Ivermectin: A Reflection on Simplicity

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THE BEGINNING

I am using the word "simplicity" here in the context of science, but I do not mean to suggest that science is simple; nor will I suggest that the development of the drug ivermectin was an exercise in simplicity. I want rather to call attention to the element of simplicity within science—and I want to do that by pointing out the prominence of simplicity in the genesis of the drug ivermectin. It has long been acknowledged that simplicity has an intrinsic appeal to scientists (as to others), and indeed simplicity is widely celebrated in science as a matter of beauty. But I want to speak of it, not as a matter of beauty, but as a matter of practical utility.

Consider an actual real-life event. On a particular day, the ninth of May 1975, there was a mouse in a mouse-box in a laboratory. It had been purposely infected with worms—but not enough to cause illness. On that day its diet was altered—some liquid was stirred into its regular food. And the mouse ate that food for almost a week. Then its normal diet was restored. And about a week after that—its worms had gone! From that moment a train of events was set in motion. It would lead, some years later, to an advance in medical and veterinary science; and *that*, in turn, would lead to practical changes in the management of parasitic disease. To a very large extent the drug ivermectin was brought about by simple science. It was not conventional science; it was not obvious science; but it was simple science.

There is a question that warrants a slight digression here. In the past few weeks I have often been asked how I felt when I heard that I had won the Nobel

Prize. I can say without hesitation that my mind was instantly flooded by two emotions. One was a sense of joy and gratitude. The other was a feeling of sadness—sadness that so many of the people who made this discovery a success could not be named individually. But I represent the research team at Merck & Co., Inc., and in that role I feel honored and grateful beyond imagining.

The mouse I mentioned a moment ago was a single mouse. I do not mean that the mouse was unmarried. I mean that the special diet that proved to be so very special was tested, not in a conventional experimental group of mice, but rather in just one mouse. The diet was special because it had been supplemented with a liquid in which a bacterium had been allowed to flourish. Other solitary mice got other diets supplemented with other liquids in which other bacteria had flourished. But the bacterium that cured the mouse of its worm infection was the only one that did so. This method of testing "fermentation broths" for anti-worm (anthelmintic) efficacy had been developed by Dr. John Egerton and his technical staff in the Merck Laboratories, where also the reduction of experimental group-size to a singleton had been pioneered by Dr. Dan Ostlind [1, 2].

The liquid that had been added to the diet of that mouse had been fermented by a bacterium that was one of hundreds of microbes that had been sent to Merck & Co. Inc. by Satoshi Ōmura and his team of chemists and microbiologists at the Kitasato Institute in Tokyo. I had the pleasure of visiting Dr. Ōmura in Tokyo many years later; and he shares with me the prize that has brought us here today.

Microbes do not all act alike, or look alike. Both the Kitasato Institute and Merck & Co., Inc. were interested in microbes that stand out from the crowd, and they collaborated in trying to find them. Microbiologists grow weary of finding microbes that have already been found. Professor Ōmura sent us microbes that were unfamiliar to microbiologists. In our new mouse assay, as described above, we found that one of those unfamiliar microbes produced an unfamiliar substance—and that the substance had antiparasitic activity. Furthermore, the antiparasitic activity was of unmatched potency.

Simplicity, in the history of ivermectin, was just a beginning. From then on, there was *complexity*—years of complex basic research and years of complex developmental research. Pharmaceutical development is the epitome, not of simplicity, but of complexity.

