

**PARASITES AND THE
NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE**

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Frank F. Katz, Ph.D.

The awarding of Nobel Prizes began in 1901. Through 2015, the Nobel Prize in Physiology or Medicine has been awarded to 210 persons. Of that number, eight have won that prize for work involving parasitic organisms.

Alfred Nobel's fortune began with his patent in 1867 on the manufacture of dynamite. In his will (27 November 1895), he directed that portions of his estate were to be used to endow "prizes to those who, during the preceding year, shall have conferred the greatest benefit to mankind."¹

RONALD ROSS

The first Nobel Prize in Physiology or Medicine was awarded in 1901 to Emil Adolf von Behring, a German physiologist, "for his work on serum therapy, especially its application against diphtheria."² The second Nobel Prize, and the first for work in parasitology, was awarded in 1902 to Ronald Ross, a physician in the Indian Medical Service, "for his work on malaria, by which he has shown how it enters the organism [that is the mosquito transmission to a vertebrate host] and thereby has laid the foundation for successful research on this disease and methods of combating it."³ The experiments that were the basis for this award were

published by Ross in 1898.⁴ It is noteworthy that of the remaining five laureates central to this report, the research of four was concerned directly or indirectly with malaria.

CHARLES LOUIS ALPHONSE LAVERAN

Charles Louis Alphonse Laveran received the Nobel Prize in 1907 "in recognition of his work on the role played by protozoa in causing diseases."⁵ As an army physician posted at the military hospital in Constantine, Algeria, Laveran worked to identify the cause of malaria. In 1880, he associated the pigment he found in organs and erythrocytes with the malarial parasite and fortuitously observed exflagellation, the formation of the parasite's male gametes. Exflagellation, which normally occurs inside the mosquito, led Laveran to conclude that malaria was caused by a protozoan.^{6,7} It should be kept in mind that Laveran observed the plasmodia in fresh blood. The fixation and staining of blood cells was introduced in 1891 by Russian physician Dmitri Leonidovich Romanowsky.⁸

JOHANNES ANDREAS GRIB FIBIGER

The 1926 Nobel Prize in Physiology or Medicine was awarded to Johannes Andreas Grib Fibiger for his 1913 discovery of the *Spiroptera carcinoma*.⁹ The causative agent is a parasitic nematode (round worm) now classified as

Gongylonema neoplasticum.¹⁰ As the species name indicates, the worm produces abnormal growths of tissue.

Or so it was thought. Further studies by others led to the conclusion that Fibiger's rats were fed a diet deficient in vitamin A, which is known to induce gastric tumors.¹¹ While Fibiger's conclusions were incorrect and he may not have deserved the Nobel Prize, he did pave the way for studies of various organisms and viruses for their possible and actual roles in cancerous conditions. The prize has since been awarded several times for discoveries in the field of tumor-inducing viruses.¹² It should be noted that William Campbell, a 2015 Nobel Laureate for his work in parasitology, gave a talk on Fibiger before the Medical History Society of New Jersey in 1996.¹³

JULIUS WAGNER-JAUREGG

The next Nobel Prize in Physiology or Medicine for research involving a parasite was awarded in 1927 to Austrian physician Julius Wagner-Jauregg. Wagner-Lauregg was a psychiatrist whose research was in the area of pyrotherapy, the induction of a fever in the treatment of a mental disorder.¹⁴ In 1917, he inoculated victims of neurosyphilis complicated by dementia paralytica (general paresis of the insane) with *Plasmodium vivax*, a malaria parasite. *Plasmodium vivax* typically induces malarial fevers in the tertian (every other day) pattern. The

treatment was successful.¹⁵ In 1927, Wagner-Jauregg was awarded the Nobel prize "for his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica."¹⁶

