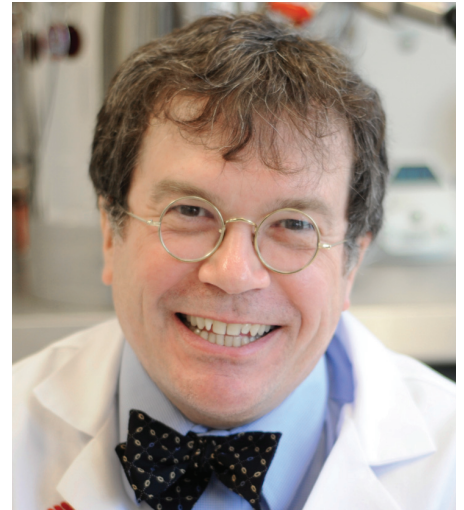


The Medical Biochemistry of Poverty and Neglect

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BEGINNINGS

One of the happiest memories from my early 20s was returning on the train from New York on a winter evening in 1980. Earlier that day, I had just met Professor Anthony Cerami, one of the youngest full professors at Rockefeller University and head of the Laboratory of Medical Biochemistry. I had just interviewed for the MD/PhD biomedical scientist training program at Rockefeller and Cornell Universities and was headed back to New Haven, Connecticut, where I was a Yale undergraduate senior major in molecular biophysics and biochemistry.

My life's ambition was to explore the then emerging field of molecular biology and apply it to the study of medically important parasites. Earlier, a Yale professor I had met at a seminar and reception, the eminent protozoologist, Luigi Provasoli (1908–1992), had informed me that Rockefeller University was expanding its commitment to tropical pathogens and had begun studying them at the cellular, im-

munological, and molecular level. At that time, some of Rockefeller's greatest and most important scientists—including the Nobel Laureate Christian DeDuve, Zanzvil Cohen, William Traeger, and, of course, Tony Cerami—were creating a new field of molecular and immunological parasitology. During my interview, I was captivated by Tony's philosophy of science, which (briefly stated) was to focus on the disease rather than a particular field of scientific inquiry and to use all tools then available to identify a disease target and develop new therapies. I knew shortly after meeting Tony at my MD/PhD interview that he was someone with whom I needed to work and from whom I could learn much. Today, in the little library of my office at Baylor College of Medicine, I still have in my possession the 1978–79 Rockefeller University catalog, which I remember devouring on that train ride back to New Haven. Under the section entitled "Laboratory of Medical Biochemistry," it read: "The objective of the labo-

ratory is to apply the knowledge of chemistry to understand the pathogenesis of diseases and to develop drugs to treat them" (1). I knew even then that this would be my calling and place in the world.

Starting in the summer of 1980, and especially in the first years of the MD/PhD program, I remember how generous Tony was with his time, often meeting me for breakfast in the Rockefeller University cafeteria to kick around new ideas for a doctoral dissertation. Tony liked to push his graduate students to come up with new and innovative projects for their research. I always remember how proud he was of his MD/PhD students and their ability to break new ground and create game-changing paradigms.

My passion for studying human hookworm infection happened around this time and was written about in 2007 in a book by Dr. Gerald W Esch titled *Parasites and Infectious Disease: Discovery by Serendipity and Otherwise* (2). Briefly, while thinking about new projects in Tony's lab, an epiphany came to me when I read a 1962 paper published in *Experimental Parasitology* by a Rockefeller parasitologist named Norman Stoll, who had since retired. The paper had the title "On Endemic Hookworm, Where Do We Stand Today?" (2,3). In that paper, Stoll wrote: "As it was when I first saw it, so it is now, one of the most evil of infections.

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Figure 1. A meeting of the Rockefeller Foundation GND program in Woods Hole during the early 1980s.

Not with dramatic pathology as are filariasis, or schistosomiasis, but with damage silent and insidious. Now that malaria is being pushed back, hookworm remains the great infection of mankind. In my view, it outranks all other worm infections of man combined . . . in its production, frequently unrealized of human misery, debility, and inefficiency in the tropics.”

Despite the fact that hookworm infection was generally acknowledged as a leading cause of global anemia, I can remember going to *Index Medicus*—the PubMed of its day—to discover that almost no molecular biology had been applied to hookworm during the 1970s and into 1980 (2). I thought initiating molecular biology on hookworms could open some interesting doors in the field of molecular parasitology.

