

## Our Nobel Laureate, Dr. William C. Campbell

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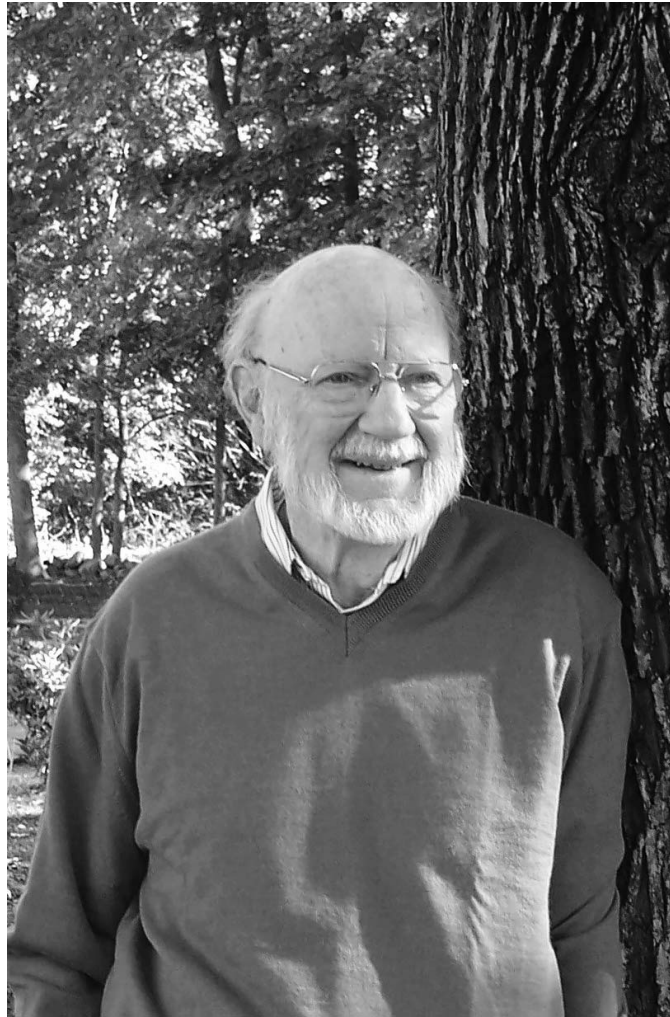
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## OUR NOBEL LAUREATE, DR. WILLIAM C. CAMPBELL

On 5 October 2015, the Nobel Prize winners for Medicine were announced in Stockholm. Half of the prize was shared by Dr. Tu Youyou, a Chinese medical scientist-pharmacologist, who searched the ancient literature of China in an effort to find a possible herbal medicine for the treatment of malaria. She was successful when she rediscovered *Artemisia annua* (sweet wormwood), a plant that produces the drug artemisinin. It was used more than 2,000 years ago for the treatment of malaria and is again widely employed in the treatment of malaria, especially in southeastern Asia. The other half of the Prize was shared by Satoshi Omura, a microbiologist at the Kitasato Institute in Tokyo, Japan, and Dr. William (Bill) C. Campbell, a parasitologist at Merck Pharmaceuticals in Rahway, New Jersey. The Kitasato Institute was contracted to isolate “unusual” soil samples throughout Japan and ship them to Merck, where they were examined for anti-parasitic potency. This begins

the story regarding the isolation of ivermectin. However, before referring to the drug's discovery, I wanted to provide a brief biographic sketch of Bill Campbell.

A couple of days after learning that Bill would be sharing the Nobel Prize for Medicine, I spoke with him by phone at his home. I had made no effort to call earlier because I knew “well wishers” wanting to congratulate him would choke his telephone line. I was correct. His lovely wife, Mary, answered my call and confirmed my guess by announcing Bill was hoarse from talking. During our conversation, he said something that caught my attention, i.e., “The American Society of Parasitologists is my Society,” which is one of the reasons I volunteered to write a brief biography for our *Journal of Parasitology*. I am quite proud to say he is one of us, and has been for 63 years.