The antiparasitic effect seen in the test mouse was an anthelmintic (against parasitic worms) effect. It was quickly confirmed in additional tests, and its potency was so striking that intense interest was aroused. Soon many things were going on at once. The microbiologists described the bacterium as a new species of *Streptomyces* [3]. Fermentation chemists and biologists isolated the mystery substance that killed worms; and they persuaded the bacterium to make it much

more abundantly [4]. Analytical chemists removed the main mystery when they used highly sophisticated technology to show that the substance consisted of a complex of eight closely related molecules [5]. It was seen to have structural similarities to the milbemycin pesticides. We named it avermectin. The synthetic chemists made hundreds (eventually thousands) of related compounds, while the parasitologists provided efficacy data and preliminary toxicity data to guide the derivatization program [6, 7]. One of the derivatives (Figure 1) had an efficacy-and-safety profile that was judged to be superior to that of avermectin. The improved structure was made by hydrogenation of the chemical bond of avermectin at the Carbon 22–23 position. It seemed logical that the hydrogenated avermectin should be named "hyvermectin." It was soon learned that in some language "hyver" means "testicle," and so "hyvermectin" became "ivermectin."

Despite being unique in its origin, ivermectin now has many relatives—including doramectin (from a mutant strain of *Streptomyces avermitilis*; selamycin, a derivative of doramectin; nemadectin (from *Streptomyces cyanogriseus*); moxidection a derative of nemadectin; milbemycin oxime (from the macrocyclic lactone milbemycin); eprinomycin (ivermectin derivative with favorable pharmacological distribution in dairy animals).

Meanwhile, the research continued. The parasitologists found out which worms it would kill; [8, 9] the biochemists found how it would kill them—or rather how it would paralyze them [10]. In the case of parasitic worms, paralyzing them is just as good, or from the worm's point of view just as bad, as killing

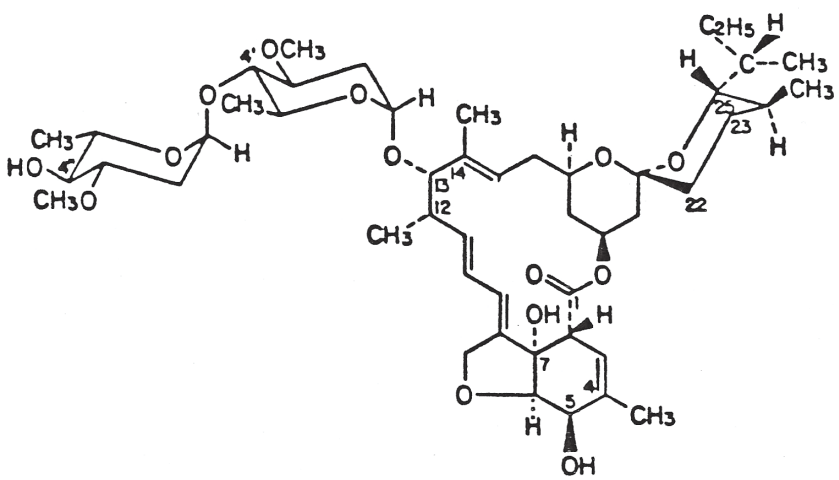

FIGURE 1. The chemical structure of ivermectin (22,23-dihydroavermectin B1a). Its precursor avermectin B1a differs in that the bond at Carbon 22-23 (in the spiroketal group, shown at upper right) has not been hydrogenated.

them. The body will get rid of paralyzed worms. It was discovered that some ectoparasitic arthropods (including lice and mites) were susceptible to ivermectin, as were endoparasitic insect larvae. The family of macrocyclic lactone antiparasitic agents would become known as "endecticides."

THE MIDDLE

The flood of incoming news was exciting. But those of us who work with new drugs learn to allow ourselves only a subdued form of excitement—for we know that the whole project is likely to collapse with the arrival of tomorrow's bad news. Eventually the project was so promising that it was given 'developmental' status, and even more scientific disciplines were brought into the project. That meant more scientists. In an earlier paper I named 125 Merck scientists and technicians who were listed as authors on some 70 papers published within 10 years of the original discovery [1]. To mention just one discipline: veterinarians with parasitological expertise were recruited. They were graduates of veterinary colleges all over the world, and the breadth and depth of their knowledge was truly astonishing. Under their leadership ivermectin was evaluated against many parasite species in many domestic animal species in many lands. Their expertise was undoubtedly an essential element in the success of ivermectin. The new drug would go on to become the predominant agent in controlling the parasitic diseases that plague the animals on which humans depend for food and fiber—and companionship. Despite the complexity, all the pieces came together to result in the launching of ivermectin as an animal health product in 1981.