Moreover, working on hookworm for my dissertation was a great fit with the Rockefeller Foundation’s new Great Neglected Diseases of Mankind (GND) program, launched in 1977 by Dr. Kenneth Warren (1929–1996) (2,4). Like Tony, Ken was also a scientific and medical visionary, who had the idea to fund world-class scientific units in the United States,

including the Rockefeller’s Laboratory of Medical Biochemistry, and link them to leading overseas laboratories in Oxford, Cairo, Israel (Weizmann Institute), Stockholm, Mexico City and Bangkok to solve neglected disease problems. The emphasis was on parasitic infections that plagued people living in poverty. Ultimately, the activities of these molecular parasitology units would be integrated into a GND network that would meet regularly in Woods Hole or elsewhere (Figure 1) (2,4). In addition to an extraordinary track record of scientific productivity and international scientific collaboration, the GND program and network trained an entire generation of scientists committed to tropical infections, many of whom remain close colleagues.

Tony and I took the approach to try to better understand the hookworm parasite and its relationship with the human host by identifying molecules that adult hookworms release as they feed on human blood. One of those, published in the *Journal of Experimental Medicine*, turned out to be a protease that had the ability to degrade host fibrinogen and other blood products (5). Working daily with Dr. Nguyen Le Trang, a senior re-

search scientist at the Laboratory of Medical Biochemistry, we were able to isolate one of those proteases and even propose the idea that it might be possible to immunize people with such molecules as a potential vaccination strategy (6). Thus, in the true spirit of the Laboratory of Medical Biochemistry, we were able to take a global public health threat that today affects more than 400 million people—roughly one-third of the world’s people who live in extreme poverty—and identify a promising approach to preventing that disease.

HUMAN HOOKWORM VACCINE

After leaving Tony’s lab and completing the MD/PhD program in 1987, I trained in pediatrics and pediatric infectious diseases at Harvard and Yale before becoming a Principal Investigator at Yale. During the decade of the 1990s, we identified and cloned some exciting molecules from larval and adult hookworms, and then in 2000, we received large-scale support from the Bill and Melinda Gates Foundation to develop these molecules as recombinant vaccines for clinical testing. I was entering a new phase of scientific inquiry, which took me from being a conventional laboratory investigator, to heading an organization that could actually turn a discovery in the lab into a bottle of vaccine for clinical testing.

Learning how to actually make vaccines required new skill sets. Coming from Tony’s laboratory, I had a deep appreciation of the importance of not being constrained by one’s scientific background, but instead focusing on the disease and then recruiting talented people, each with unique skills. In this case, that included people with previous experience in the biopharmaceutical industry. I was also fortunate enough to learn from Major General Dr. Philip K Russell (now retired). His mentorship, based on decades of expertise in making vaccines for the U.S. military, was absolutely critical, as were my relationships with my longstanding scientific collaborator and colleague of more than 15 years, Dr. Maria

Elena Bottazzi, and Dr. Bin Zhan, who has been with me for more than 20 years. Other key scientific collaborators in our global Human Hookworm Vaccine Initiative include Drs. Alex Loukas and Mark Pearson (Australia), Rodrigo Correa Oliveira, Coreen Beaumier, Kathryn Jones, Elena Curti, Chris Seid, Jeff Bethony, David Diemert, John Hawdon, Ricardo Fujiwara (Brazil and the United States), and Remko van Leeuwen (Netherlands), in addition to a staff of more than 15 scientists based in Houston, Texas.

I learned quickly that vaccine development and production required going beyond a traditional academic structure and instead required working through a new type of organization and infrastructure that, before the late 1990s, was largely nonexistent. Recognizing the financial challenges of developing products for diseases (such as hookworm infection) that only affect people who live in extreme poverty, the Gates Foundation provided important seed funding to launch more than a dozen so-called product development partnerships (PDPs). PDPs use industry approaches and practices but conduct them through nonprofit organizations. In 2000, Dr. Russell and I created a PDP at the Sabin Vaccine Institute, initially based at George Washington University (Washington, DC) for 10 years, before relocating it in 2011 to the Texas Medical Center (Houston, TX), where it partners with Texas Children's Hospital and Baylor College of Medicine.

The human hookworm vaccine currently under development is comprised of two recombinant antigens, each encoding a hookworm (*Necator americanus*) enzyme used for the parasite to successfully feed on host blood (7). Thus, some 30 years after the concept was proposed, the first human hookworm vaccine is in clinical trials in Brazil, with plans to expand clinical testing to Gabon in sub-Saharan Africa. In addition to the Gates Foundation, the human hookworm vaccine is also supported by the European Union through a new HOOKVAC Con-

sortium, as well as the Dutch Ministry of Foreign Affairs, the Brazilian Ministry of Health, and the Michelson Medical Research Foundation (MMRF). MMRF is also helping us to expand the coverage and disease targets of the hookworm vaccine to include all three major intestinal worm infections—ascariasis, trichuriasis and hookworm infection (8), and possibly schistosomiasis as well (Figure 2) (9).

