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Ivermectin and River Blindness

Science and philanthropy put an end to blindly following the next generation

Philip A. Rea, Vivian Zhang and Yelena S. Baras

Imagine: itching so intense that you are forced to sleep resting on your knees and elbows; the stigma of persistent rashes, skin discoloration and disfiguring protuberances under your skin. Or, as epitomized by the statue outside the World Health Organization's (WHO) Geneva headquarters depicting a young boy leading a not-so-old blind man with a stick, imagine the prospect of never again seeing your child's face, a child who will likely have to suffer what you are suffering *(see Figure 1)*. If you can imagine this, you have a sense of what it is like to be afflicted by river blindness and live in a community for which it is a fact of life.

The need for this article came from the realization that despite the immensity of the problem, very few of us in the western world know of the existence of river blindness, and even fewer know of the connection between it and something that most of us do know something about—the "deworming tablets" we give to pets and livestock to protect them from heartworm and similar parasitic infections. Yet, the fact of the matter is that if your dog has been given preventive medication for heartworm, it was almost certainly given the very same drug, ivermectin, that has been and continues to be used to treat literally tens of millions of people in the developing world—people who would otherwise have to live lives of interminable suffering and anguish.

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The River Eats Your Eyes

River blindness, otherwise known as onchocerciasis (pronounced "ong-koh-ser-kahy-uh-sis"), gets its name because of its prevalence among populations living and working near rivers. Onchocerciasis and rivers go together because the black fly vector, *Similium* spp *(see Figure 2)*, that spreads the disease from person to person breeds in fast flowing, oxygen-rich waters. The perpetrator of the disease carried by the fly vector (the reason for the designation "onchocerciasis") is the nematode worm *Onchocerca volvulus*, a filarial parasite worm belonging to the same superfamily (the Filarioidea) as the model worm of RNAi fame, *Caenorhabditis elegans*, and its cousins *Wuchereria bancrofti*, *Brugia malayi* and *B. timori*, which is responsible for another widespread and similarly disfiguring disease, elephantiasis.

River blindness came out of Africa, where its foothold is strongest, and is now endemic in 34 countries: 27 in Africa, 1 in the Arabian Peninsula and—because of the slave trade—6 in Latin America. The disease came about because of a rather special combination of host-parasite interactions (and as we will learn shortly, a host-endosymbiont interaction). These are the interactions between the filarial parasite and the intermediate host, the black fly vector, and between the parasite and the definitive host, men and women unfortunate enough to fall foul of the disease *(see Figure 4)*. If the parasite is to develop from the microscopic prelarval "microfilarial" L_1 stage to larval stage L_3 and then be injected into the host, it needs the fly host. If it is to develop from larval stage L_3 through L_5 to the reproductively active "macrofilarial" adult worm stage, it needs the human host.

If left to run its course, river blindness is a disease for life. Adult worms can live for 12 to 15 years and be sexually active for 9 to 11 of them. Adult females dwell in nodules under the skin—the telltale protuberances averaging 3 centimeters in diameter associated with this condition. Each nodule harbors two or three individuals measuring 50 centimeters in length and about 0.5 millimeters in diameter, between which the smaller, 4 centimeter x 0.2 millimeter, iterant males migrate to cause their mischief—insemination of the females. This is when and where the problems start, because each female releases a staggering 1,300 to 1,900 microfilariae per day throughout her reproductive life.

It is the microfilariae that precipitate onchocerciasis. Measuring only 250 to 300 micrometers in length, microfilariae once released from the mother worm move easily through the skin and lymphatic system and into the interior chamber of the eye as well as the retina and optic nerve. In the skin they cause intense itching, rashes, dermal thickening and skin discoloration; in the eye they cause scarification, visual impairment and eventually blindness. Note that it is not live microfilariae, which

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Figure 1. River blindness (onchocerciasis) is caused by the parasitic worm *Onchocerca volvulus*. It is prevalent in 34 countries in Africa, Central and South America, and the Arabian Peninsula, and has infected at least 37 million people in Africa alone. As the name implies, one of its effects is loss of eyesight; 300,000 Africans are blind as a result. Were it not for a community-directed program of ivermectin administration, that number would continue to grow. The two daughters shown here leading their mothers in Sudan would otherwise likely have joined their parents in blindness if not for this program. Originally developed to prevent heart worm in pets and livestock, ivermectin has been donated by Merck to the World Health Organization and is showing great success in relieving untold suffering. (Photograph by Andy Crump, courtesy of the World Health Organization/TDR.)

live for about two years, but dead ones that cause the disease. Onchocerciasis arises from the progressive accumulation of localized inflammatory foci associated with the death of 100,000 or more microfilariae per day—a sum total of 100 million or more in a heavily infected individual!

An(other) Inconvenient Truth

Now ramp up your scaling and think not just in terms of the individual but on a global scale. It is estimated (as of 2005) that approximately 100 million people in Africa are at risk of contracting onchocerciasis. Of these, upward of 37 million already have it, of which 500,000 are severely impaired visually and 300,000 are already blind *(see Figure 5).* The numbers for Latin American are not quite as unnerving in absolute terms and in terms of the prevalence of perhaps the most severe consequence of the disease, blindness, but nevertheless must be taken very seriously. Some 500,000 Latin Americans are at risk of the disease—they live within striking distance of 13 endemic foci—and those at greatest risk include coffee plantation workers, those living in river coastal regions, and the various nomadic groups whose very existence depends on lengthy treks through and across the Amazonian rainforest.

In the stark numerology of health economics, healthy life-years lost due to disability and mortality (disability-adjusted life years, DALYs), the consequences of river blindness are appalling. They amount to about 1 million (years!) per year—a metric that does not even take account of the dire socioeconomic consequences for those who have been forced to abandon their homes on fertile alluvial plains, or those parents who have been robbed of the wherewithal to take care of their children, children who as a result must forfeit a school education to take care of sick parents.

