I want to thank Professor Colley [phonetic] and Professor Thomas for inviting me to this series. What's being assembled here in global health is very impressive and it's a small but very determined group of individuals. Actually, not so small considering that the number of people who work on parasitic diseases and diseases of developing countries is dwindling in American universities and Professor Colley and Thomas have assembled a very strong team here and this has become -- this university is really being put on the map in terms of an important force in the area of global health. And I would like to thank Professors Colley and Thomas for two things in particular in addition to them inviting me here.

One, I have to say this is probably one of the most beautiful venues I've ever given a lecture in, this is just a gorgeous place to speak and I'm very honored to be here for that and secondly, is I don't know how they got so many people to hear one of my lectures. The low point of my career is when I went to give a talk at the University of Pittsburgh and the only person who showed up was the person who invited me to give the talk. You see hookworm is very much a neglected disease and, of course,
who cares about hookworm in the United States. So I'm very used to speaking to crowds of five or six people, so I'm really very grateful that Professor Colley, Professor Thomas stood out there with their van on College Avenue and Shanghaied people into the back of the van and dropped them here and it's very nice of you to do that. I was asked to make my remarks somewhat personal and a little bit autobiographical to give you a flavor of how someone like myself who grew up in parts of Connecticut and should have been dreaming either of pitching for the Yankees or pitching for the Red Sox because you're halfway in between the two cities, would want to come to work on something like hookworm, and I don't quite know all the reasons for it but I'm probably one of the more goal directed people you'll meet. When I was 13, 14 years old, I had a copy of Manson's Tropical Disease on my night table and even knew back then that I wanted to study parasitology and parasitic disease. Although I probably couldn't have predicted it would have taken the form that it did. So I can say that while, my friends all wanted to pitch for the Yankees or the Red Sox, I wanted to study tropical diseases. So I'm a very happy individual because

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for me this is just like pitching -- pitching for the Yankees in this venue is particularly
gratifying. So along that autobiographical vein I want to take you here first and this is really
where I got started working on hookworm. It's a place called the Rockefeller University and many people in Manhattan are not even aware that this university exists. It's on the East Side, I don't have a pointer here but that body of water that you're looking at is the East River with Queens on the other side. So, if you know anything about Manhattan it goes Madison Avenue, then Park Avenue, Lexington then Third, Second, First and there's one additional avenue after you get to First and that's York Avenue and this is located right along York Avenue and it's this beautiful swatch of green, green oasis in the middle of a lot of concrete. And it's a very tiny university that has a very small graduate program for people like myself who have copies of Manson's Tropical Disease at their night table, who come into school more or less having an idea of what I wanted to do. I didn't know exactly what I wanted to do but
I knew I wanted to study parasitic diseases and they bought into the idea that they would accept me and one of the great things about this place, in addition to being so beautiful, is that they give you a full scholarship, a full ride to medical school and they pay your stipend so that you don’t come out of medical school with an enormous debt and force you to go into intervention and radiology maybe you can go into something like parasitic diseases. Well, that’s the upside of the place, the downside of the place is extremely pretentious. It’s one of the most pretentious places you’ll ever be and justifiably so. What I’m showing you here is the list of the Nobel Laureates that have gotten their Nobel Prize at this very small and tiny university. So it probably has the highest Nobel Prize to person ratio of any university in the United States and arguably in the world and so, when you come there as a student, the expectations are very high and they look you straight in the eye and say, Peter, we expect you to come out of this university and do something extraordinary. Now the truth is most people my age who come out of the university not
necessarily do something extraordinary but they wind up working on what their professor is working on like any other PhD -- pretty much any other PhD student with a lot of pretense to go along with it. But I actually took them literally and said, Okay. I have to do something extraordinary. And so what I would do is I would sit in the Rockefeller Library my first year at this university, and the Rockefeller Library is very pretty. It's right along the water and you're looking out at the water having great thoughts watching the ships go by and it was during that first year in 1980 that I read the following statement -- I was looking through some of the archives of the Rockefeller University and journals in the university library and I came across this statement by a man whose name is Norman Stoll and Stoll was the last person to study hookworms in terms of a public health problem. He did most of his work in the 30's, 40's, and 50's when he had more or less retired and this is a speech he gave upon his retirement from the Rockefeller University, at that time it was called the Rockefeller Institute for Medical Research.
and he published this and it got --

it was a speech that was given as part of the New York Academy of Tropical Medicine as it was called then and they published it in this journal of Experimental Parasitology. And I'm sorry the pointer is not working, so you'll just have to read along with me.

And what he wrote the following statements which was something that still resonates with me today and what he said was: As it was when I first saw it, so it is now one of the most evil of infections, referring to hookworm, not with dramatic pathology as our filariasis or schistosomiasis which are other tropical diseases, but with damage, silent and insidious. Now that malaria is being pushed back -- because back then they actually thought they were on the verge of eradicating malaria but he got that part wrong. Now that malaria is being pushed back, hookworm remains the great infection of mankind. In my view it outranks all other worm infections of mankind combined in its production, frequently unrealized, of human misery, debility and inefficiency in the tropics. So right then and there I had my epiphany in the Rockefeller University library and I went around to the various
And said, I'm going to work on hookworm. And the response was, hook what?