Things that are usually bad sometimes turn out to be good. If a broad-spectrum antiparasitic drug turns out to be ineffective against an important parasite, the drug is usually doomed to oblivion. But not always! In dog heartworm disease, caused by the filarial nematode *Dirofilaria immitis*, the adult worm is the most pathogenic stage. Ivermectin is not effective against it—but that is good! Because of their location in the left ventricle and pulmonary artery, injuring and dislodging the worms may result in pulmonary aneurysm. Thus, in the routine de-worming of dogs, killing the adult heartworm can be hazardous to the dog—and to the reputation of the attending veterinarian. Ivermectin, in other words, is ineffective exactly where one would like it to be ineffective.

Nevertheless, ivermectin is commonly used in the prevention of heartworm disease in dogs. Shortly before the discovery of ivermectin, I had instituted a program at Merck to find an agent for the control of heartworm disease. There had been, at the time, few laboratory projects devoted to filarial worms, mainly because of a lack of convenient laboratory models. To establish the life cycle of *D.*

immitis in the laboratory, Lyndia Blair and I proceeded to cultivate large numbers of the mosquito that is the required intermediate host (vector) of the parasite. Initially there was no alternative to using dogs as the definitive host; but then we found that the ferret (*Mustela putorius furo*) is a highly susceptible host for *D. immitis* [11]. It is a suitable host for studying the immature (pre-cardiac) stages of the worm, but the small ferret heart does not readily allow the development of the adult form. Later, in collaboration with Dr. John McCall, we showed that the ferret was also a suitable laboratory host for another filarial parasite, the one that causes lymphatic filariasis (including 'elephantiasis') [12]. Thus, when ivermectin came along, we were immediately able to do the research that led to the first once-a-month treatment for prevention of heartworm in dogs [13]. The product quickly became extremely popular.

The potential value of ivermectin in human medicine was not overlooked. I had always insisted that our written departmental objectives would include the development of new drugs for control of parasites in humans. In the 1960s Nelson in the United Kingdom reported the migration and visualization of onchocercal larvae in the ears of experimentally infected mice, and I had considered the observation as a basis for possible chemotherapeutic assay. When my colleagues found that ivermectin was active against the larvae of *Onchocerca cervicalis* in the skin of horses [14], I knew it was time to take action. My chief, Dr. Jerry Birnbaum, enthusiastically approved my suggestion that Dr. Bruce Copeman in Australia be invited to undertake (with Merck financial support) a trial of ivermectin against a related parasite, *Onchocera gutturosa* in cattle. A trial was arranged through the courtesy of Dr. Ian Hotson, head of Merck animal-health research in Australia, and the ivermectin treatment proved to be effective.

The results of our trials against various parasites in various animals suggested that ivermectin might be effective against several parasitic infections in humans. Being aware of the therapeutic needs in human parasitology, I had no doubt that the greatest potential for filling an unmet need was in River Blindness, which is caused by yet another species of Onchocerca—*Onchocerca volvulus*. The clinical exploration of possible ivermectin usage in humans could not be undertaken lightly; but nor could the prospect of an exceptional clinical benefit be dismissed lightly. Birnbaum and I took that message to the highest levels of Merck research management.

It was an exciting moment for both of us. The head of Merck research at the time was Dr. Roy Vagelos—and he and his top advisers approved a trial of ivermectin in humans. It would be a very cautious test of the efficacy of ivermectin in patients with the beginning stages of River Blindness—before any eye damage had occurred.