It has been a long time since a parasitologist received such recognition. Sir Ronald Ross won the Nobel Prize in 1902 for his work in identifying mosquitoes as vectors for *Plasmodium*

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*relictum*. Parasitology has made giant leaps in our understanding of host–parasite relationships since the work of Ross in India during the late 19th century. One of these steps was the work that Bill Campbell and his colleagues accomplished at Merck some 40 years ago, and this is the story of their success. I am grateful to Bill for providing a copy of his CV to help with some details of his early career. I also had the good fortune of interviewing him at the 2004 meeting of the American Society of Parasitologists in Philadelphia for a book I was writing at the time. That too was a great experience for me because I learned something about the details of his research at Merck.

Bill is a U.S. citizen (naturalized in 1962) with Irish roots, having been born Londonderry, County Derry, Ireland, in 1930. As a youngster, he attended boarding school situated in a luxury hotel on the coast of the Irish Sea near Belfast, Northern Ireland. When WWII broke out, the school children were moved there, since, as part of the United Kingdom, the city of Belfast was sure to be targeted for bombing.

In a brief essay recounting his “wartime boyhood,” he described traveling from the coastal school to his home in Londonderry. Along the way he would pass by RAF airfields rife with Spitfires and Hurricanes lined up on tarmacs and ready to fly. During these trips, Bill often fantasized himself as a pilot in an RAF uniform, replete with ribbons won in air battles against the enemy. Eventually, the war came to an end and he wrote, “I knew enough to understand that peace, when it came, was a blessing beyond all imagining.”

The next step in his life came when he enrolled in Trinity College, Dublin. While at the boarding school, his headmaster had urged him to pursue a career in medicine, but his biology teacher thought he should study natural science, specifically biology, and that was the direction he took. Very early at Trinity, he encountered J. Desmond Smyth, one of the great parasitologists of the era, and Bill was soon to view him as his “hero.” Several years later, I spent a sabbatical in London for 9 months learning how to do *in vitro* culture of taeniid cestodes from Professor Smyth and, like Bill, developed the same kind of fondness that he had for this kind and gentle person.

When Bill started at Trinity, there were 48 biology students in his in-coming class. However, the attrition rate was high, leaving just 14 to enter the honors program in their fourth year. In the English system, each honors student picks a topic and conducts research independently, using faculty members as tutors. At Trinity, the faculty member would typically have a maximum of 2 honors students. Bill learned that 2 other boys had already picked Smyth for their tutor, and he was certain he would be left out of working in Desmond’s lab. However, when Bill returned to begin work in the fall of his fourth year, he quickly learned that Desmond had also included him as a third honors student. He proudly said during our Philadelphia interview, “Yes, he picked me.” Bill felt that, presumably, Smyth sensed what he wanted to do, and he declared to me that it changed his life! I would add that his being selected by Smyth was to change a lot more lives later.

In the spring of his honors year, he and the other 2 boys were called together by Smyth and read a letter from Arlie Todd, a professor of parasitology at the University of Wisconsin School of Veterinary Medicine in the United States. Although Todd and Desmond had never met, Arlie was looking for potential graduate students who might like to come to the veterinary school at Wisconsin to pursue their Ph.D.s. All 3 accepted the invitation,

but the other 2 soon dropped out, leaving Bill as the only student from Trinity to head for Wisconsin.

Arranging for his trip, however, was to become somewhat of a chore. When Bill applied for his visa to enter the United States, he was told at the consulate office the amount of money (the grand sum of \$1,280) he would earn as a teaching assistant was not enough to support him. Todd helped “save the day” by writing a letter assuring the consulate this amount was adequate. While waiting in line for his visa, he heard the consulate agent mutter, “Well, it wouldn’t be enough in New Hampshire where I came from.” Bill thought to himself, “I don’t even know where New Hampshire is!” The next issue was paying for the trip to the United States, for which he did not have enough money. This was resolved with a Fulbright travel scholarship, the first ever given to a Trinity student. Finally, he discovered that the most money he could bring into the United States was \$15. Bill was rescued again when his father received a letter from a man named Cavanaugh who was born in County Donegal, left Ireland, traveled to the United States, and became a successful lawyer in Chicago, Illinois. With his father acting as a conduit, Cavanaugh loaned Bill \$200 to cover his travel expenses from New York City to Madison, Wisconsin. When I interviewed Bill in 2004, he was still puzzled about this situation because he could never learn how Cavanaugh knew of his trouble. Finally, before leaving Ireland, one of his student friends sent a letter to Bill saying, “For God’s sake, don’t panic when you get off the boat in New York City!”