PAUL HERMANN MULLER

Paul Hermann Müller was a Swiss chemist employed by the J.R.Geigy company.¹⁷ He conducted research on tanning agents and pesticides, but he is best known for the synthesis of dichlorodiphenyltrichloroethane.¹⁸ This compound, commonly known as DDT, was granted a Swiss patent in 1940. DDT is an insecticide whose activity against arthropods of medical importance – such as mosquitoes that transmit parasites – proved to be of immeasurable value during World War II and in subsequent decades. Interestingly, DDT was first synthesized in 1873 by an Austrian student, but its usefulness was not known until Müller's rediscovery.¹⁹ For his "discovery of the high efficiency of DDT as a contact poison against several arthropods," Müller was awarded the 1948 Nobel Prize in Physiology or Medicine.²⁰

Parasites were not again involved in the Nobel Prize in Physiology or Medicine until 2015, when the prize was jointly awarded to Youyou Tu "for her discoveries concerning a novel therapy against malaria" and William C. Campbell

and Satoshi Omura "for their discoveries concerning a novel therapy against infections caused by roundworm parasites."²¹

YOUYOU TU

Born in 1930 in China, Youyou Tu (sometimes written as Tu Youyou) was affiliated with the China Academy of Traditional Chinese Medicine in Beijing at the time of the award.²² During the Cultural Revolution in China in the 1960s, malaria and its resistance to chloroquine became a major problem in North Vietnam, a Chinese ally, as well as in the region of China that borders on that country.²³

At the request of Zhou Enlai (first premier of the People's Republic of China), Mao Zedong (chairman of the Chinese Communist Party) sought assistance from the China Academy of Traditional Chinese Medicine. In the early 1970s, Tu, at the Institute of Chinese Materia Medica, proposed the use of artemisinin, a traditional Chinese medicine.^{24,25} Tu is the first Chinese Nobel laureate in physiology or medicine and the first citizen of the People's Republic of China to receive the Nobel Prize in natural sciences, as well as the first Chinese scientist to receive the Lasker-DeBakey Clinical Medical Research Award (2011).²⁶ Interestingly, Tu does not hold an earned doctoral degree, likely due to the restrictive educational structure of Maoist China during her professional

formative years.²⁷ As is typical of antimalarial drugs, the parasites later developed resistance to artemisinin and dihydroartemisinin. The search for new medications for this disease continues.

SATOSHI OMURA

Satoshi Omura was born in 1935 in Japan and holds two Ph.Ds: the first, in pharmaceutical sciences, was awarded in 1968 by the University of Tokyo and the second, in chemistry, was awarded in 1970 by the Tokyo University of Science.²⁸ His expertise is in bioorganic chemistry and the derivation of pharmaceuticals from microorganisms. Omura is currently Distinguished Emeritus Professor and Special Coordinator of the Research Project for Drug Discovery from Natural Products in the Kitasato Institute for Life Sciences, Kitasato University.²⁹ He is credited with the discovery of the bacterium, *Streptomyces avermectinius*, which was isolated from a soil sample found at a golf course.³⁰

In 1975, as a result of the research partnership that began in 1973 between the Kitasato Institute and the American pharmaceutical giant, Merck, Sharpe & Dohme, materials were sent to the Merck Institute for Therapeutic Research to be screened for possible therapeutic efficacy.³¹ One sample of soil contained *Streptomyces avermectinius*, from which an antiparasitic agent, called avermectin, was extracted.³²

(Readers will do well to read Campbell's history of avermectin and ivermectin, as well as some aspects of the history of other antiparasitic drug research at Merck.³³ It helps one understand how three years after its publication, the Nobel Committee named him, together with two fellow parasitologists, a Nobel Laureate.)

WILLIAM C. CAMPBELL

William C. Campbell was born on 28 June 1930 in Derry (officially Londonderry) in Northern Ireland. He grew up in the town of Ramelton which is in the County of Donegal.³⁴ His undergraduate education was in Ireland at Trinity College in Dublin. One of his professors there was James Desmond Smyth who, as Bill stated, "changed my life by developing my interest in this particular field – parasitic worms."³⁵ After graduating from Trinity in 1952 with first class honors in zoology he went to the University of Wisconsin–Madison on a Fulbright Scholarship.³⁶ He earned his Ph.D. in 1957 for his work on the large American liver fluke, a parasite of sheep.³⁷ It appears that Campbell's first scientific publication appeared in 1955 and was based on research for his dissertation.³⁸ He began his employment at Merck in 1957.³⁹