In February 1981, the first trials were conducted in Senegal by Dr. Mohammed Aziz of Merck, Dr. Samba Diallo of the University of Dakar, Dr. Michel Larivière of the University of Paris and their colleagues. The initial trials showed that ivermectin was effective against the microscopic worm larvae in the skin of River Blindness patients [15]. That proved to be a landmark in the development of ivermectin for use in humans.

To understand why this was so important, it is necessary to understand that, in River Blindness, unlike the situation in dog heartworm disease, the adult worm is not the primary pathogen. It is the offspring, the microscopic baby worms, that cause the damage to the skin and the eyes. If they can safely be killed, the onset of clinical disease will be blocked. And that is what ivermectin does—as was soon confirmed by many investigators [16].

Onchocerciasis was known to be broadly endemic in francophone Africa. For that reason, results of the clinical trials were compiled and presented, under the leadership of Dr. Philippe Gaxotte of Merck, to the French regulatory

FIGURE 2. The author (right) talks to Dr. Mohammed Aziz (center) and Dr. Kenneth Brown (left) at the 1987 press conference in Washington DC, during which Dr. Roy Vagelos announced that Merck & Co., Inc. would donate ivermectin for the prevention of River Blindness.

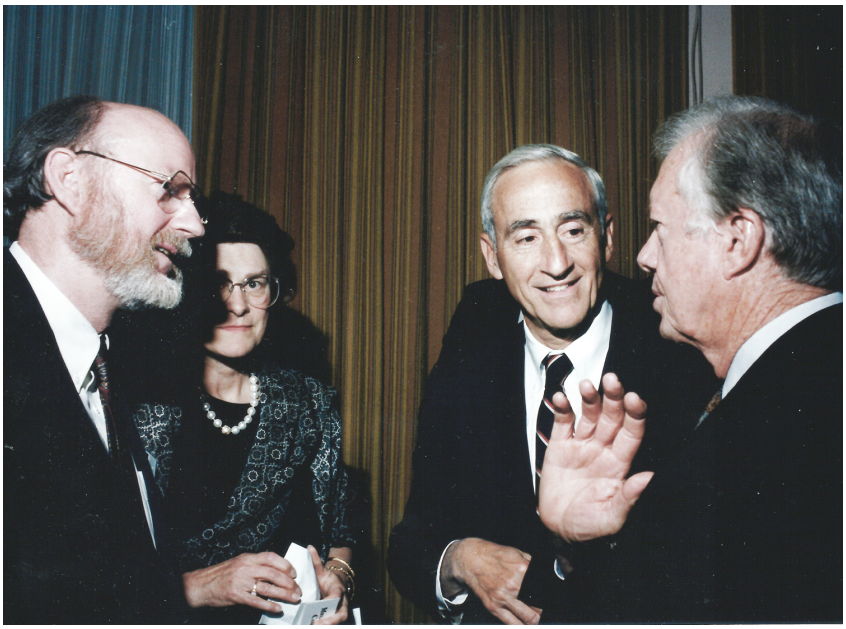

FIGURE 3. Former President Jimmy Carter, head of the Carter Center, discusses River Blindness control with Dr. P. Roy Vagelos, former CEO of Merck & Co., Inc, and the author and his wife. At the United Nations, New York, September 23, 1992.

authorities. Approval of ivermectin for human use was granted in October 1987. The response of Merck leadership came in less than a month.

