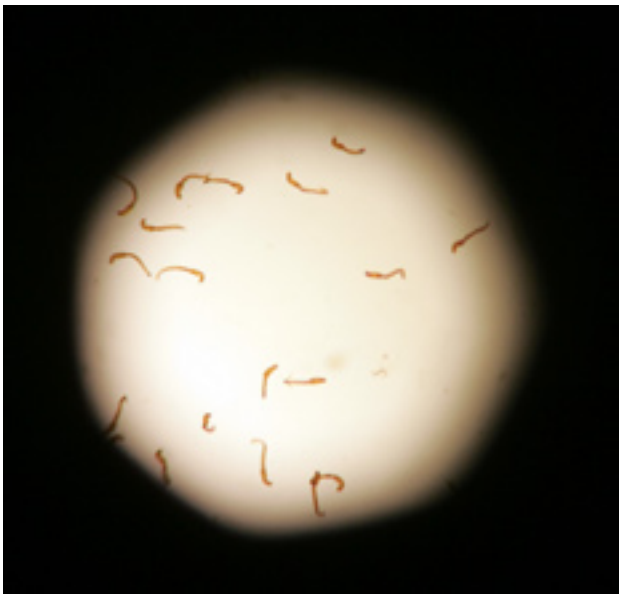
Ending Disease, Ending Poverty

An Interview With Lee Hall and Peter J. Hotez

It is a widely accepted fact that vaccines are among the safest and most cost-effective ways available to prevent disease and improve the overall level of health in a population. That fact balances on two uncertain variables: Has science found a vaccine effective against a given disease? If so, can that vaccine be delivered to an entire vulnerable population?

Global poverty might be significantly reduced if the answers to those two questions were "yes" when it comes to a certain class of ancient diseases. Neglected tropical diseases (NTDs) disproportionately affect people of the poorest nations, while they are almost unheard of in the industrialized world. But there is a growing recognition that an invigorated effort to prevent these diseases and their resulting disability and dysfunction could have an enormous impact on improving the quality of life and alleviating poverty in many nations.

Two experts in this field discussed these developments with Global Issues *managing editor Charlene Porter. Lee Hall, MD, chief of the Parasitology and International Programs Branch at the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, and Peter J. Hotez, MD, PhD, Walter G. Ross Professor and Chair of Microbiology, Immunology, and Tropical Medicine at the George Washington University and Sabin Vaccine Institute, have been watching developments in this area of medicine and health policy.*



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Schistosoma mansoni worms cause schistosomiasis. The parasitic, microscopic worm found in contaminated water penetrates human skin, causing illness that plagues more than 200 million across the globe.

Question: Dr. Hotez, you've referred to these diseases as the "biblical diseases." What does that name suggest about the long history of these ailments and how severely they have plagued the human race?

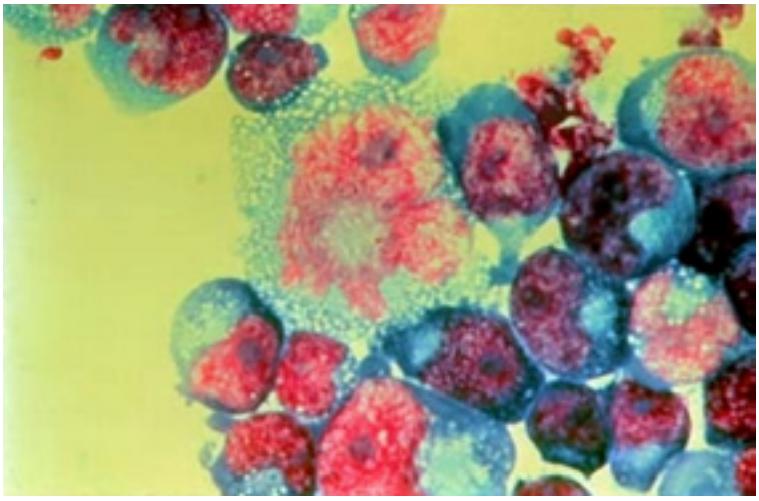
Hotez: The "biblical diseases" refer to a set of tropical diseases that are sometimes known as the neglected tropical diseases. It's a group of primarily 13 infections that are chronic and disabling in their nature, and they occur almost exclusively among the world's poorest people.

