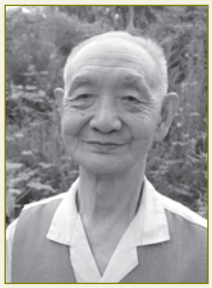
Ancient Chinese anti-fever cure becomes panacea for malaria



WHO/Cui Weiyuan

Professor Zhou Yiqing

The son of peasants, Professor Zhou Yiqing was born in 1929. He joined the Eighth Route Army (later part of the People's Liberation Army) at the age of 16. During the Sino-Japanese War and the War of Liberation (Chinese Civil War) he served as a nurse, head of a nursing squad, assistant physician and eventually doctor-in-charge. In 1960, he graduated from the Shanghai No. 2 Military Medical University and later became a researcher at the Institute of Microbiology and Epidemiology (IME) of the Chinese Academy of Military Medical Sciences (AMMS).

In April this year, Zhou Yiqing and his team won the 2009 European Inventors of the Year award (in the non-European countries category) for developing the first artemisinin-based combination therapy (ACT) for malaria, known as Coartem. He talks to reporter Cui Weiyuan about this achievement.

Q: Did malaria ever affect people in China?

A: Malaria was an epidemic disease in China for more than 3000 years. The symptoms were described in ancient writings. For example, Nei Jing (the Canon of Internal Medicine) described them as early as 270 BC. When the People's Republic of China was founded in 1949, malaria was endemic in two-thirds of Chinese counties, but it has not been a major public health problem since the 1980s.

Q: What was your first experience of malaria?

A: In the battle to cross the Yangtze River in 1949, I contracted the disease for the first time and suffered recurring bouts. No effective medicine was available. The pain left a sharp impression on me. I received an arsenic injection and, later, Atabrine (quinacrine) pills. The pills made me turn bright yellow. Although the side-effects were serious, I survived. Some female comrades suffered psychosis from drug toxicity after being treated.

Q: Is that what spurred you to do research to find antimalarial drugs?

A: While I worked as a battlefield doctor, one thing bothered me most: wounded soldiers begging me to save their lives because sometimes I just could not help them. I had only four years' primary school education. I vowed to improve myself. In 1960, I graduated from medical school and was assigned to become a researcher at the Chinese AMMS but was first sent to the Soviet Union for further study. Contracting malaria made me realize how bad the disease can be. However, my official participation in the research project stemmed from the Viet Nam War. When I returned from the Soviet Union in 1964, the war had broken out. I was ordered to conduct field research on tropical diseases in Viet Nam. China was supporting North Viet Nam and providing it with medical aid. Following orders, my comrades and I travelled along the Beibu (Tonkin) Gulf and through the Ho Chi Minh Trail in the jungle – it was the only way to maintain supplies for North Viet Nam because the United States of America had bombed it so intensely. We were accompanied by showers of bombs during the trip. There, I witnessed rampant malaria that reduced the combat strength by half, sometimes by up to 90% when the soldiers became ill. There was a saying, "We're not afraid of American imperialists, but we are afraid of malaria," although in fact the disease took a huge toll on both sides. Later, we submitted a report to China's Central Military Committee, stressing the importance of developing China's own antimalarials. Taking our advice, the central government set up a panel of more than 500 medical military and civilian experts to develop new antimalarial treatment for stricken soldiers. This was classified as a top secret state mission named Project 523, after the date, 23 May 1967, it was established.

Q: What made you and your team think of using artemisinin to treat malaria?

A: Project 523 included two groups engaged in antimalarial drug development: one to devise chemical medicines, another to examine traditional Chinese medicines. The latter group included researchers as well as traditional Chinese medicine doctors, who, as part of Chairman Mao's barefoot scheme, scoured the nation to collect folk remedies. By the time Project 523 had got under way, the Cultural Revolution had started and the research provided shelter for scientists facing political persecution. From 1970, the focus of the project shifted to traditional Chinese medicine because producing antimalarials became less of a priority after China produced chemical combination antimalarials and provided them to North Viet Nam. Experts screened a list of herbs and folk remedies, a few of which were found to have a curative effect against malaria. In the end, the *Artemisia annua* plant was chosen for further research. In the early 1970s, a Project 523 team first isolated artemisinin from the plant. Clinical trials confirmed its antimalarial effects. Between 1976 and 1978, the molecular structure of artemisinin was identified and more artemisinin derivatives were developed. In 1979, artemisinin-based antimalarial drugs were first used in the battlefield in the Sino-Vietnamese War (the Third Indo-China War). Chinese scientists in Project 523, unlike Western researchers looking to find new medicines, identified herbs with curative effects first, before targeting active ingredients, drawing on their knowledge of traditional Chinese medicine.

Q: What was artemisia annua *traditionally used for in China?*

A: As early as the second century BC, the Qinghao plant (sweet wormwood) had appeared as an anti-fever medicine in the *Fifty-two remedies*, a medical treatise. In 340 BC, the *Artemisia annua* plants were first described as having

antimalarial properties by Ge Hong, an alchemist and medical expert of the East Jin Dynasty. The folk remedies that Project 523 collected around the 1970s also registered these usages.