EXPANDING A PORTFOLIO OF “ANTIPOVERTY VACCINES”

Today, the Sabin Vaccine Institute and Texas Children's Hospital Center is developing a portfolio of vaccines that target parasitic infections beyond hookworm, including new vaccines for schistosomiasis (9), onchocerciasis (10), Chagas disease (11) and leishmaniasis (12) (Table 1). We are also producing a new antiviral vaccine for severe acute respiratory syndrome (SARS) (13), which could also lead to a vaccine for Middle East respiratory syndrome (MERS) (14). Our funding comes from a variety of sources including those mentioned above, as well as the Carlos Slim Health Institute, the U.S. National Institutes of Health and other private donors, including Mort Hyman (the Sabin Vaccine Institute Board Chair) and the Blavatnik Family Foundation.

An important concept for the vaccines we are developing is that many of them target diseases of high morbidity, but not necessarily high mortality. In other words, the neglected tropical diseases that we target are great disablers rather than killers. Moreover, they also hinder economic productivity so that the vaccines we develop could one day become important antipoverty technologies. The concept of antipoverty vaccines means that the impact of our vaccines could extend beyond global public health and improve economic development (15). Additional information reveals that these diseases are also major scourges that affect the health of girls and women living in poverty (16). The fact that we may be producing technologies to ameliorate poverty and im-

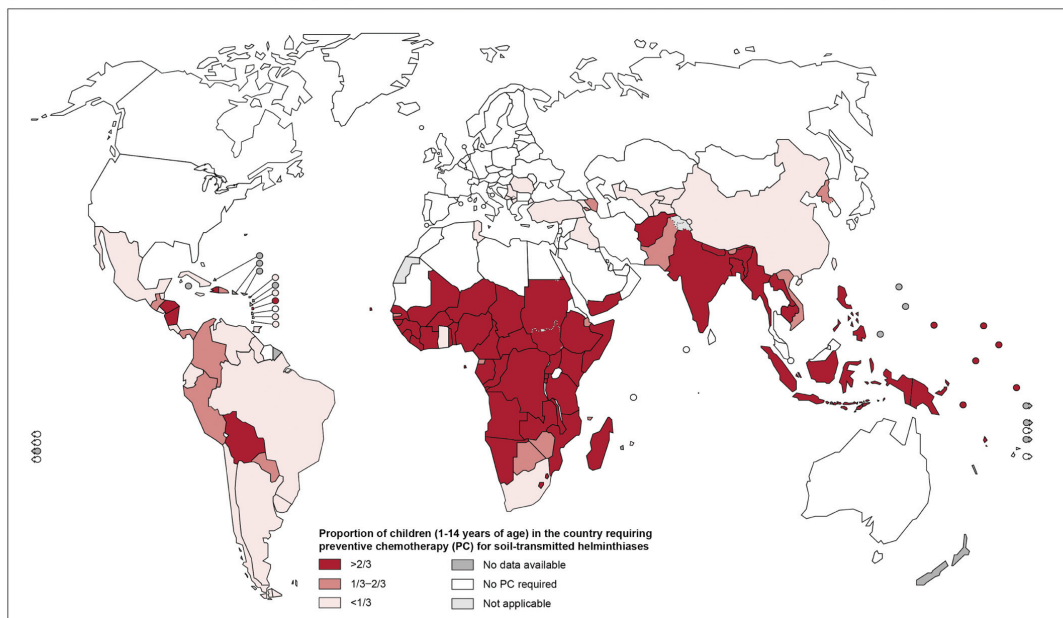
prove women's health has brought me into a fascinating dialogue with experts in economics and other social sciences, policymakers in the U.S. government and internationally, and even activists for the poor and women's rights.

I am especially excited about the prospect of a schistosomiasis vaccine being used as a “backdoor” HIV/AIDS prevention strategy. This research is based on emerging studies on the important role of female genital schistosomiasis as a major cofactor in Africa's AIDS epidemic (16).