Of the 2.7 billion people who live on less than $2 a day, approximately half have one or more of these diseases. Their common features are that they are disabling and have huge impacts on the growth and development of children, on pregnancy and pregnancy outcome, and on worker productivity and capacity. Because of those features and their chronic, disabling nature, they're able to keep the poorest populations mired in poverty. The diseases themselves promote poverty.

These are a group of afflictions that have occurred in humans since ancient times. You can find vivid descriptions of these neglected tropical diseases in ancient texts—in the Bible, the Talmud, the Bhagavad-Gita, the writings of Hippocrates, Egyptian papyrus. They're sometimes referred to as biblical diseases because of their very ancient character.

So when you look at the neglected tropical diseases in aggregate, they're as important as AIDS, they're as important as malaria, and they're as important as tuberculosis. Now we have a great opportunity to do something about them in a very substantive way.

Q: Dr. Hall, why is it that there has not been a great



Courtesy Dr. Tom Folks, NIAID

T-cells are a key component of the immune system, and their function is impaired when infected with HIV virus, as shown here.

deal of attention paid to the development of vaccines for these conditions in the past? And how do you see the situation changing?

Hall: There's been a lot of interest in intervention in these diseases for a long time, but it has waxed and waned. Back in the early part of the 20th century when there were Western military forces deployed in these world regions, there was actually a fair amount of interest. Then as those military forces were pulled back, interest began to wane.

Over the past couple of decades, there has been a complete change in technology, in biotechnology, and how we approach these diseases now. These diseases typically are caused by organisms that are much more complex than many of the viral and bacterial diseases we usually think about. With newer technologies, we're in a position to address the science that underlies many of these diseases and start to develop new interventions.

Another key factor that has changed is our recognition of the interconnectedness of the globe. The areas where these diseases have predominated, as Peter said, were impoverished. They did not have the ability to translate this unmet medical need into some sort of global demand that could be recognized by the pharmaceutical industry and capitalized upon in order to produce new interventions.

That is now changing, and we realize these diseases are a product of poverty and contribute to poverty. As new technologies make new tools available, we can actually break this cycle of disease by bringing these interventions to where they are most needed.

Hotez: One of the great challenges that we face now is that our technology has, in some sense, raced ahead of our ability to distribute products to the people who need them. How do you establish a company that's going to make a product for people who can't afford to pay for the product when they live on less than $2 a day? You can never expect a for-profit organization that's responsible to its shareholders to take the leadership in making these vaccines.

One of the ways that we've been working to overcome that challenge is to work with the National Institutes of Health, work with the Bill and Melinda Gates Foundation, to set up new nonprofit organizations that are actually going to make vaccines. We're looking at a new paradigm where vaccines will not only be made by large pharmaceutical companies, but we'll create a new entity—sometimes known as PDPs or Product Development Partnerships—that's going to take the lead in making vaccines for things like onchocerciasis or schistosomiasis.

That's going to help revolutionize all the wonderful technology that the National Institutes of Health has funded over the past two decades. That's now going to be leveraged into manufacturing this new generation of products.

Q: The AIDS epidemic also brought greater recognition in the donor community about the importance of a population's overall health in overcoming poverty and maintaining national security. Isn't there heightened recognition that other tropical diseases also merit attention on those grounds?

Hotez: Absolutely. There's this very fascinating, but still not completely well-defined relationship between health and security. If you look at the nations of the world that have been engaged in conflict over the last 20 years, the vast majority of them suffer from neglected tropical diseases.

Think of where the hot spots have been over the last two decades. They've been places like Somalia, Sierra Leone, and Liberia. The common feature is that they all suffer from high rates of malaria, neglected tropical diseases, and HIV/AIDS. That may be more than just coincidence. There may be an opportunity now to use health and prevention as a means of reducing conflict and reducing tensions in these most devastated nations.

Q: Dr. Hall, let's explore further the advances in

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A Nicaraguan boy stands near his mother, who was diagnosed as having leishmaniasis cutaneous, also known as mountain leprosy, during a 2005 outbreak northeast of Managua.

biotechnology that are helping you address these diseases. Where is the progress being made?

Hall: Let's start with malaria, for example. We know that the three components necessary to maintain the parasite's life cycle are the parasite, the mosquito vector, and the human host. We now have completely sequenced genomes for all three of them. That allows us to study in a much more rigorous way the whole life cycle at a genomic and a molecular level. We're now beginning to achieve that same level of scientific knowledge with a number of these other diseases.