Out of Japan

What is ivermectin and how was it discovered? In crude terms it is a modified metabolite whose precursors were detected in a humble microbe found in a patch of dirt on a golf course. More specifically, ivermectin is a polyketide

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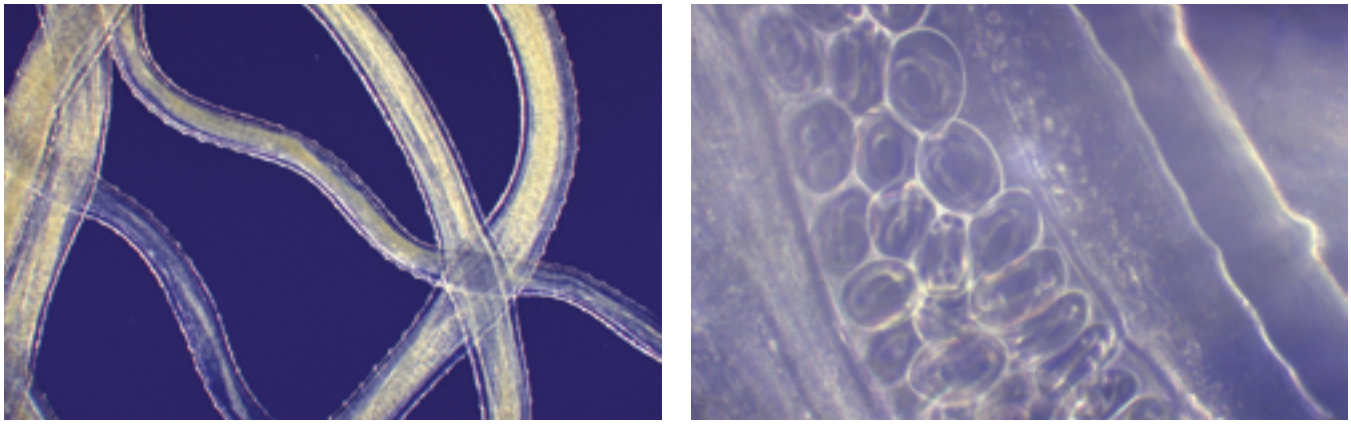
Sinclair Stammers/Photo Researchers

Figure 2. The parasite responsible for river blindness, the filarial parasitic worm *O. volvulus (right)* is shown here in the vector that transmits it—small black flies of the genus *Simulium (left)*, which breed in fast-flowing, oxygen-rich rivers and streams. The adult black fly shown is taking a blood meal on human skin. (Image at right courtesy of R. C. Collins, Centers for Disease Control.)

antibiotic derived from two of the avermectins originally purified from bacterial strain MA-4680, which was isolated from soil sample OS3151. Soil sample OS3153, collected from the Pacific Oceanside Kawana Golf Course in Japan in 1974, was the only sample of a total of about 40,000 gathered under the auspices of this research program that yielded culture filtrates with activity against parasitic infections. Subsequently named *Streptomyces avermitilis* and later renamed *S. avermectinius*, MA-4680 was one of the many microbial isolates to come from the transcontinental collaboration initiated in 1973 between the Kitasato Institute, Tokyo, under the leadership of Dr. Satoshi □mura, and Merck, Sharp and Dohme (MSD) Research Laboratories, Rahway, New Jersey, U.S.A. Members of the Kitasato Institute took the lead in isolating the microorganisms, identifying culture filtrates containing bioactive compounds and performing pilot *in vitro* screens. MSD scientists took the lead in performing *in vivo* screens and in further refining any promising candidates identified. Remarkably (certainly by comparison with the time it now takes to get most drugs from the laboratory to the disease target), come 1975 the avermectin fraction from MA-4680 had been purified, screened and determined to have excellent antiparasitic activity in the "mouse model"—laboratory mice infected with the nematode worm *Nematospiroides dubius*. Two compounds, avermectins B1a and B1b, in particular were found to be especially effective. After chemical hydrogenation to their corresponding dihydro derivatives to minimize toxicity toward the mammalian host and maximize antiparasitic efficacy, these two compounds were to enter the veterinary market as ivermectin.

Ivermectin was to assume many trade names—Ivomec, an injected formulation for cattle and pigs; Ivomec liquid for sheep; Equalan for horses; and Heartgard-30 for dogs, to name a few. (Its applications were eventually to be expanded beyond the veterinary to the horticultural and arboricultural to the control of insects and mites in greenhouses and, after its injection,



John Walsh/www.micrographia.com

Figure 3. Adult *O. volvulus* worms *(left)* are as long as 50 centimeters and can live for 12 to 15 years. An adult female can produce 1,300 to 1,900 microfilariae *(right)* per day. Microfilarial loads can reach 100 million in a heavily infected individual, and it is the death of these microfilariae—as many as 100,000 per day—that causes onchocerciasis.

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leaf miners in trees). In its 1987 annual report, Merck could state with justification that veterinary ivermectin is "the Company's second largest selling product, the first for an animal health product." To this day, ivermectin has continued to hold a prominent position with annual sales averaging $1 billion, making it the best selling veterinary drug in history.

A Day to Remember

On the same day (May 9, 1977) that *Time* magazine announced "Nixon Talks," the now famous televised Frost-Nixon interview, William Campbell, a senior scientist in Merck's Basic Animal Science Research who was involved in the discovery and development of ivermectin for veterinary purposes, sent a memo to his supervisor. This memo, which was forwarded to P. Roy Vagelos, who was then president of Merck Research Laboratories, proposed that ivermectin might have human applications. What was evident from screens of ivermectin against *Onchocerca cervicalis*, another fly- (in this case, midge-) disseminated nematode parasite responsible for horse neckworm, was the efficacy of this drug, and the possibility that it would be similarly effective against the closely related black fly-disseminated human parasite *O. volvulus*. Vagelos, who was still quite new to the business world (he joined Merck from Washington University in 1975) and had never before been forced to think about "things parasitological" (he was an cardiologist and lipid biochemist), sent a personal reply to Campbell encouraging him to continue exploring this possibility. This is exactly what Campbell did. He combined forces with his colleague Mohammed Aziz to start the enterprise that was eventually to give rise to Mectizan, the human formulation of ivermectin.

Aziz, a native of Bangladesh, would prove to be a central figure in this enterprise. A senior director for Clinical Research at Merck, Aziz had worked for the WHO in sub-Saharan Africa before joining the company. He was an expert in tropical medicine and had already witnessed directly the untold suffering caused by this disease; if anyone at Merck had an appreciation of the numbers involved it was he. Aziz and a small group of investigators from Merck were dispatched to Dakar, Senegal, on the African Atlantic coast to work with the Onchocerciasis Control Programme (OCP) to determine if ivermectin was really as effective as he, Campbell and colleagues suspected.