In 1987 Vagelos, then Merck CEO, announced that Merck & Co. would donate the drug for use against River Blindness (Figure 2). Mohammed Aziz attended that event, but died later in the year. He was succeeded by Dr. Kenneth Brown as director of Merck's development of ivermectin for human use. The extraordinary donation decision has been widely applauded as a historic moment in disease control. It needs no further comment here. The decision led to an unprecedented effort to translate donation of the medicine into distribution of the medicine. The program was undertaken by many groups. I will mention only the World Bank, Merck's Mectizan Donation Program; the World Health Organization; and the Carter Center, but many other agencies participated (Figure 3,4). Over the subsequent 30 years, some 2 billion treatments were distributed. The result was an expanding control of River Blindness, and eventually its certified elimination in several countries [17]. The leaders of that huge program were also numerous—but I will mention one of them here—because he is Swedish! He is Dr. Björn Thylefors [18], and I am honored that he is taking part in some of this week's activities. More recently ivermectin has found a place

FIGURE 4. Dr. Daniel G. Sissler presenting Helen Keller International Award to Merck & Co., Inc. (accepted by the author for Merck & Co., Inc.). At the United Nations, New York, September 14, 1998.

FIGURE 5. One of the remote villages in northern Togo visited by the author. River Blindness was endemic and some of the early community-based trials were being carried out.

in the clinical treatment of several other human diseases, including scabies, and has come to play an important role in the campaign to control lymphatic filariasis (using albendazole in combination with ivermectin or diethylcarbamazine).

THE END

The end of ivermectin is nowhere in sight. This disquisition, however, will end with a glance at the past and a thought for the future.

The accompanying photographs (Figures 5, 6, 7) which I took in West Africa in 1988, are tokens of transition. The bench work had been done; essential field trials in veterinary and human applications had been completed; the feasibility of community-based drug administration for River Blindness control was being explored and the photographs are illustrative of that process. The vast control campaigns directed against River Blindness and lymphatic filariasis were in the offing. They were soon to be carried out by a multitude of care-givers, health workers, administrators and visionary leaders. Their heroic story will be told by others. The photographs shown here are mementoes of a time long gone.

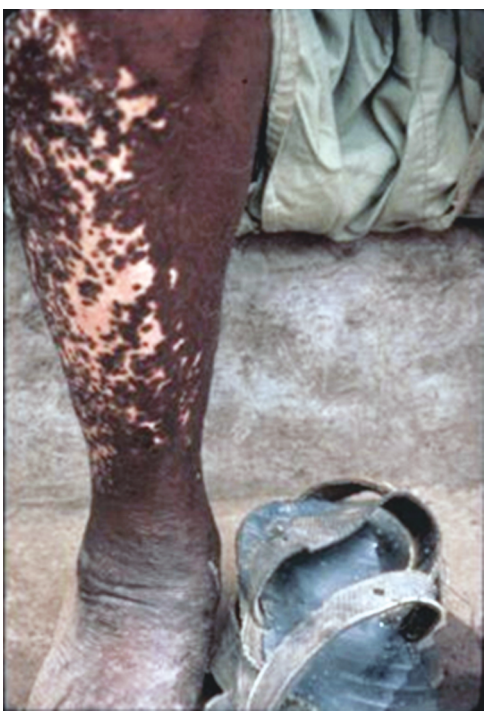

FIGURE 6. One of the many kinds of skin lesion that develop in onchocerciasis over a period of years, following a period of excruciating itching.

FIGURE 7. An outdoor temporary clinic, where ivermectin was being administered and detailed records were kept.

I now return to that mouse assay with which I began. The operation of that assay was obviously simple. But so was the principle! Thinking it up was a different matter—that was innovative thinking on the part of my colleagues; but the underlying scientific principle was simple. It was bizarre!—but simple. I have described it this way: You line up a series of individual infected mice. You treat each mouse with an unknown amount of an unknown substance that might not be there. Then you check to see if the treatment worked.