RAPID IMPACT

Within the policy framework highlighted above, I also became interested in the concept of treating people's neglected diseases as a fundamental human right. Thus, when the Millennium Development Goals for poverty reduction were launched at the United Nations in 2000, I grew concerned that their major focus was on the “big three” diseases—HIV/AIDS, tuberculosis and malaria—thus leaving out the helminth infections, as well as other related parasitic diseases. Accordingly, beginning in 2005, together with colleagues in the United Kingdom (Professors Alan Fenwick and David Molyneux), the United States (Professor Jeffrey Sachs and Dr. Eric Ottesen) and the World Health Organization (Dr. Lorenzo Savioli), we led global efforts to get 13–14 of these conditions recognized as “neglected tropical diseases” (NTDs), of which at least seven NTDs could be targeted almost simultaneously with low-cost generic drugs or ones donated by the multinational pharmaceutical companies (17–19). Today, it is estimated that up to 1 billion people may have received partial or complete “rapid-impact packages” for their NTDs in low- and middle-income countries, mostly through support from the U.S. Agency for International Development and its United Kingdom counterpart, the British Department for International Development, as well as through other government and private support (including the END [ending neglected diseases] Fund) (20). We also established

Proportion of children (1-14 years of age) in the country requiring preventive chemotherapy (PC) for soil-transmitted helminthiases, worldwide, 2011

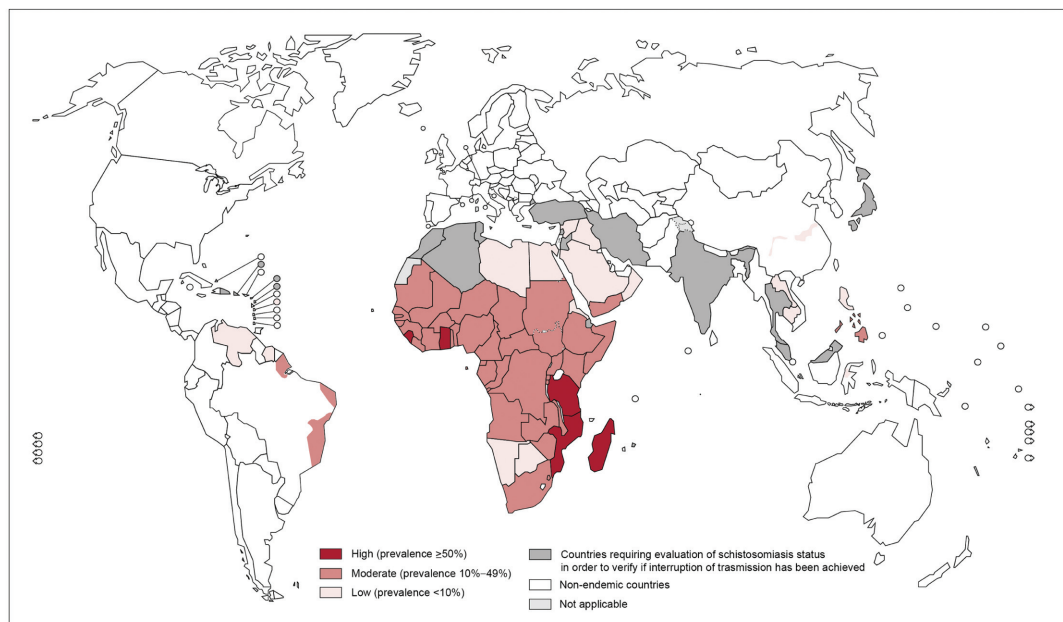


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Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization



Distribution of schistosomiasis, worldwide, 2012



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2013. All rights reserved

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Map Production: Control of Neglected Tropical Diseases (NTD)
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Figure 2. A multivalent vaccine could target all three soil-transmitted helminths and schistosomiasis. Reproduced, with the permission of the publisher, from Global Health Observatory Map Gallery, Geneva, World Health Organization: top panel (28), © 2012 (http://gamapserver.who.int/mapLibrary/Files/Maps/STH_2011_global.png, accessed 2014 Nov 25); bottom panel (29), © 2013 (http://gamapserver.who.int/mapLibrary/Files/Maps/Schistosomiasis_2012.png, accessed 2014 Nov 25).

Table 1. The neglected tropical diseases and other infections targeted by the Sabin Vaccine Institute and Texas Children's Hospital Center for Vaccine Development.