Trials were conducted over a seven-year period and involved hundreds of thousands of individuals in 12 countries including Ghana, Cote d'Ivoire, Liberia and Mali as well as Senegal. The results were as close to unequivocal as any drug trial ever gets. Ivermectin worked brilliantly: Not only was it effective in alleviating the symptoms of onchocerciasis and arresting ocular disease progression, but it was also well tolerated. Doses as high as 800 micrograms per kilogram were tolerated, yet a single dose of 200 micrograms per kilogram was sufficient to bring the dermal density of microfilariae down close to zero after a month and keep it at that level for up to a year.

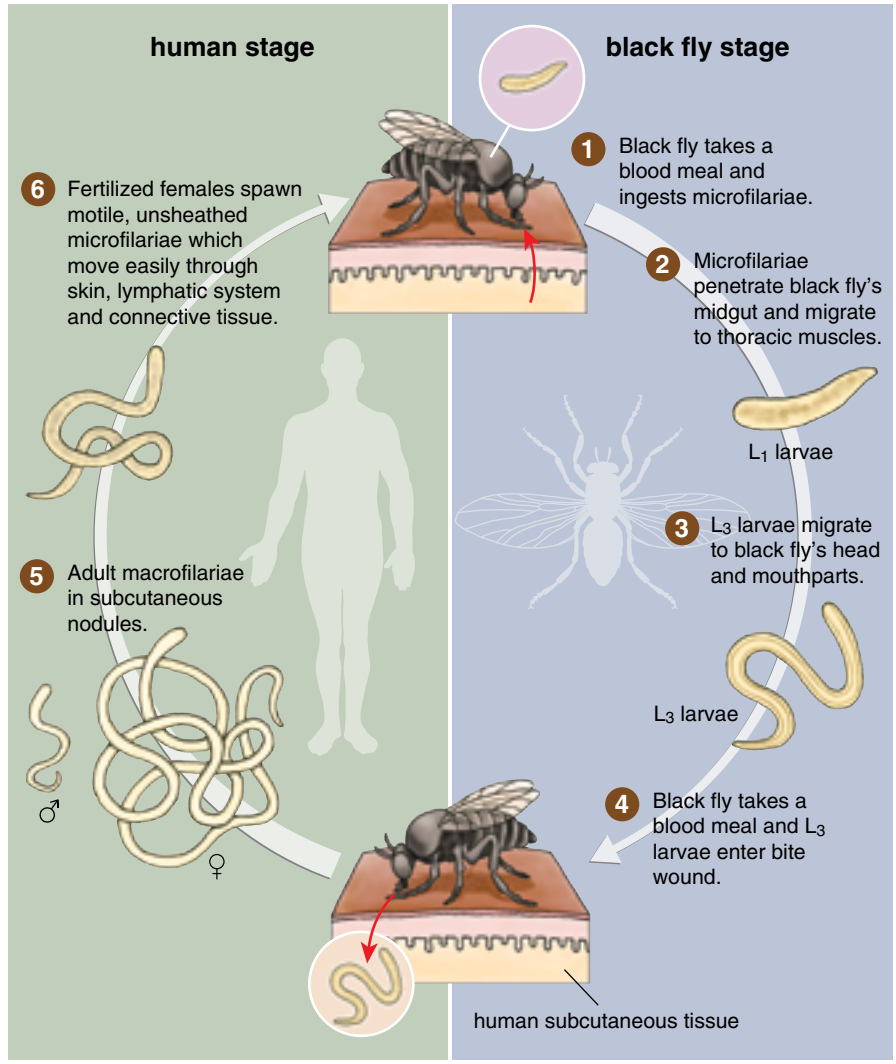

Figure 4. The life-cycle of *O. volvulus* starts with the pre-parasitic or black fly stage, when the fly takes a blood meal from the human host and ingests microfilariae *(1)*. Those microfilariae that survive the early stages of digestion, penetrate the midgut and migrate to the fly's flight muscles *(2)*. There they differentiate first into L_1 larvae and then, after two cycles of molting, into L_3 larvae *(3)*. It is the L_3 larvae that migrate to the fly's mouthparts and enter the bite wound the next time the fly feeds *(4)*. The second phase of *O. volvulus*'s development, the parasitic or human stage, starts when L_3 larvae enter the subcutaneous tissue of the human host. Within one week of infection, the L_3 larvae differentiate into the L_4 stage and thereafter to the L_5 stage, the immature, presexual adult. L_5 larvae give rise to mature male and female worms, macrofilariae, within 1 to 3 months. The transition from newly injected L_3 larvae to sexually mature worms usually takes 10 to 12 months *(5)*. Fertilized mature females spawn the motile unsheathed microfilariae, which move easily through the skin and lymphatic vessels of connective tissues to bring the cycle full circle when black flies next feed on the human host *(6)*. (Adapted from figures created by the World Health Organization and the Centers for Disease Control.)