For example, we now have fully sequenced the genomes of the parasites that cause leishmaniasis, Chagas' disease, and African trypanosomiasis. They are all very closely related, and yet they have certain distinct features. We can do some comparative studies with these now and understand better how the parasites actually function and what determines their ability to cause disease. There are research groups that are sequencing the genome for the vectors that transmit some of these parasites like the species of fly that transmits human African trypanosomiasis, and we'll soon have that information as well.

We have already sequenced the human genome and understand a variety of biochemical pathways in the human host. By comparing genomes and biochemical pathways between the parasite and the human host now, we hope to be able to identify pathways and targets that are unique to the parasite and not shared by the human host. Those unique features then allow us to identify leads for new drugs, diagnostics, and vaccines. I chose three protozoan parasites as examples, but we're rapidly approaching the same situation for diseases caused by parasitic worms, such as filariasis [also known as elephantiasis] and for schistosomiasis.

Q: Dr. Hotez, you mentioned the various partnerships that are taking shape to help achieve those ends. Explain how an increasingly sophisticated pharmaceutical industry in the developing world is also contributing.

Hotez: One of the things that is happening along with the Product Development Partnerships is that the partnerships will actually include what we call public sector vaccine manufacturers in developing countries. I'll give you an example. I head an organization called the Human Hookworm Vaccine Initiative, which is part of our Global

Network for Neglected Tropical Disease Control *[http://www.GNNTDC.org]*, and the Human Hookworm Vaccine Initiative is based at the Sabin Vaccine Institute. It's a Product Development Partnership with the goal of making a new recombinant antigen vaccine for human hookworm infection, a disease of 576 million people in the developing world.

In Washington, D.C., we've been able to make pilot-scale amounts of vaccine for early-phase clinical testing, which is underway in Brazil. The problem is the amount we can make in our laboratories through the PDP here in Washington is limited, and certainly not enough to vaccinate all of Brazil or all of the Americas.

So we've now partnered with an organization known as Instituto Butantan, which makes 86 percent of the vaccines for Brazil, including their own recombinant hepatitis B vaccine. So now our scientists are working with this public sector vaccine manufacturer in Brazil in a collaborative manner. They're coming up here; we're going down there and transferring our technology so that they can do the scale of production for all of the Americas. We look forward to the opportunity of working with public sector vaccine manufacturers in this group of low-income and middle-income countries that also have endemic tropical diseases and have great pockets of poverty, and yet have somehow managed to overcome their poverty and achieve a certain level of innovation that they can actually make their own vaccines. We call these types of countries IDCs, Innovative Developing Countries, low- and middle-income countries that have gone that next step to take on biotechnology and do it in a very sophisticated way.

They include countries such as Brazil, China, Indonesia, India, Thailand, and Malaysia, and we think that these countries and their public sector vaccine manufacturers could lead the way in making a whole new generation of products for the developing world.

Q: That trend has been driven to a degree by the AIDS epidemic in these countries. Dr. Hall, what are the recent findings about the biologic interrelation of these diseases with AIDS?

Hall: There are lots of studies going on to try to define that relationship and see how these diseases might affect each other, whether HIV makes them worse, whether these diseases actually contribute to making HIV worse. We've not defined that relationship as closely as we would like, but our knowledge base in this area is rapidly expanding.

Hotez: Two very exciting papers were published in 2006 in *AIDS*, one of the leading HIV/AIDS journals. One of them looked at women living in Zimbabwe with schistosomiasis, a worm infection, and showed that a large percentage of those women—up to 75 percent—have lesions resulting from the presence of these parasitic

A Quick Strike Against Disease

The Global Network for Neglected Tropical Disease Control is an alliance of the major public-private partnerships devoted to the control of the most prevalent neglected tropical diseases (NTDs) worldwide. The Global Network is advancing a plan to control these diseases through the integrated administration of the "rapid-impact package," so named because the drugs can be quickly deployed with rapid reductions in morbidity and disability, improvement in well-being, and, in some cases, interruption of transmission. The package is comprised of a combination of up to four drugs, all of which have been in use, tested, deployed and utilized by millions for more than a decade. Combining these drugs in an integrated health care package is a new approach that deemphasizes specific tropical diseases and, instead, focuses on neglected populations with multiple tropical infections. Worldwide, there are a total of 56 countries with five or more endemic NTDs. Most of these are in sub-Saharan Africa where the rapid-impact package will be deployed extensively.