Q: Why did you research ACT for malaria at a time when there were no concerns about resistance to artemisinin?

A: There was a risk of resistance in theory, even though artemisinin could kill the blood parasite before quickly evacuating the body, allowing no time for drug resistance to build up. We also found that artemisinin, when used alone, cannot clear all the parasites. But combined with lumefantrin, the ACT eliminates any residual parasitic stragglers. Meanwhile, through screening *Plasmodium falciparum* models for AMMS and other research institutes, I learned the characteristics of different antimalarials and had the new synthetic antimalarials to hand. Consequently, I proposed a project to delay possible drug resistance to artemisinin and its variants. With permission from the National Chinese Steering Committee for Development of Qinghaosu (artemisinin) and its Derivatives, I started the research on ACT in 1981. For four years, I worked virtually on my own. The only assistant I had thought her job was to transform my mind revolutionarily, a leftover from the Cultural Revolution. From 1985, things improved. Professor Ning Dianxi and others joined me. They helped improve the fixed combination by replacing artemisinin with [one of its derivatives], artemether. But there was still a lack of research funds. I was lucky to have access to the new medicines, but it was a hard-earned luck. My colleagues and I had to try many combinations of ingredients before we found the most effective one. We found that the long-lasting effect of lumefantrine complemented the quick and potent effect of artemether, greatly improving curative effectiveness. It's like combining the short fist and long fist in Kung Fu. We also found that they reduce each other's toxicity. In 1985, we combined artemether and lumefantrine into a single tablet, creating the first ACT, which was registered as a new medicine in China in 1992, and later it became known as "Coartem".

Q: What role did the World Health Organization (WHO) play in the early development of ACT?

A: In the early 1980s it seemed that antimalarial research was over for good. Fortunately, essays published by Project 523 scientists caught the eye of WHO. In around 1979, TDR (Special Programme for Research and Training in Tropical Diseases) [sponsored by the United Nations Children's Fund, the United Nations Development Programme, the World Bank and WHO] expressed interest in cooperation on antimalarial research. But after Project 523 was disbanded in 1981, there was no one to negotiate the issue. In 1981, TDR held the first international conference in Beijing on artemisinin and its variants. The next year, thanks to WHO/TDR's efforts, the National Chinese Steering Committee for Development of Qinghaosu and its Derivatives was set up under the Ministry of Health to replace Project 523. The project was saved. Although the cooperation between the National Committee and WHO and TDR was suspended, they continued to provide support. My research was informed by WHO guidelines. Chinese scientists at the time had never seen those guidelines, which had become standard in the West. WHO also provided us with researcher exchange opportunities and training.

Q: Why did you introduce ACT outside China?

A: Today, our discovery, Coartem, has proven to be highly effective and well tolerated, with high cure rates of over 95%, even in areas of multi-drug resistance. But in an emerging economy like China, nobody has the money to support development of a medicine that has no domestic market and is mostly consumed by poor people outside China. Yet I knew it could cure patients and bring hope and health back to those having malaria. How could I watch such a good medicine die silently in the laboratory and do nothing about it? In 1988, even the National Committee was disbanded. Again, I feared a hiatus in research and discontinued state-level attention would mean that it would be lost forever. No Chinese pharmaceutical company was capable of introducing this medicine to the rest of the world. So I went to the Ministry of Science and Technology, which introduced me to China International Trust and Investment Corporation (CITIC), the only Chinese state enterprise at the time that was authorized to deal with foreign investors. With the State's approval and CITIC's help, we were introduced to Novartis. At first, we were wary about dealing with a Western team, but soon the mistrust melted away because of their professionalism and eagerness to cooperate.

Q: How did you and your team manage to patent Coartem?

A: China passed its first Patent Law in 1985. Due to the previous absence of a patent law, the molecular structure of artemisinin and its derivatives had been published in the late 1970s and early 1980s, and therefore patents for those formulas could no longer be registered. The ACT that later became known as Coartem was the only invention we had that was still patentable. In 1990, my team and I applied for the original patent in China. [Editor's note: the patent was only granted in 2002 under Chinese patent law that was revised in 1993.] The patent now belongs to my institute, IME, and the nation. In 1991, to help our team get patents around the world, Novartis established a partnership with the IME/AMMS and Kunming Pharmaceutical Corporation, through CITIC. Together, we co-developed Coartem. In 1994, Novartis received worldwide licensing rights for Coartem outside China and in 1998 also gained regulatory approval for the drug, which became China's first internationally patented pharmaceutical product. Coartem is now approved in more than 80 countries. [Editor's note: in China, it is not mandatory to patent a drug before it is licensed.]

Q. Looking back, you must be very proud of your achievement.

A: I am proud of what 'we' achieved with our partners. To date, Novartis has provided over 250 million Coartem treatments at cost to patients in the developing world, helping to save an estimated 630 000 lives. The credit goes to my country and the thousands of scientists, researchers and barefoot doctors – some of them died before they could see the great things Coartem could do – together with government officials and our partnership companies and organizations. Coartem would not have been possible without them. ■