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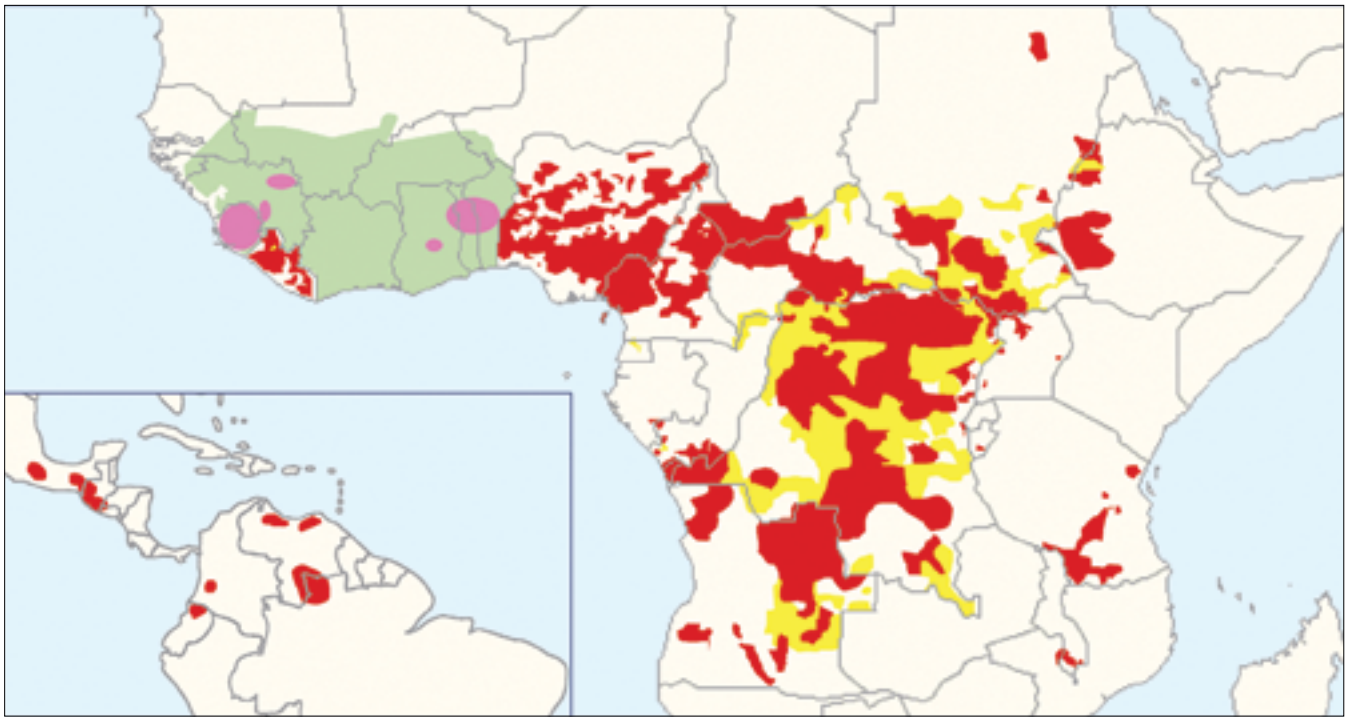


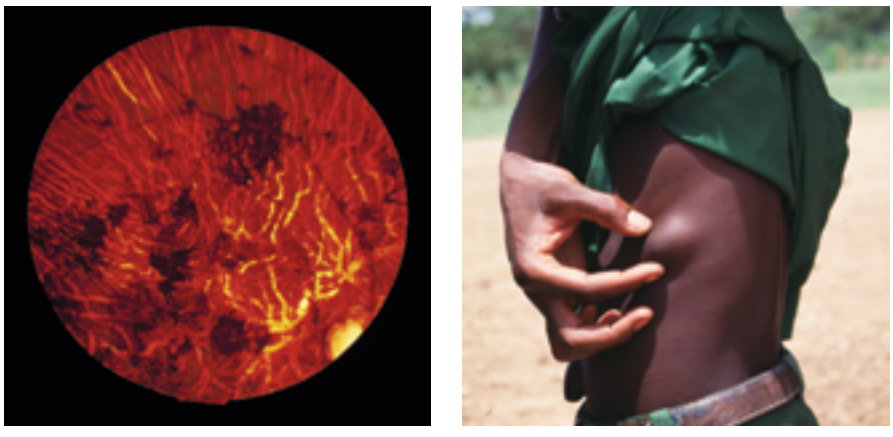
Figure 5. River blindness affects the inhabitants of 27 African nations, 6 Latin American nations and one nation on the Arabian Peninsula. As of 2006, the areas where people were receiving ivermectin are shown in red. Areas shown in yellow are those that require further epidemiological research. Green denotes the extent of the Onchocerciasis Control Programme (OCP) in West Africa. Pink denotes OCP areas that previously received ivermectin as well as other control measures directed at eliminating the black fly vector using pesticides. (Courtesy of Basáñez et al. 2006.)

Because most of the OCP countries were former French colonies and had expatriates living in France who had the disease and were eligible for participation in clinical trials, regulatory approval for the human use of ivermectin was sought from the French Directorate of Pharmacy and Drugs. Approval was granted in 1987 and the human formulation was registered as Mectizan. (Approval from the U.S. Food and Drug Administration was not sought at the time because onchocerciasis was unheard of in the United States. It was some years later in 1996 that the FDA approved ivermectin for the treatment of onchocerciasis and another disease caused by filarial parasites, strongyloidiasis.)

A Moral Corporation

Having established that ivermectin was very likely capable of meeting a huge unmet need, the treatment and possible eradication of onchocerciasis, Merck found itself having to contend with another problem: how to get it to the people who need it most. After all, Merck was and is a for-profit company answerable to its stockholders and board of directors, yet it was obvious not only to its marketing people but also to Vagelos, Campbell, Aziz and their immediate colleagues that there was no chance of a profit being made on Mectizan. The vast majority of the people afflicted with river blindness were impoverished and could not even come close to affording $1 per dose, never mind the usual asking price of $3.

Vagelos, who by this time was chairman and CEO of the company, did what the circumstances necessitated. He made the rounds among both national and international organizations, including the WHO, the U.S. Agency for International Development, the U.S. Department of State, European and African governments, and private organizations, seeking material support but getting only moral support in return. Even the urging of Senators Bill Bradley, Ted Kennedy, Frank Lautenberg and Richard Lugar failed to persuade Congress to support ivermectin's worldwide distribution. As of 1986, shortly before its regulatory approval, the prospects for the truly global deployment of Mectizan looked dismal.



CNRI/Photo Researchers

Figure 6. Onchocerciasis attacks the retina *(left)*, causing impaired vision or even blindness. The dark pigmented areas in this ophthalmoscopic image are sites of scarification and loss of retinal function. Mature worms clustered below the skin form lumps several centimeters in size *(right)* and often produce skin lesions. (Photograph by Andy Crump, courtesy of WHO/TDR.)

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Merck's decision to institute the historic Mectizan Donation Program (MDP) to treat river blindness in countries where the disease is endemic was announced formally on October 21, 1987, at a press conference in Washington, D.C. Vagelos made it plain that ivermectin would be provided free of charge for the treatment of river blindness for "as long as it is needed." This was the first global health initiative of its kind, but one that was to prove to be a model for many similar initiatives that were to follow.