It seems to fly in the face of what we are taught about science, with its well-regulated systems and its emphasis on measurement. But we need to understand

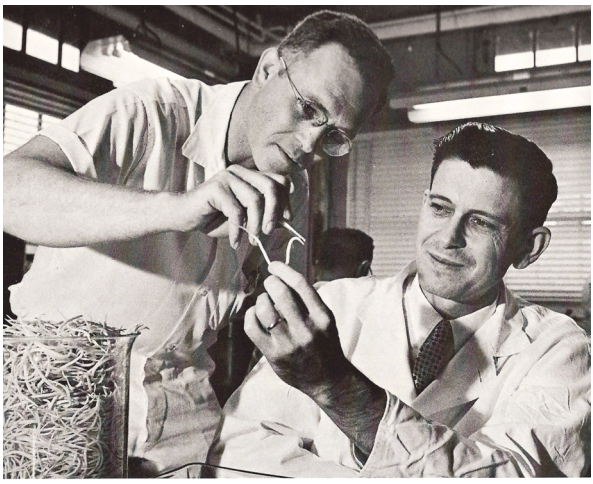

FIGURE 8. Thiabendazole, like other antiparasitic agents, was discovered by simple empirical science. The photo shows two Merck scientists who played key roles in the discovery: parasitologist John R. Egerton (left) and chemist Horace D. Brown (right). Thiabendazole was introduced as a broad-spectrum anthelmintic in 1961.

that this, too, is well-regulated science. Empirical research has been the foundation of the discovery of antiparasitic agents (Figure 8). But "trial and error" research has in recent years been beaten into disrepute and desuetude. And when it is abandoned, we cannot know what price has been paid in "non-discovery."

I have recently made a proposal to search the earth more broadly for new "natural products" as a means of finding novel molecules for chemotherapeutic development [19]. The focus would be primarily on substances produced in microbial fermentation, but could be broadened to include substances made by other forms of life. The target utility of screening new substances would not necessarily be limited to the field of infectious diseases, or even to medicine at all. I have, on occasion, called it my "unpopular proposal"—unpopular because it is destitute of the glamour of "high science;" but though it harkens back, it also looks forward. It would not rely only on science—it would depend crucially on the talent abundantly available in the realms of logistics, finance and management.

The empirical testing of natural products for antiparasitic activity may eventually yield drugs that would be helpful in the multi-agency campaigns that are already underway to control insidious worm diseases such as the soil-transmitted worm infections. Nevertheless, chemotherapeutic disease-control should not be seen as the ultimate objective. Unnatural measures are likely to have unforeseen natural consequences. The broader the activity spectrum of a biodynamic

substance, the more we must guard against the hazards of indiscriminate use. Since we cannot count on discriminate use, we should try to control disease without recourse to chemical agents. Despite the current paucity of acceptable vaccines for worm diseases, we may learn how to stimulate or simulate the effective immune responses in a natural yet controllable manner.

In late afternoon I often climb a nearby hill—not a mountain, just a grassy half-mile hill called . . . "Half-mile Hill." From the top I see a marvelous vista of woodland and lake, and a sky often tinted with color as evening falls. It is a moment of uplifting tranquility; and with it comes the realization that many do not live amidst natural beauty and peace. To redress the terrible imbalance, many people around the world are making heroic efforts, and one of their objectives is the improvement of global public health. As we bring science to bear on the problem, I hope we will keep in mind that solutions are sometimes to be found in science that is simple.

ACKNOWLEDGEMENTS

The photographs in Figs 5–7 were taken by the author, and with permission of the subjects. The other photographs are reproduced by permission of Merck &Co., Inc.