Well, why are you going to do that?

Because it's the great infection of mankind in its production frequently unrealized of human misery, debility and inefficiency in the tropics.

And they said, well, we never heard of it. And this was very disappointing for me because most of the professors that I went to would not allow me to work on hookworm, and I will never forget it was at a parasitology meeting -- it was a Gordon Conference held in New Hampshire. This was about 1981 it was one of the first Gordon Conferences on Parasitic Diseases because this was the first time that people were really starting to look very seriously at applying molecular techniques to the study of parasitic diseases, and I remember one of the professors at Rockefeller was there and there were two men shouting at him and one was a man named John Davis, who is now an Emeritus Professor of Tropical Medicine at Harvard. Another one was the late Ken
Warren who was working at the Rockefeller Foundation and he led a program that was called the Great Neglected Diseases of mankind. And I'll never forget John Davis shouting at my -- who ultimately became my thesis advisor saying, if he wants to work on hookworm, I let him work on hookworm and that's when it was decided at this Gordon Conference and then that's what I did and that's how we got started. So what is it. And this, this was a tough road to hoe because hookworms are organisms which are difficult to work with in the laboratory. You can't get much in the way of the organisms to work with, so it's hard to do biochemistry on them. It's hard to purify proteins from them, there are no genetics that one can do on hookworms. It's impossible to do cell biology, so what I used to tell people other than the fact that you can't do biochemistry, cell biology or genetics on them, they're really great organisms to work with and thus the reason why somebody would work on something like this is, indeed, their enormous burden of disease in the developing world and at the time we didn't have club.med or any of the computer searches.
that we have available today
to do look<br/>
up existing literature on a subject.<br/>
Back then it was something
called Index<br/>
Medicus and you would go<br/>
to these big volumes off the
library shelf in<br/>
1980 and look up all the current literature<br/>
on hookworms and no
surprise<br/>
there was really nothing on it.<br/>
So here was the great
infection of mankind<br/>
and there was essentially no work being done<br/>
at the biochemical and
molecular level.<br/>
So and, since I was told I
had to<br/>
do something original and great,<br/>
I thought well maybe this is
the one.<br/>
So let me tell you a little
bit about that<br/>
story and a little bit about what hookworms are<br/>
and why we think they're so
important especially in the developing world.<br/>
So first of all hookworm, what is it?<br/>
It's a parasitic worm
infection.<br/>
In fact, it's a particular
type of parasitic<br/>
worm called a nematode spelled, n-e-m-a-t-o-d-e.<br/>
and together with two other parasitic
infections these comprise what we now call the<br/>
soil-transmitted helminth infections or the soil-transmitted helminthiasis.<br/>
They're so-called because they have environmental stages that live<br/>in the moist warm soil of the
developing world and where they're practically ubiquitous.

So what I'm showing you on the top are the three major soil transmitted helminth infections of humans and those are ascariasis, the large common roundworm, trichuriasis, and hookworms which are hookworms. And look at those numbers, so what is it mean that there are 1.2 billion people in the world with ascariasis? How many people are in the world? About six and change maybe 6.4, so what I'm telling you is that about a fifth or a sixth of the world's population are infected with these parasitic worms, an enormous number. I often like to say that if Carl Sagan didn't become an astronomer and go into cosmic science and decided to become a biomedical scientist this is what he would work on because what else could he talk about billions and billions being infected. So these are arguably the most common infectious agents of humankind. So I want to start out this evening giving you a sense of what it means to have a billion people infected with these worms, and we're going to go look at these kids who are a bunch of kids who, they do look a little scruffy perhaps not too
ill until we realize that they are all stunted.
Their weight, they're all stunted; their heights and they're not growing and they do poorly on tests of IQ and cognition. These are kids that are growing up along the coffee plantations, the coffee bean goods in this case in southwestern Guatemala in this particular village of Pachalum. They're poor kids living in poor rural areas of Guatemala. Now there's an increasing body of evidence now indicates that the reason why these kids are stunted for height and weight and they do poorly on tests of IQ and tests of cognition is because they have a belly full of one or more of those three parasitic worms, ascariasis or trichuriasis or hookworm. In fact, there's an old term that Harold Brown, professor of parasitology at Columbia coined called the unholy trinity to remark on the fact that it was very common, if you have a child infected with one of these worms, they were infected sometimes with two or all three. And so how do we know that they're infected with the worms? Well, we take advantage of the fact that, when people have these parasitic worms,
In their intestinal tract, they’re male and female worms and they mate and they produce eggs. And so one can establish a diagnosis of the unholy trinity by looking in their stool, looking in their feces under a microscope and looking for the characteristic egg, each of the worm produces an egg that has a characteristic morphology. So we’re going to do that now in this village of Pachalum in Guatemala and here you see age class on the X-axis you see 0 to 3, 4 to 7, 8 to 12, and on the Y-axis you see prevalent the percent -- percentage of these kids that are infected with either ascariasis, in the white, trichuriasis, in the dark green, and hookworm in the, I guess that’s a teal color. So what percentage of the kids in this village harbor ascariasis worms? It means that they all do, right. 80, 90 close to 100 percent. Almost as many harbor trichuriasis and almost again as many harbor hookworm. Now what we’re going to do is we’re going to go to the next village over from Pachalum in Guatemala, I don’t even know what the name is, but I can promise you that this is exactly what
In fact, you go to any rural village in Guatemala and you will see the same recurring theme that there are 100 percent of the kids infected with ascariasis, almost as many again with trichuriasis, the whipworm, almost as many again with hookworm. In fact, you go to any rural village in Central America, in Nicaragua, Honduras, Panama this is what you'll find. You go to any rural village in tropical regions of the Americas: Venezuela, Brazil, Peru this is what you'll find. If you do this exercise in southeast Asia, in Thailand, Vietnam, Laos, Cambodia, South China, in sub-Saharan Africa where there's probably more infections than anywhere else, this is what you'll find. So then you start getting the sense that, gee, maybe there really could be a billion people in the world with this many parasites. Now we do a fair amount of work in China and my Chinese colleagues have completed a study in the early 1990's that I like to think all of the Chinese could do which is they needed to know who had parasites in their country and they set out and collected fecal exams on 1,477,742 individuals, one of the
largest health surveys ever done. They found 45 percent of their population infected with ascariasis.