Aside from the sheer magnitude of the river blindness problem and Vagelos's powers of persuasion, three other factors likely helped make MDP happen. First, Merck's philanthropy in this instance was not without precedent. Merck had already donated considerable quantities of streptomycin to Japan, which had faced especially high levels of tuberculosis in the aftermath of WWII—a philanthropy that was repeated in 1958 when the Merck Medical Outreach Program donated antibiotics, antiparasitic agents and vaccines for humanitarian efforts in developing countries and disaster zones. Second, ivermectin in the guise of the veterinary formulation, Ivermec, had already brought sizeable profits and was promising to continue doing so. At the time, Merck's profits from Ivermec were running at $300 million and sales were growing at 15 percent per year. With a pledge amounting to about $200 million per year to MDP, Merck could in principle donate ivermectin and incur no net loss, because Ivomec's sales alone were capable of covering the costs of Mectizan's production and distribution.

Blocked Open

Despite its remarkable success, a lot less is known of the mode of action of ivermectin than might be expected. What is known is that it binds to glutamate-activated chloride (GluCl) channels in the membranes bounding certain nerve cells and jams them in the open state *(see Figure 7)*. Negatively charged chloride ions then spill out of the cells through the open channels, and the membrane potential is collapsed (becomes less negative), thus abolishing neural excitability. What is not known is how this relates precisely to the principal effects of ivermectin on the intact parasite—paralysis of the body wall muscles involved in microfilarial locomotion and the precipitous decline in the otherwise extraordinary fecundity of mature *O. volvulus* females. The explanations for both effects are indirect and based on deduction by elimination. Since body wall muscle cells lack GluCl channels, microfilarial locomotory paralysis is suspected to arise from the disruption of interneuron function, possibly through the interaction of ivermectin with neurons in this part of the neural circuitry that have GluCl channels. By a similar line of reasoning, namely that the female reproductive structures of nematodes do not appear to have GluCl channels and the intrauterine development of embryos from the oöcyte to microfilarial stage is not affected by this drug, ivermectin is thought to interfere with the reproductive potential of mature females by blocking the contractile activity needed for microfilarial release. Regardless, ivermectin stops microfilaridiae in their tracks and triggers the accumulation, degeneration and eventual resorption of microfilaridiae in utero such that the fraction of females harboring live offspring is decreased by as much as 70 percent within one to two months of treatment.

Note that ivermectin is a microfilaricide, not a macrofilaricide: It does not kill adult worms outright. This has both an up and a down side. The upside is that the kill is not so wholesale as to expose the patient's immune system to a massive onslaught by the products of worm death, which in itself could be lethal for the patient. The downside is that since the lifespan of a mature worm is 12 to 15 years, the drug needs to be taken for about this length of time before the patient can be said to be "cured."

Unlike the first generation drugs for onchocerciasis, sumarin and diethylcarbamazine (DEC), which had to be discontinued in the mid-1970s because of their toxicity, ivermectin does not elicit an acute inflammatory response. Again, it is not known exactly why this should be, but it may be because ivermectin does not kill the microfilariae immediately. Ivermectin instead paralyzes them in the subepidermal tissue spaces and lymphatic vessels, and they are then swept from the subepidermal layer into deeper dermal layers and regional lymph nodes where they are killed and removed efficiently from the system by eosinophils and macrophages. Sumarin and DEC, by contrast, instigate large-scale destruction of the microfilariae within the skin spaces and peripheral lymphatic vessels, where they remain to promote the multisite inflammatory foci characteristic of the disease. Indeed, the "no missing it" severity of the hypersensitive response to DEC is the basis of the patch test for onchocerciasis—a relatively unobtrusive diagnostic procedure involving the topical application of DEC to a relatively small area of the skin to elicit a localized inflammatory response to microfilariae, which if present are killed by the drug.

This is not to say that ivermectin does not have side effects, including

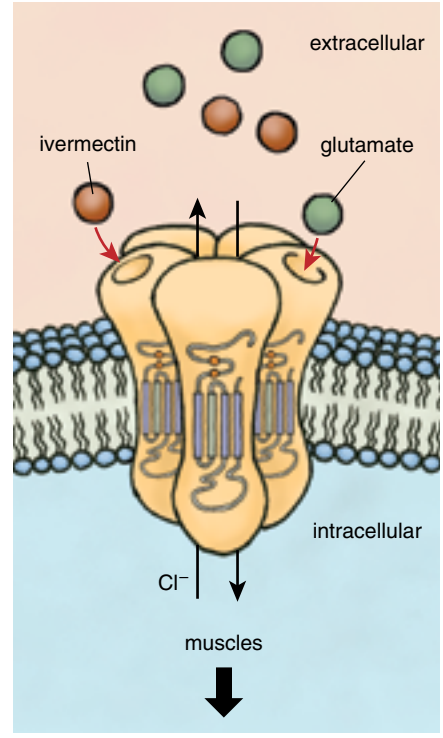

Figure 7. Although much remains unknown about ivermectin's mode of action, it does appear to bind to glutamate-activated chloride (GluCl) channels in the membranes bounding nerve cells, jamming them in the open state. Negatively charged chloride ions spill out, and the membrane potential collapses, blocking neural excitability. Note that ivermectin and glutamate do not interact with (compete for) the same binding site on the GluCl channel but instead exert complementary, potentially additive, effects on channel opening. This may, in part, contribute to the efficacy of ivermectin. Interaction of the GluCl channel with endogenous glutamate primes the channel for interaction with ivermectin such that lower concentrations of the drug are required to keep the channel in its open state. (Adapted from Raymond and Sattelle 2002).