LITERATURE

1. Campbell, W.C. 1992. The genesis of the antiparasitic drug ivermectin. In *Inventive Minds: Creativity in Technology*, ed. R.J. Weber, D.N. Perkins, pp. 194–214. New York: Oxford University Press.
2. Campbell, W.C. 2012. History of ivermectin and abamectin: with notes on the history of later macrocyclic lactone antiparasitic agents. *Current Pharmacology and Biotechnology*, **13**: 853–865.
3. Burg, R.W. and E.O. Stapley. 1989. Isolation and characterization of the producing organism. In: Campbell, W.C. 1989 (ed.). *Avermectin and Abamectin*. New York: Springer-Verlag. 363 pp.
4. Omstead, N.M, L. Kaplan, and B.C. Buckland. 1989. Fermentation development and process improvement. In: Campbell, W.C. 1989 (ed.). *Avermectin and Abamectin*. New York: Springer-Verlag. 363 pp.
5. Albers-Schonberg, G., B.H. Arison, J.C. Chabala, A.W. Douglas, P. Eskola, M.H. Fisher, A. Lusi, H. Mrozik, J.L. Smith, and R.L. Tolman. 1981 Avermectins: structure determination. *Journal of the American Chemical Society*, **103**, 4216–4221.
6. Chabala, J.C., H. Mrozik, R.L. Tolman, P. Eskola, A. Lusi, L.H. Peterson, M.F. Woods, and M.H. Fisher. 1980. Ivermectin, a new broad-spectrum antiparasitic agent. *Journal of Medicinal Chemistry*, **23**, 1134–1136.

7. Fisher, M.H. and H. Mrozik. 1989. Chemistry. In: Campbell, W.C. 1989 (ed.). *Avermectin and Abamectin*. New York: Springer-Verlag. 363 pp.
8. Egerton, J.R., D.A. Ostlind, L.S. Blair, C.H. Eary, D. Suhayda, S. Cifelli, R.F. Riek, and W.C. Campbell. 1979. Avermectins, a new family of potent anthelmintic agents: efficacy of the B_1a component. *Antimicrobial Agents and Chemotherapy*. **15:** 372–378.
9. Ostlind, D.A., W.G. Mickle, S. Smith, D.V. Ewanchiw, and S. Cifelli. 2013. Efficacy of ivermectin versus dual infections of *Haemonchus contortus* and *Heligmosomoides polygyrus* in the mouse. *Journal of Parasitology* **99**: 168–169.
10. Turner, M.J. and J.M. Schaeffer. 1989. Mode of action of ivermectin. In: Campbell, W.C. 1989 (ed.). *Avermectin and Abamectin*. New York: Springer-Verlag. 363 pp.
11. Campbell, W.C. and L.S. Blair. 1978. *Dirofilaria immitis*: experimental infections in the ferret (*Mustela putorius furo*). *Journal of Parasitology* **64**: 119–122.
12. Campbell, W.C., L.S. Blair, and J.W. McCall. 1979. *Brugia pahangi* and *Dirofilaria immitis*: experimental infections in the ferret, *Mustela putorius furo*. *Experimental Parasitology* **47**: 327–332.
13. Blair, L.S. and W.C. Campbell. 1978. Trial of avermectin B_{1a}, mebendazole and melarsoprol against pre-cardiac *Dirofilaria immitis* in the ferret (*Mustela putorius furo*). *Journal of Parasitology* **64**(6): 1032–1034.
14. Egerton, J.R., E.S. Brokken, D. Suhayda, C.H. Eary, J.W. Wooden, and R.L. Kilgore. 1981. The antiparasitic activity of ivermectin in horses. *Veterinary Parasitology* **8**: 83–88.
15. Aziz, M.A., B.H. Diallo, I.M. Diop, M. Lariviere, and M. Porta. 1982. Efficacy and tolerance of ivermectin in human *onchocerciasis*. *Lancet* **2**: 171–173.
16. Greene B.M., K.R. Brown, and H.R. Taylor. 1989. Use of ivermectin in humans. In: Campbell, W.C. 1989 (ed.). *Avermectin and Abamectin*. New York: Springer-Verlag. 363 pp.
17. Mectizan Donation Program 2016. Online website: http://www.mectizan.org.
18. Thylefors, B. and M. Alleman. 2006. Towards the elimination of onchocerciasis. *Annals of Tropical Medicine and Parasitology*, **100**:733–746.
19. Campbell, W.C. 2016. Lessons from the history of ivermectin and other antiparasitic agents. Animal.annualreviews.org: doi: 10.1146/annurev-animal-021815-111209. *Annual Review of Animal Biosciences*, in press.