When Bill matriculated at the University of Wisconsin, he was faced with yet another shock—he was obliged to take more academic courses. In the European system of graduate education, Ph.D. students are not required to take additional coursework, but not so in the United States. In addition, although he found a place to rent, he quickly discovered that he did not have enough cash to sustain him at first. So, Arlie Todd generously wrote a check to see him through for a brief period of time. Bill quickly paid off his debt and settled down to complete what he came to do, obtain his Ph.D.

Toward the end of his time at the University of Wisconsin, he became concerned about what would come next, a job he hoped. He had decided to stay in the United States rather than return to Ireland, and, like many of us who have been in a similar situation, he began actively searching for a teaching position. At about the same time, Arlie Todd received a letter from Ashton Cuckler at Merck, asking if he had any Ph.D. students who were just finishing their degree work. Bill told me that at first he was not very captivated by the idea of an industrial job. However, Arlie, who was very pro-industry, said to him, “Why don’t you just go back and talk to them about it. What do you have to lose?” So, at Merck’s expense, he headed for Rahway, New Jersey. His interview at Merck went well. He was very impressed with Ashton Cuckler and the research responsibilities offered. When Bill returned to Madison, there was a letter waiting from Cuckler, with a job offer and the promise of a salary starting at \$9,080. Although Bill was still anti-industry, he decided to accept their job offer, feeling that he could always leave if a better opportunity became available.

During our 2004 conversation in Philadelphia, Bill discussed some of his philosophy in dealing with infectious disease. He explained that while he dealt with chemotherapy as a way of preventing or treating the disease agents, immunization was still the best way of dealing with a disease problem in an animal. He

said, “Antibodies are to some extent magic bullets, which seek out their own target without harming the organism. Consequently, in all circumstances where it is feasible, the immunization method is preferable to any other procedure.” However, as he then noted, when immunotherapy cannot be used or if it is shown to be impractical, as is the case with a great many of the tropical diseases, chemotherapy must be employed.

The research environment at Merck he described as absolutely superb. He never felt pressure and was treated like an “old hand,” not at the bottom of the research ladder. He especially enjoyed Fridays when all of the research folks would gather in Cuckler’s office for a group luncheon and discuss new advances in chemotherapy, their research, etc. When he began at Merck, his research was focused on schistosomiasis. He said, “I worked on schisto for seven years and . . . had an absolutely unblemished record of failure.”

At this point, the focus of his research shifted. Bill was to write, “We began looking for something that was not just incrementally better than an existing molecule. We were looking for something that was radically different, with properties against parasites, and we found what we were looking for . . . something radically different” (Campbell, 1992). Not only were Bill and his group looking for something unusual, they were willing to pursue it in different ways as well. For example, they devised a novel system for assaying the effectiveness of potential drugs. Based on the efforts of John Egerton, a colleague of Bill at Merck, they developed what they called a “tandem assay.” In this procedure, a protozoan parasite, *Eimeria muris*, and a helminth, *Nematospiroides dubius*, were simultaneously used to infect a mouse, which was then treated with the potential new drug. After infecting the animal and then subjecting it to treatment with the drug, the mouse would be killed and necropsied. If either the protozoan or the helminth were not present, then a more careful follow-up treatment would be employed.

Another procedure used was microbial fermentation. The latter process, as Bill put it, “was the mainstay in bacteriology where the emphasis was on in vitro systems.” He continued, “With helminths, we have bioassays . . . but it’s very difficult to use with fermentation products.” They ended up employing crude fermentation broths with which to “contaminate” mouse food. The fermentation broth procedure, he explained, “was not a very sophisticated approach, and no one was using it at the time, but it worked for us.”

Then, in 1973, Merck entered into an arrangement with the Kitasato Institute in Tokyo to supply soil microorganisms isolated in Japan. At the beginning of the agreement, the Japanese microbiologists already had several thousand isolates in hand. It was Bill’s understanding that the institute did not send these isolates to Merck for anti-parasite testing; they were to simply supply “unusual” isolates.