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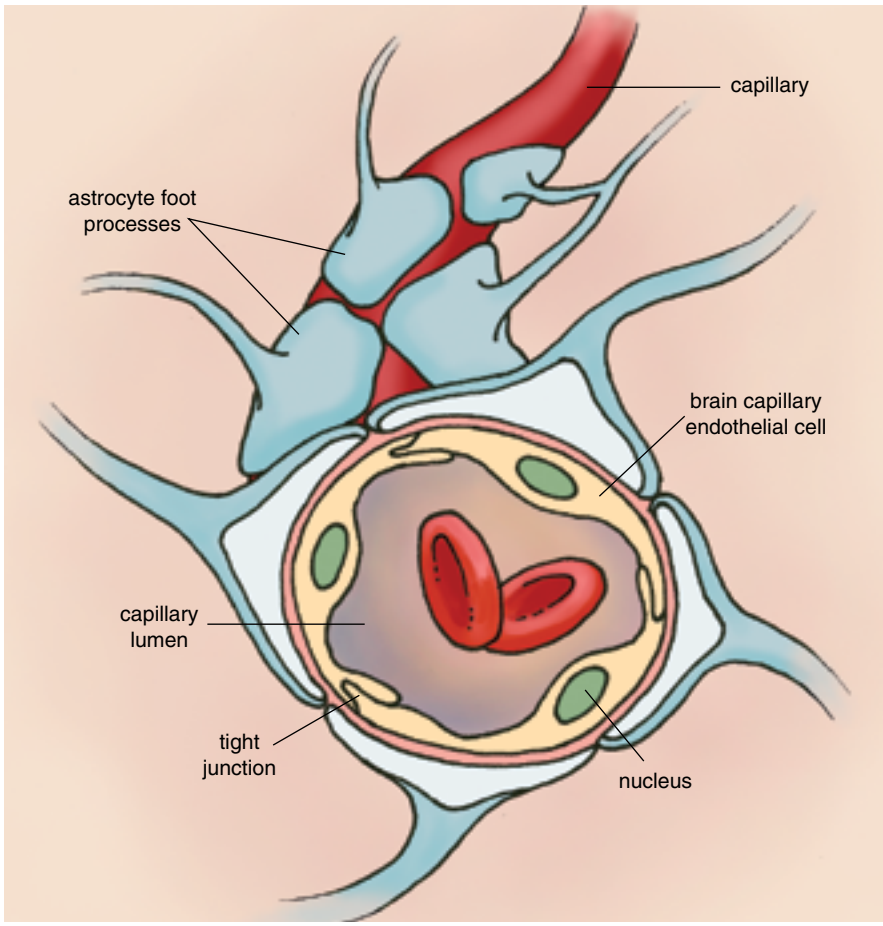

Figure 8. Ivermectin is well tolerated in patients at a wide range of doses owing, in part, to the medication's inability to cross the blood-brain barrier. A brain capillary in cross section shows tight junctions between endothelial cells and their encapsulation by astrocyte foot processes. (Adapted from Goldstein et al. 1986.)

itching, fever and occasionally pain. They are generally mild, short-lived and easily treated by healthcare workers or trained members of the local community, however—a small price to pay for the long-term benefits. When severe adverse events do occur they do so at a very low frequency—on the order of 1 per 800,000 treatments. This is the general case.

A special case is when *O. volvulus* is co-endemic with another filarial parasite, *Loa loa,* which is found mainly in central Africa. Although *L. loa*, which is transmitted by a deer fly vector, does not ordinarily cause severe dermal or ocular symptoms, it can nonetheless attain levels in excess of 50,000 microfilariae per milliliter of blood in some infected individuals. Treatment of individuals infected with both filarial parasites can result in severe adverse reactions, including fatal encephalopathy, presumably because of the massive accumulation not only of dead *O. volvulus* but also of dead *L. loa* microfilaridiae.

An Enabling Barrier

Nematodes are not unique in having ivermectin-sensitive GluCl, or GluCl-like, channels. In fact, in 1981, not long after ivermectin was brought to market for veterinary purposes, electrophysiological experiments established that the drug increases the chloride conductance of mammalian neuron membranes. What invertebrates don't have that mammals do, however, is a blood-brain barrier, which serves to protect the central nervous system (CNS) from a wide range of blood-borne toxins *(see Figure 8)*. This barrier literally makes the difference between kill or cure. Cells termed "astrocytes" in the central nervous system provide support for neurons and regulate the composition of the extracellular medium. Projections—foot processes—on the astrocytes envelop neurons to physically insulate them from the blood carried in the capillaries and promote the formation of tight junctions between the endothelial cells lining the capillaries. In this way, a physical barrier is formed that limits the passive transport of substances into the brain. That is one level of exclusion. The other level is exerted by ATP-energized drug efflux pumps, P-glycoproteins in the case of antiparasitic and chemotherapeutic agents. P-glycoproteins play a gatekeeping role as clearly implicated by the rare but serious neurological side effects of ivermectin seen in some vertebrates—certain collie dogs and mouse lines that have mutations in the gene, *mdr-1*, encoding one of these transporters, P-glycoprotein 1. Found predominantly in the membranes of brain capillary endothelial cells facing the bloodstream, these transporters pump ivermectin and other relatively bulky lipophilic "toxins" from the inside of these cells back into the bloodstream. What is bad news for the vast majority of chemotherapeutic agents—for instance those that would, if things were different, be used to treat brain tumors—is good news for ivermectin.

By the People for the People

One of the keys to ivermectin's success is that its margin of safety is so wide that the appropriate dose can be determined very easily. Young children who can walk under a stick held only a few feet above the ground get only one pill; others, adults and adolescents, who cannot, get two. Combine this with the fact that the drug can be transported and stored without refrigeration and that it takes only one or two doses per year in pill form to curb the disease and the implication is obvious: Ivermectin is unusually amenable to management by the people for the people.

WHO's Special Programme for Research and Training in Tropical Diseases (TDR), in the same year that Merck announced its donation program, initiated research of and eventually put into practice Community-Directed Treatment with Ivermectin (CDTi), which was to be the *modus operandi* for the African Programme for Onchocerciasis Control (APOC). The power of APOC, founded in 1994, which assists in the provision of funds and other resources for nongovernmental development organizations and local community officials, is that the role of the health worker is simply to communicate the benefits of the program and then to transfer program management skills to community members. It is all about the mobilization of unpaid

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community workers who have been trained to treat themselves and their neighbors, complete records and keep track of drug distribution. If there was one thing that ensured the sustainability of mass treatment with ivermectin while at the same time enabling the distribution and administration of the drug in parts of the world, for instance dangerous war-torn regions or regions that might otherwise be geographically isolated, it was CDTi—a coalition forged between Western medicine and local activism. Intent on treating 90 million people and protecting in excess of 115 million, APOC was originally projected to run from 1995 through 2007 but has since been extended to 2015. The Onchocerciasis Elimination Programme in the Americas (OEPA) was originally founded in 1992 and sponsored by the Carter Center. Seeing the effectiveness of APOC's Community-Directed Treatment, OEPA adopted much the same model in achieving the same end in Latin America.

