

Malaria: Recognising a Chinese Triumph

Malaria is a disease that has been with us for all of human history. Malarial parasites are known to infect all terrestrial vertebrates. They are notable for their ability to survive and develop in the environment of vectors that transmit them from host to host, spreading disease. A recent account by Francis Cox traces, in engaging fashion, the 'history of the discovery of the malaria parasites and their vectors' (Cox, F. E. G., *Parasites and Vectors*, 2010, 3, 5). The earliest references to malaria in recorded history may be found 'in a Chinese document from about BC 2700, clay tablets from Mesopotamia from BC 2000, Egyptian papyri from BC 1570 and Hindu texts as far back as the sixth century BC'. Modern research on malaria really began only in the 19th century; driven by the imperatives of colonial expansion. The causative agent of malaria, a protozoan parasite, was first detected in human blood by a French army officer, Charles Laveran, stationed in Algeria. Laveran who was to later receive a Nobel Prize in 1907, made a discovery that was, in Cox's assessment, 'without precedent as no protozoan had previously been found inhabiting any kind of human blood cell'. Ronald Ross' subsequent demonstration that mosquitoes, specifically anopheline mosquitoes, are responsible for transmitting the disease was based on work at Secunderabad and Calcutta (now Kolkata), when he served as an army medical officer in India, between 1898 and 1899. The story of Ross is now legend, recognized by the Nobel Prize in 1902. A century later the complete genome sequence of *Plasmodium falciparum*, the most feared of the pathogens that cause human malaria, was announced (Gardner, M. J. *et al.*, *Nature*, 2002, 419, 489).

Malarial parasites are unimaginably old, coevolving with their hosts over millions of years. Monkeys and men, mice and birds, even lizards, can harbour malarial parasites; each one fashioned by natural selection to survive and multiply within a specific host environment. *Plasmodium falciparum* is the most dangerous of the parasites that cause human disease. Its origins are still shrouded in an aura of mystery and uncertainty; a common situation when science attempts to trace the evolutionary history of living organisms. Recent DNA analyses of host populations across sub-Saharan Africa suggest that the human malaria parasite, '*P. falciparum* is of gorilla origin and not of chimpanzee, bonobo or ancient human origin'. The most virulent of the parasites that infect man may have 'resulted from a single cross-species contamination event' (Liu, W. *et al.*, *Nature*, 2010, 467,

420). While parasites rarely, indeed very rarely, switch hosts, it is precisely this ability that has been advanced 'as an important adaptive trait of the parasite' (Hayakawa, T., *Mol. Biol. Evol.*, 2000, 25, 2333). While the origins of the parasites are obscure, their resilience and adaptability have ensured that malaria remains a major public health issue in many parts of the world, even in the 21st century. An estimated 250 million people are afflicted by malaria today, with the annual death toll from the disease approaching one million. Vector control, in the case of diseases that are spread by insects, requires elimination of breeding sites; a task that can be a formidable civic problem in many countries. The 'mosquito net', an old reliable in the fight against malaria, remains a mainstay in current attempts to battle the spread of disease in some parts of the world, most notably Africa.

Malaria research, in the century after Laveran and Ross, has greatly advanced our knowledge of the biology of the parasite and its mosquito vector; their genomes have been laid bare by the successes of sequencing efforts, while immunology has provided many insights into the responses of human hosts to infection. Yet, vaccines, so eagerly sought after, have remained a mirage. DDT raised the hope that an alternate strategy which eliminated the mosquito vector, would break the vicious cycle of disease transmission. The spraying campaigns of the 1950s and 1960s ran into public opposition, as the long term deleterious effects of DDT exposure became widely known. DDT and the family of insecticides have proved a double edged sword, in the war on insect pathogens in agriculture and in vector control in the arena of public health. With children being at the highest risk of mortality from malarial infection, especially in Africa, widely different opinions currently prevail on the strategies for vector control. The issue of balancing short term gains versus long term concerns is difficult and, at times, contentious. The old adage that 'prevention is better than cure' has been the basis for the push towards vaccines and vector control. However, the mainstay in the battle against malaria has always been the use of agents that clear parasites from infected patients. The Spanish colonisers who descended on South America quickly encountered both the disease and remedies that were favoured by local inhabitants. The curative properties of the cinchona tree were recognized; knowledge relayed by Jesuit priests working in Peru, to the salons of Europe in the 17th century. The long trail of research, beginning with the isolation of the alkaloid quinine by Pelletier in the 1830s to

Woodward's synthesis of the molecule in the 1940s, is now part of the folklore of natural products chemistry. Quinine quickly became the key weapon in the war on malaria; the mainstay of therapy until the appearance of the synthetic antimalarials. Herbal concoctions have always been central to the practice of traditional medicine in China and India, with a long recorded history of the use of plant materials for medicinal purposes. Indeed, it is from China that artemisinin emerged as the drug of choice for the treatment of malaria caused by parasites resistant to the attack of chloroquine. The 2011 Lasker-DeBakey Clinical Medical Research Award honours Tu Youyou, a Chinese scientist for her stellar role in steering the project that led to the discovery of artemisinin.

