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Chronicle

The Nobel Prize 2015 in physiology or medicine for highly effective antiparasitic drugs

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This year's Nobel Prize in Physiology and Medicine was awarded to Dr. William C. Campbell, Professor Satoshi Ŏmura and Professor Youyou Tu who have developed effective chemotherapy against common and very devastating parasitic diseases as malaria, river blindness and lymphatic filariasis. This note provides a few reflections on the discovery of two chemotherapeutics which has revolutionized the treatment of above mentioned, global parasitoses.

The Swedish Academy of Science presented on 5 October 2015 laureates of Nobel Prize 2015 in physiology or medicine: Dr William C. Campbell (Ireland, US) and Professor Satoshi Ŏmura (Japan) for the discovery of avermectin and Professor Youyou Tu (China) for the discovery of artemisinin [1]. Both drugs have appeared very powerful antiparasitics: avermectin and its derivatives lowered the incidence of river blindness and lymphatic filariasis and artemisinin reduced the mortality rates in malaria. The Nobel Assembly at Karolinska Institut has inderlied "The consequences in terms of improved human health and reduced suffering are immeasurable".

Artemisinin. The first description of Chinese plant Quing hao (means green herb, *Artemisia annua*) as a natural source of effective drugs for the treatment of intermittent fevers dates back to the year 168 B.C. [2]. In the framework of Chinese military program launched in 1967, one team headed by Youyou Tu explored the active components of many preparations commonly used in traditional medicine and recognized a preparation from *A. annua* leaves as the most efficient [3]. Further studies on chemical structure of antimalarial constituent of *A. annua*, named artemisinin, showed that it is a sesquiterpene lactone with endoperoxide brigde C-O-O-C, which is a relatively stable moiety. Protozoan *Plasmodium* sp. enters erythrocytes, degrades hemoglobin in parasite food vacuole and liberated Fe^{2+} activates artemisinin. Peroxide bridge is reduced yielding oxygen-centered radicals and after rearrangement – carbon-centered radicals that affect parasite. Recently numerous derivatives of artemisinin as dihydroartemisinin, artemether and artesunate have been developed. They represent better bioavailability and at present are widely used in combined antimalarial therapies (ACT) [4,5]. Because demand for artemisinin is great and *A. annua* planting surface is limited and fluctuates annually, a new semi-synthetic and high-level production strategy has been recently developed [5]. In recombinant yeast *Saccharomyces cerevisiae* a precursor of artemisinin, artemisinin acid, has been obtained and transformed chemically to final product, artemisinin.

Recent report of WHO/UNICEF from 17. September 2015 informs: "Despite tremendous progress, malaria remains an acute public health problem in many regions. In 2015 alone, there were an estimated 214 million new cases of malaria, and approximately 438 000 people died of this preventable and treatable disease. About 3.2 billion people – almost half of the world's population – are at risk of malaria" [7]. The most lethal form of malaria is caused by *Plasmodium falciparum*. Apart from human suffering and premature deaths, malaria is also a major obstacle to social-economic

progress in many developing countries, mainly in Sub-Saharan Africa. Currently artemisinin-based combination therapy is recommended for its effective treatment. Fast acting artemisinin-based compounds are combined with a drug from a different class for instance mefloquine. This chemotherapy revealed very successful and the global death cases from malaria during last 15 years has decreased by 50% [7].

Avermectin. Avermectin is a natural compound produced by *Streptomyces avermitilis* (renamed to *Streptomyces avermectinius*), soil bacterium isolated in 1974 by Satoshi Ŏmura. His research group succeeded in isolating and elucidating chemical structure of antihelmintic agent contained in *S. avermitilis* culture broth and named it avermectin [8]. Avermectin is glycosylated macrolide with spiroacetal and tetrahydrofuran moieties. Avermectin, more precisely avermectins are a family of four closely-related major components (A1a, A2a, B1a and B2a) and four minor components (A1b, A2b, B1b and B2b). The latter are lower homologues of the corresponding major components. The hydroxyl group at the C5 position and the disaccharide moiety are essential for the potency of all avermectins. Avermectin was evaluated for its antiparasitic activity by a scientific team at the MSD (Merck Sharp & Dohme) company headed by William C. Campbell [9]. The company developed the semi-synthetic derivative of avermectin B1, namely ivermectin (22,23-dihydroavermectin B1, trademarked as Mectizan), which turned out to be more potent antiparasitic than avermectin and highly effective against a variety of human and animal parasites, including those causing river blindness (*Oncocerca volvulus*) and lymphatic filariasis (*Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*) [5,9]. The target of the antihelmintic macrolides are glutamate-gated chloride channels, prevalent in nematode neurons and pharyngeal muscle cells. In consequence, permeability of the cell membrane to chloride ions increases resulting in hyperpolarization of the cell. Even at very low concentrations of the compounds the parasites are readily paralyzed and killed (slow death). Target ion channels are present in nematodes, insects and arachnids and partly in mammalian central nervous system. In mammals they prove, however, low affinity and are protected by the blood-brain barrier. Ivermectin is the drug of choice for the treatment onchocerciasis (river blindness), elephantiasis (lymphatic filariasis) and strongyloidiasis but its antiparasitic spectrum is wider, for instance against scabies.

Referring to the therapy of river blindness, an additional note should be done. Avermectins kill only the larvae but not adult forms of filariae. Thus, it is recommended to apply doxycycline (or other antibiotic) to weaken adult parasites. Doxycycline (antibacterial tetracycline) acts indirectly by killing *Wolbachia*, an intracellular bacterial symbiont of filariae [4].

This year's Nobel Prize, awarded to international scientific trio, has been commonly welcomed with the hope that the treatment of parasitic disease based on natural products may be a very promising way for solving major health problems, particularly of developing countries. Both antiparasitic drugs, artemisinin and avermectin, were discovered by improved understanding the indigenous knowledge of plants (artemisinin) and extensive screening of biological activity of environmental bacteria (as *Streptomyces* producing avermectin). Plant or bacterial products provide templates for the development of structurally simpler analogues that serves as effective antiparasitics. The achievements of this year's Nobel laureates indicate the importance of a good cooperation, not only between scientists from different disciplines but also science and industry. Besides, consequently performed global actions (public-health programmes) to eliminate parasitic diseases, supported by bilateral and multilateral funding, confirmed that eradication of deadly parasitic diseases is near [10,11].

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