At Merck, the macrocyclic lactone with potential pharmacological activity that was isolated from *Streptomyces avermitilis* was modified to reduce its toxicity

and given the generic name ivermectin. Later, for its use in humans, it was given the trade name Mectizan.⁴⁰ Ivermectin was first marketed in 1981 as a broad spectrum veterinary drug; by 1986 it was being used worldwide as a highly effective agent against parasites of cattle, sheep, pigs and horses.⁴¹

One parasite of horses is *Onchocerca cervicalis*, a filarial nematode that has been associated with periodic ophthalmia or recurrent uveitis (river blindness) due to microfilariae circulating in the blood.⁴² In the United States, where *O. cervicalis* is common, it is not considered to be of clinical importance. However, this helminth proved to be useful for a trial treatment with ivermectin in 1978. Campbell wrote that the results of the experiment

. . . yielded clear evidence of the efficacy of ivermectin against the microfilariae of *Onchocerca cervicalis* in horses. The formal report of the trial, submitted to me as Director of Basic Parasitology, attached no special significance to that finding, presumably because *O. cervicalis*, unlike the intestinal worms in those horses, was not of clinical or commercial importance. Nevertheless the implication for possible use against *O. volvulus* and river blindness [onchocerciasis] seemed to me to demand further experimentation.⁴³

Campbell now arranged for a trial of ivermectin against *Onchocerca gutturosa* in cattle in Australia.⁴⁴ In November 1978 he was informed that the drug was effective against this parasite at all the dosages used.⁴⁵

The following month, Campbell informed Jerome Birnbaum, Executive

Director of Basic Animal Science Research at Merck, that the observed efficacy against *Onchocerca microfilariae* was “a very exciting development” because of the role played by the microfilarial stage of the parasite in the pathogenesis of human onchocerciasis. The data suggested “that ivermectin could be of great value in preventing dermatological lesions and blindness in [human] populations at risk.”⁴⁶

Campbell went on to recommend “that discussions be held with representatives of the World Health Organization to determine the best approach to the problem — from the medical, political and commercial points of view.”⁴⁷

Campbell received the support of the Merck administrators as well as colleagues outside of Merck necessary to move his ideas forward. After a trial of ivermectin in humans against hookworm—it had already been found effective against dog hookworm—studies on onchocerciasis in humans began in Dakar, Senegal, under the direction of Michel Larivière, professor in the parasitological faculties of the University of Paris and the University of Dakar.⁴⁸ The first trial with human volunteers was in 1981–82 and it was found that 50 mcg/kg of avermectin resulted in “either complete elimination or near elimination of detectable mf-load.

[microfilaria-load]”⁴⁹ Studies of these patients 7-8 months later showed they had low levels of microfilaraemia, which suggested, but did not prove, that treatment had been responsible for a lasting effect, and raised the further possibility that

periodic treatment could disrupt transmission. From then on, numerous trials, varied in scope and intent, were carried out to assess the role that ivermectin might play in onchocerciasis and other parasitic diseases of humans.⁵⁰

A number of persons and organizations were involved in the ivermectin and onchocerciasis story. Of particular note are the late Dr. Mohammed Aziz, a Merck researcher and major figure in the clinical development of ivermectin/Mectizan for onchocerciasis, and the World Health Organization for its cooperation and participation in various studies of this medication.⁵¹ Their efforts and, without question, Merck's "Mectizan Donation Program," which began in 1987 and will be continued "for as long as needed," has produced remarkable results: "Several countries in Africa are making significant progress towards eliminating ... [river blindness and lymphatic filariasis]. In Latin America, three countries – Colombia, Ecuador and Mexico – have already received WHO verification of river blindness elimination."⁵⁴

All of this would not have happened without William C. Campbell's extensive knowledge of parasitology, vision for the use of ivermectin in filarial diseases, and compassion for victims of parasitic diseases. The Nobel Committee chose wisely.

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THIS PAPER AND THE AUTHOR

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