Tu Youyou, now 81, tells a remarkable story, 'The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine', in a recent commentary in *Nature Medicine* (2011, **17**, xix). Tu began her career in 1955, at an institution devoted to traditional Chinese medicine. She credits a training course 'designed for professionals with backgrounds in Western medicine' for guiding her 'to the wonderful treasure to be found in Chinese medicine'. Tu was assigned to work on Project 523 which, as the Lasker award citation notes, derives its name from the date it was announced – 23 May 1967. The project was a covert operation, launched at the beginning of the cultural revolution, even as the Vietnam war intensified. This research was 'apparently prompted by the requests of Ho Chi Minh to Zhou En Lai for antimalarial drugs to protect his Vietnamese troops' (White, N. J., *Science*, 2008, **320**, 330). Tu headed a group 'comprising both phytochemical and pharmacological researchers', quickly beginning an exhaustive survey of herbal preparations. In initial work the group screened 'more than 2000 Chinese herb preparations and identified 640 hits that had possible antimalarial activities'. Using a mouse model for malaria Tu and her colleagues evaluated 'more than 380 extracts obtained from ~200 Chinese herbs'. She notes that 'progress was not smooth and no significant results emerged easily'. The observation that a qinghao (*Artemisia annua* L.) extract 'showed a promising degree of inhibition against parasite growth' was the 'turning point'. A stumbling block was encountered almost immediately; the observations were irreproducible. The Chinese team realized that the only relevant reference to the use of qinghao appeared in a classic text dating back to 340 AD – Ge Hong's *Handbook of Prescriptions for Emergencies*. A single statement provided a clue: 'A handful of qinghao immersed with 2 liters of water, wring out the juice and drink it all'. Up to this point Tu and her group had extracted the plant material at high temperature, a step that destroyed activity. Lowering the temperature did the trick. On 4 October 1971 the Chinese obtained an 'extract that was 100% effective against parasitemia', in both infected mice and monkeys. The absence of toxicity was established when Tu and her colleagues consumed the extract themselves. Clinical trials carried out quickly in Hainan demonstrated recovery of patients in a cohort where chloroquine proved

ineffective. Artemisinin (qinghaosu) was purified and characterized in 1972 and its unusual structure determined in 1975. The road from the molecule to the drug was rapid. In beginning her account of the road to artemisinin, Tu draws attention to an essay of Joseph Goldstein, where he suggests that 'creation and revelation' are 'two different routes to advancement in the biomedical sciences' (*Nature Medicine*, 2007, **11**, 1151). For Tu Youyou the discovery of artemisinin was 'the revelation'; transforming the molecule into a drug was 'creation'. The artemisinin project was carried out almost entirely during China's Cultural Revolution, which lasted for an entire decade between 1966 and 1976. Both Zhou En Lai and Mao Zedong died in 1976. By 1981 an international meeting on the Chemotherapy of Malaria was held in Beijing. In 1985, a review in *Science* announced the arrival of an antimalarial drug from China (Klayman, D. L., *Science*, 1985, **228**, 1049). Artemisinin was undoubtedly discovered in China under the most difficult circumstances. Tu and her colleagues had no contact with the world of Western science.

While much of cutting edge modern, biomedical science has flourished in the West, malaria has always been a cross that has been borne by the underdeveloped world. Colonial interests drove malaria research until the middle of the 20th century; the subsequent American military involvement in the killing fields of South East Asia, home to malaria, provided a rationale for research investments until the 1970s. Pharmaceutical companies, necessarily constrained by commercial interests, have never found any strategic advantage in malaria research. Current efforts to control and combat malaria rely largely on rapidly growing funding from philanthropic foundations. But increases in resources alone may be inadequate in the war on malaria. Resistance is a constant threat, as natural selection renders both the parasite and the mosquito vector impervious to chemical attack, after constant exposure. The first signs of artemisinin resistance in *P. falciparum* malaria appear to have surfaced along the Thai–Cambodia border, 'historically a site of emerging antimalarial resistance' (Dondorp, A. M. *et al.*, *New England Journal of Medicine*, 2009, **361**, 455).

In concluding her account of the artemisinin saga, Tu suggests that there may be other gifts from Chinese medicine. In a statement that may resonate with proponents of Ayurveda, Tu notes: 'However, the use of a single herb for the treatment of a specific disease is rare in Chinese medicine. Generally, the treatment is determined by a holistic characterization of the patients syndrome, and a prescription comprises a group of herbs specifically tailored to the syndrome'. In reading about Tu Youyou I turned, inevitably, to *Wikipedia*. She is described (albeit under the heading 'trivia') as 'the *Professor of Three None's* (no postgraduate degree, no study/research experience abroad, not a member of any Chinese national academies'. Artemisinin and its life saving properties are surely an unmatched reward.

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