The control of onchocerciasis is now almost exclusively based on annual or semiannual treatment with ivermectin in such a way that its distribution and administration have become a way of life for the affected communities. It has given those who stand to benefit the most a sense of ownership, so allaying what might otherwise be perceived as a paternalistic relationship between the developed world, in general, or Merck, in particular, and disadvantaged onchocerciasis-endemic communities. If there ever was a need for endorsement of the CDTi model up and above its impact on onchocerciasis, many of the local volunteers recruited by APOC are now also central players in the distribution of vitamin A, whose deficiency is another cause of blindness, and the coordination of home-based malaria and HIV/AIDS care for the very same communities.

Blindness Once Lived Here

While we were researching this article, the first clear evidence appeared indicating that the elimination of river blindness through the community-directed administration of ivermectin is becoming a reality. These findings, published in the open-access journal PLoS *Neglected Tropical Diseases*, came from studies conducted by research teams from the ministries of health of Mali and Senegal in collaboration with the WHO Multi-Disease Surveillance Centre in Burkina Faso. It showed that 15 to 17 years of treatment with ivermectin arrested transmission of the parasite and alleviated the symptoms of individuals who already had the disease in three specific areas in Africa where onchocerciasis, manifest as dermal microfilariae, had previously been hyperendemic (had a prevalence of 60 percent or more). In a massive skin-snip survey of 17,801 people living in 126 villages, the prevalence of dermal microfilariae was less than 1 percent in all three areas, and of a total 157,500 black flies that were collected and screened for *O. volvulus* using a specific DNA probe, less than 1 in 2,000 contained the parasite. In other words, except for one small section of the areas screened, the indices for infection and transmission were below what is considered to be the threshold for elimination.

There is more: When treatment was stopped in 5 to 8 of the villages in each test area and the screens were repeated 16 to 22 months later, no infected persons or infected black flies were detected. To quote Dr. Uwe Amazigo, one of the champions of community-directed treatment, from a July 21, 2009, WHO news release, "This evidence is an historic milestone—it has far-reaching implications for the fight against this disease. Prior to this study we did not know if we would ever be able to stop the treatment." In the light of these encouraging findings, the board of APOC has established a new objective: to determine when and where in the 16 African countries treatment can be discontinued safely.

As with most things epidemiological, discretion should be exercised because it does not necessarily follow that because onchocerciasis can be eliminated from Mali and Senegal it can be eliminated from all other endemic areas in Africa. Many other factors that may differ markedly between regions, such as vector competence, human and vector migration, treatment frequency, duration and compliance (as well as other factors that perhaps have yet to be identified) play into the elimination equation. That said, it is nevertheless inspiring, especially for those communities involved in the trials, when the investigators who conducted the research can state that "not a single skin snip positive person or infected black fly was detected in the test areas." At very least the principle that the vicious circle of infection can be broken has been firmly established.

Guilt By More than Association

There can be little doubt of the importance of the worm-fly connection for river blindness, but a connection of a

Figure 9. Another key to ivermectin's success is its community-based program of distribution and administration. Members of the community are taught to distribute the medication, which needs to be administered orally only twice per year, thus improving the program's success rate and keeping costs down. Here a community member in Nigeria explains the difference between the older 6-milligram and the newer 3-milligram tablets. (Photograph by Andy Crump, courtesy of the WHO/TDR.)

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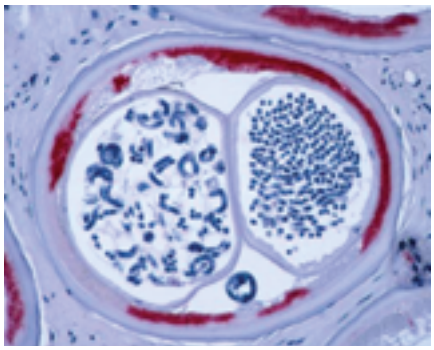

Figure 10. *Wolbachia* (stained red) is an endosymbiotic bacterium of filarial nematodes (and also incidentally arthropods). This bacterium is implicated in eliciting the inflammatory responses underlying onchocerciasis and is being explored as a new target for treatment of the disease. (Image courtesy of Mark Taylor, Anti-Wolbachia Consortium.)

different kind came to the fore in the mid-1970s—one that may in the long run prove to be of comparable, possibly greater, significance therapeutically. This is the symbiotic, strictly endosymbiotic, interaction between filarial nematodes and the bacterium *Wolbachia (see Figure 10)*. Although the exact nature of the interaction between *Wolbachia* and *O. volvulus* is unclear (it is not known if it is strictly mutualistic, parasitic or commensal), in those *Wolbachia*-filarial associations that have been examined in sufficient detail, transmission of the endosymbiont is vertical, from one generation to the next, and does not occur horizontally between individuals within a generation. Because the bacteria have been found in the female reproductive structures in all worms examined, and have yet to be identified in male reproductive structures, transmission is probably through the female germ line.

Wolbachia is of special interest because it is clearly implicated in provoking the inflammatory responses that make filarial diseases such as onchocerciasis so debilitating. *Wolbachia* recruit and activate neutrophils during the infiltration of subcutaneous nodules—a process that is arrested when the bacteria are cleared using the antibiotic doxycycline. In a mouse model of ocular inflammation, increases in stromal thickening and hazing are elicited by *O. volvulus* or other filiarial extracts containing *Wolbachia* but are diminished or abolished when extracts from doxycycline-treated *O. vulvolus* or *Wolbachia*-free filarial species are used. As would be expected if *Wolbachia* is a determinant of the severity of the disease in humans, comparisons reveal significantly higher ratios of *Wolbachia*-to-worm nuclear DNA in the more pernicious ocular disease-causing "savanna" strain of *O. vulvolus* by comparison with the milder "forest" form which is less likely to cause blindness. Moreover, *Wolbachia* behaves as an endosymbiont whose presence is obligatory for completion of certain phases of the worm's life cycle. Antibiotics active against *Wolbachia* interrupt embryogenesis and kill a fraction of the mature worms. In a very recent study deploying doxycycline, a 60 to 70 percent decrease in the number of mature *O. vulvolus* worms was achieved, making this drug the only known macrofilaricide tolerated by the host.