This packaging approach has been successful with early childhood vaccines. By packaging a combination of vaccines and inoculating infants against different diseases at the same time, the costs are diminished and the benefits are enhanced.

Identification of the first countries to be included in the Global Network's rapid-impact treatment scheme is currently underway.

The Global Network is based in Washington, D.C. ■

worms. As a consequence, they have a threefold increased risk of acquiring HIV.

So what if you could be giving drugs for parasitic worm infections at the same time you're giving antiretroviral drugs for HIV/AIDS? The great thing about these parasitic worm drugs is they're cheap, less than 20 cents a dose, and could be given to large populations fairly easily. That's why we set up this Global Network for Neglected Tropical Disease Control: to find a way to administer these antiparasitic drugs to large populations. We think treating these worm infections throughout sub-Saharan Africa will clearly have a huge benefit in terms of health impact because of the diseases that the worms cause, but a secondary impact could also result from actually reducing the transmission of HIV/AIDS.

By adding an additional 20, 30, 40, or 50 cents to the hundreds of dollars spent each year per person on antiretrovirals in large AIDS treatment programs such as the President's Emergency Program for AIDS Relief, you could possibly double your impact. But the studies are still at an early stage.

Q: Dr. Hall, Dr. Hotez has mentioned the drugs that can be very cheap and available to treat many of these conditions; but why is it that vaccines still seem preferable even when drugs would be available?

Hall: There are a number of reasons. First of all, for some diseases, it's going to be very hard to develop vaccines even with a great deal of technology. Parasites themselves are fantastic immunologists and have actually developed ways to escape the immune response, and they've been doing this longer than we have thought about it, so it's a real challenge.

In other situations, where we can develop vaccines, we want to develop them because we would like to prevent disease, rather than treat it. The pathology of these diseases is really cumulative as it occurs over time, whether it's schistosomiasis or filariasis or some of these other diseases. There's a gradual build up of disease, and treatments of an advanced disease aren't going to necessarily reverse that pathology.

We'd like to catch people early on and prevent disease, so they don't develop these diseases.

Hotez: I agree, and at the Global Network, what we think is going to be the important way to move forward on tropical diseases is not looking at the choice of either drugs or vaccines, but in fact, the two need to be linked in a tightly coordinated, controlled program.

Q: To conclude then, is there a single development in this field that you think is the most promising for short-term delivery?

Hall: One has to look at research as a long-term endeavor. The pace of research is accelerating as a result of success with genome sequencing and a variety of post-genomics activities. That's really where we're going to see a lot of progress in the near future.

In addition to that, a number of candidate vaccines have already entered clinical development. Peter has mentioned the Hookworm Vaccine Initiative. There are also vaccines that are in development now for schistosomiasis and for leishmaniasis as well. Those are very exciting.

We're at a fantastic point in the research where activities are moving forward in this area, and they're beginning to accelerate because of the technology.

Hotez: We have a great opportunity now to control morbidity [the incidence of disease] from the seven most prevalent neglected tropical diseases—ascariasis, hookworm, trichiuriasis, schistosomiasis, lymphatic filariasis, onchocerciasis, and trachoma—through a program of integrated control that employs donated and generic drugs. Better controlling those seven diseases could make a huge impact on these co-infections that occur among the very poorest populations of sub-Saharan Africa, Southeast Asia, and the Americas. We're going to see dramatic gains in health, education, and economic development and, possibly, even biosecurity as a consequence of widespread use of these drugs.

One of our projects at the Global Network on NTD Control is the distribution of a rapid-impact package of drugs. With this package of drugs, which are proven, safe, inexpensive treatments for these conditions, we could eventually either reduce the morbidity or control the seven most prevalent neglected tropical diseases. In addition, for two of the NTDs—lymphatic filariasis and trachoma—we could even interrupt their transmission and eliminate them as public health problems.

So while we're doing widespread administration of the rapid-impact package, we want to step up our research and development efforts to focus in on the development of new vaccines for the other diseases that we want to eliminate —hookworm, schistosomiasis, leishmaniasis, and Buruli ulcer—and some of these other very important neglected tropical diseases. ■

The opinions expressed in this interview do not necessarily reflect the views or policies of the U.S. government.