesunate, artemether, dihydroartemisinin, lumefantrine, pyronaridine, piperaquine).

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