Exciting as these finding are in terms of therapeutic strategies that may come into play in the years to come, the administration of doxycycline, unlike ivermectin, must be repeated daily for a minimum of four to six weeks to be effective, thus limiting its practicality as a mainstay for the majority of mass treatment programs.

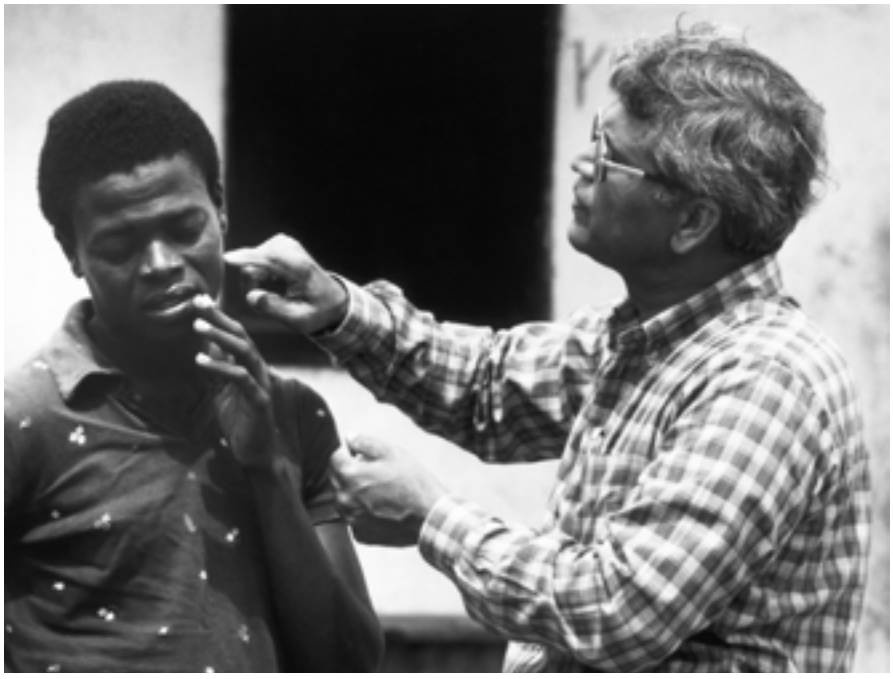

Figure 11. Mohammed Aziz, M.D., Senior Director for Clinical Research at Merck, had previously worked for the WHO in sub-Saharan Africa, which gave him a deep understanding of how to proceed with testing ivermectin (human formulation Mectizan) in the Onchocerciasis Control Programme. Although many people were important to the program's success, Aziz may have been key. Here he examines a 14-year-old boy who has already been blinded by onchocerciasis. This article is dedicated to Mohhamed Aziz. (Photograph courtesy of Merck & Co., Inc.)

Of a Profit a Gift Made

It is remarkable enough that a microorganism, collected from a golf course in Japan more than 35 years ago, spawned a formulation that first entered the market as a veterinary drug and went on to drive one of the most successful public health efforts ever. But it is even more amazing to think that none of this would have been possible if not for the synergistic intersection of disparate biological, medical, pharmaceutical, humanitarian and geopolitical factors—the special properties of the blood-brain barrier that we share with other vertebrates, the extraordinary ease of administration of this drug, the unparalleled philanthropic efforts of a major for-profit drug company, and the inception of community-directed health care as a means of getting what was needed to people inhabiting some of the most inaccessible places on Earth.

Cynics might argue that it was because ivermectin started life as a veterinary medication that this was possible. Merck could afford to underwrite their donation program because of ivermectin's huge profitability in the veterinary sector. Some might even go so far as to say that this is something that might not happen for future

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drugs unless they share, as Kimberly Collins has noted, the "double identity of human therapeutic and profitable veterinary drug." Who knows? What is known, however, is that it did happen, and its benefits remain today and will likely continue to do so for many more years.

From a more idealistic standpoint it is notable that not only Merck but also the Kitasato Institute were in the game from the outset. Founded in 1914 by Shibasaburo Kitasato, the first person to isolate the tetanus bacillus, the Kitasato Institute was based on the principle that "the results of research should be applied as quickly as possible for the protection of people from contagious diseases"—a principle reminiscent of the statement made in 1950 by George W. Merck, the company founder's son, that "medicine is for the people. It is not for the profits. The profits follow, and if we remembered that, they have never failed to appear." True to form, the discoverer of *S. avermectinus* as a source of avermectins, Satoshi □mura, who is currently President Emeritus of the Kitasato Institute, played his part in getting ivermectin to where it is needed most by relinquishing any royalties associated with its use for humanitarian purposes. It is fitting that the Japanese, themselves, are now benefitting from the joint efforts of Merck and the Kitasato Institute. In 2003 ivermectin was registered for the treatment of another nematode infection, strongyloidiasis, which is prevalent in Southeast Asia and is to be found on the Japanese island of Okinawa.

Ivermectin^{+}?

The applications of ivermectin and related compounds do not stop here, however. Formulations built around ivermectin have been adopted for the mass treatment of lymphatic filariasis, second only to malaria and tuberculosis in terms of the DALYs lost each year (5 million!), and other worm infestations such as ascariasis, trichuriasis and enterobiasis.

What is more, the quest for even better avermectin derivatives that might speed up the elimination of river blindness from Africa continues. Only a year ago, on July 1, 2009, the WHO announced the start of a phase III trial that will compare Wyeth Pharmaceuticals' moxidectin, another avermectin, with Merck's ivermectin in Ghana, Liberia and the Democratic Republic of the Congo. If as is hoped moxidectin not only kills microfilaridiae but also kills or sterilizes adult worms, it offers the prospect of breaking the chain of infection within about six years of the start of treatment instead of the minimum of 11 to 15 years required for ivermectin.

Dedication and Acknowledgement

Dedicated to the memory of Mohammed Aziz whose making of 2 + 2 = 4 transformed the lives of millions. P. Roy Vagelos's only regret about the Mectizan program was that Aziz was not to see the fruits of his efforts. He died prematurely just as the first delivery of the drug under the program was being completed. The authors would like to thank James B. ('Sparky') Lok, School of Veterinary Medicine, University of Pennsylvania, for his advice on "things parasitological."

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