Disease	Estimated number of people infected ^a	Major affected geographic areas	Type of vaccine	Reference
Ascariasis	819 million	Asia, sub-Saharan Africa, Latin America	Preventive	(8)
Trichuriasis	465 million	Asia, sub-Saharan Africa, Latin America	Preventive	(8)
Hookworm infection	440 million	Asia, sub-Saharan Africa, Latin America	Preventive	(7)
Schistosomiasis	252 million	Sub-Saharan Africa, Brazil	Preventive	(9)
Onchocerciasis	30 million	Sub-Saharan Africa	Preventive or therapeutic	(10)
Cutaenous leishmaniasis	10 million	Mesoamerica	Preventive	(12)
Chagas disease	7.5 million	Mesoamerica	Therapeutic	(11)
SARS/MERS	<1,000	Asia/Middle East	Preventive	(13,14)

^a The numbers are from (27).

an alliance of partners—the Global Network for NTDs—to advocate for people who require access to essential NTD medicines, as well as a new open-access journal, *PLOS (Public Library of Science) Neglected Tropical Diseases*.

Expanding the policy framework even further, I have since found that, while sub-Saharan Africa accounts for many of the world's NTDs, somewhat paradoxically, most of the world's NTDs can be found among the poor living in wealthier countries, including the group of 20 (G20) nations (21). This finding challenges our current narratives about global health in regards to diseases in developing countries rather than developed ones. I have given the term “blue marble health” to account for poverty as the overriding determinant, regardless if the NTDs occur in Nigeria, Nicaragua or G20 countries such as Brazil, China, India or Indonesia (21). This finding has important policy implications for large middle-income countries and G20 nations disseminating rapid impact packages among its own populations, as well as for research and development, because it means that to create new health products for NTDs, these nations will need to take greater responsibility for their own NTDs.

A NATIONAL SCHOOL OF TROPICAL MEDICINE IN HOUSTON

With respect to the concept of NTDs disproportionately affecting the poor living in wealthy countries, I have noted a high level of these diseases concentrated

in areas of extreme poverty in the United States, especially the southern United States and the U.S. Gulf Coast (22,23). For instance, today NTDs such as Chagas disease, cysticercosis, dengue fever and toxocariasis can be found in U.S. areas of poverty, where they disproportionately affect people of color (22,23). Some of them may be adversely affecting childhood cognitive development among the poor, thereby reinforcing poverty (24).

In 2011, we relocated the Sabin Vaccine Institute PDP to Houston, in part because Baylor College of Medicine, Texas Children's Hospital and the Texas Medical Center are considered world-class biomedical powerhouses. Indeed, the Texas Medical Center is a medical city of greater than 100,000 employees, considered by many to be the world's largest medical center. But another important reason was to venture into a new and exciting area of indigenous or autochthonous NTDs occurring in the United States. Given that Houston is now the major American gateway city and NTDs are found among its poor, we thought relocation was an opportunity to establish a major tropical medicine school, similar to the ones in the United Kingdom—the London School of Hygiene and Tropical Medicine and the Liverpool School of Tropical Medicine. We currently have a fourfold mission that emphasizes research, including vaccine development and epidemiological studies on NTDs (including NTDs in the United States),

education for physicians and scientists on tropical diseases, a unique tropical medicine clinic for diseases acquired in Houston and abroad, and public policy. The National School of Tropical Medicine currently has 16 core faculty members devoted to one or more of these areas.

FUTURE DIRECTIONS: DISEASE ELIMINATION AND SCIENCE DIPLOMACY

In the coming years, both the Sabin Vaccine Institute and Texas Children's Hospital Center for Vaccine Development and Baylor College of Medicine will face a number of exciting challenges. One of them is the prospect of disease elimination. To date, only smallpox has been eradicated, with guinea worm infection (dracunculiasis) expected to follow soon. However, with expanded use of the rapid impact package, together with new control tools coming online (including hopefully some of our antipoverty vaccines), it might be possible to consider elimination of many of the NTDs discussed here (25). I also believe that how we collaborate and scientifically develop the new antipoverty vaccines may become as important as the vaccines themselves. Over the last decade, there has been a greatly expanded capability of developing country vaccine manufacturers to produce new vaccines, such as the one developed by the Serum Institute of India to prevent meningococcal A infection in Africa (26). International cooperation leading to science

diplomacy or “vaccine diplomacy” could help to ensure that these new health technologies are produced successfully in disease endemic countries and then made available to the people who need NTD products the most. In some cases, Sabin or other PDPs could be required to collaborate with nations that ideologically contrast with the United States yet have vaccine development capabilities (nations such as Cuba or Iran, for instance). It will be interesting to see how vaccine diplomacy can enhance U.S. scientific or foreign policy outreach and lead to the development and global access of new antipoverty vaccines, drugs and diagnostics.

Tony and the Laboratory of Medical Biochemistry at Rockefeller University provided me with an amazing skill set and knowledge base to tackle NTDs on many different levels and dimensions. I am forever grateful to Tony Cerami for his mentorship and wisdom.

DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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