In March 1974, Merck received a batch of 54 soil isolates from the Kitasato Institute. Interestingly, one of the isolates came from near a Japanese golf course; it has not been found anywhere else in the world, and was to quickly become “the winner” in their research. About a year later, the isolates were finally inoculated into broth cultures, where they fermented for 3 days. The fermentation products were mixed with mouse food and fed to “tandem assay” mice for 6 days, at which time the mice were killed and necropsied. Among the 54 mice fed with mouse food impregnated with an isolate, 1 mouse had no worms, but as Bill

said, “The mouse was not in good shape and nearly died.” He continued, “At the time, we all thought, this isn’t very exciting. We have a sick mouse on our hands, so what!” Moreover, the mouse had consumed only about half of its food, and had lost weight. Nonetheless, there were no worms present.

They confirmed that the broth had anthelmintic properties in a subsequent experiment using additional “tandem assay” mice. Moreover, they demonstrated its efficacy over an 8-fold range of dosages. The new bacterium was designated as *Streptomyces avermitilis*, i.e., “the streptomycete that helps kill worms to create an averminous condition” (the streptomycete that kills worms) (Campbell, 1992). Chemists at Merck showed that the molecule was associated with a component inside the mycelium, not something released from the bacterium. Using a wide range of sophisticated instrumentation, they identified the drug as “a glycosidic derivative of pentacyclic sixteen-membered lactones.” However, even though it was a successful accomplishment, the Merck chemists went ahead and developed an even more effective drug, 22, 23-dihydroavermectin B<sub>1</sub>, which worked against all the nematodes they tested, plus it was successful whether given orally or injected subcutaneously.

Bill described it as, “the most potent anthelmintic known; it acted orally or parenterally; it had an unusually broad spectrum of activity; it apparently had a wide therapeutic index; and it probably had a novel mode of action” (Campbell, 1992). As he explained to me, one of the most unusual characteristics of the drug was its ineffectiveness against adult *Dirofilaria immitis*. However, it was lethal for preadult larvae and microfilariae of the dog heartworm. Its inability to kill adult heartworms meant the possibility of producing an embolism in the lungs was nil. Bill remarked in our Philadelphia interview that, “If you wrote a script for something like this, of course you would say it couldn’t happen in real life.”

During the drug’s early development, Bill believed there was the potential for ivermectin (Mectizan) to be used in the treatment of *Onchocerca volvulus*, the cause of “river blindness,” and the leading cause of blindness in the world. At this point, he was encouraged to proceed with additional preliminary research by Roy Vagelos, Head of Merck Research Laboratories. Bill’s success in the lab was duplicated by positive results in field trials of the drug by Mohammed Aziz at the University of Dakar in Senegal during 1981. In 1987, Merck led in the establishment of a donation program for Mectizan and the treatment of onchocerciasis in Yemen, plus a number of sub-Saharan and Latin American countries where the vector-borne parasite was endemic. The goal of the program initially was to control *O. volvulus* using Mectizan. Since 1987, approximately 1.4 billion doses of the drug have been provided to literally millions of people via the Carter Center in Atlanta, Georgia, plus several other agencies. The present goal is to eliminate both the parasite and the disease. To date, 3 countries in the Western Hemisphere have been designated free of the parasite, i.e., Ecuador, Columbia, and Mexico (official elimination in the latter country was announced while this paper was being written).

As noted earlier, Sir Ronald Ross was the first parasitologist to achieve international recognition in winning the Nobel Prize for Medicine. As members of the American Society of Parasitologists, we are proud to acknowledge that 2 more parasitologists, Drs. Tu Youyou in China and Bill Campbell in the U.S., along with Dr. Satoshi Omura, a Japanese microbiologist, have also won the

Nobel Prize. As members of the American Society of Parasitologists, we are especially pleased that Bill is one of us.

While I was thinking of a good way to close this biographic sketch, I encountered a quotation that fully describes (for me, at least) the mindset of researchers like Tu, Campbell, and Omura, i.e., “We do not live to extenuate the miseries of the past or to accept as incurable those of the present” (Osborn, 1948).

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