Well, what's the population of China? It's at least a billion, right, 1.2 billion at the time. So we're talking about almost half a billion people infected with ascariasis just in China alone. And if you add India to that, you almost get up to be a billion right then and there, so this gives you a sense of the enormous numbers of people infected. So the first part of this talk: It's a very wormy world out there. And, in fact, Norman Stoll once wrote a paper called: It's a Wormy World and he's right. The next point is there's not only a lot of worm infections in the world but they're a particular problem among children and why is that? I don't know how well that shows up in the back with the color scheme and the lights, but what it shows is on the X-axis, age, and the Y-axis, number of worms per individual. This is a composite study done by a number of groups including ours but there's many other groups that have been able to replicate this pattern, and it shows that there is a period in one's life when we're
wormier than others.

Because remember these worms are not like other infectious agents you hear about.

They're not like bacteria or protozoa that are multiplying inside your body, in other words.

The more worms you have the sicker you get because they're animals inside an animal, animals inside people.

So the worms are mating and producing eggs, but they're not doubling in their numbers.

And so what this is showing is that for reasons which are still not entirely clear because these parasites are so neglected in terms of their study that there is a peak period of worminess in the life of an individual.

And when is that peak period of worminess? Starts going up around age 3 or 4 and then continues until around age 15, so you have a situation now where you have children, essentially, school age children.

Age 5 to 15 is when they're running around with their highest worm burden and the fact that they're in school is very important because, as I said, worms are stunting height, they're stunting weight and they're stunting your ability to learn in school by suppressing IQ and suppressing cognition.

So this is why even though worm infections are a particular problem among school age children, they're...
and so they're not only a medical problem but they're also an educational problem. So what does it mean to have these high worm burdens as we stated, large numbers of worms in children as opposed to other populations?

And to give you a sense of that, let's go here. What I'm showing you are some pictures of some kids, this is a child from Haiti on the left, and a child who -- that one of my students took of a kid in Paraguay on the right. And what do you notice about them? They have a kind of big distended abdomen, don't they? In fact, if you were to run your hand over the surface of their abdomen, you would actually palpate the outline of worms because there are so many worms. Now how do we know that? Well, we actually have drugs that are available to expel the worms and the two major drugs used are known benzimidazole anthelmintics, one's called mebendazole and the other one is called albendazole. And what we're going to do is we're going to take this little girl on the right here and give her one of these drugs, and these are the worms from that one child. Those enormous ascariasis
and it's pretty obvious. That's actually my student holding up the worms with a big smile on her face. I cut off her smile, being that she has a nice smile it seemed inappropriate. She was so delighted to see all these worms out, so it's pretty obvious why this child is going to get into trouble, right, these worms are going to get entangled in a Medusa-like writhing mass, you know, cause acute intestinal obstruction. So, if you go visit a hospital in a developing country, it's very common to see a child who's recently been operated on for this acute intestinal obstruction. They're going to wander. They'll sometimes wander into the pancreas and into the liver to cause a number of problems there. They will sometimes migrate up or down out the anus, and it's obviously very concerning to parents. When they see something like that, but it's clear that having these kinds of worms are going to get you into serious trouble because, if for no other reason then you're feeding a child in a developing child. You're essentially feeding the worms first before you're feeding the child. So this is a very
dramatic consequence of worminess in school-age children in a developing country. But there's something more subtle that I think is even -- something more subtle but it's something which I think is very important. What I'm showing you here on the left is what looks like a growth chart that you might see in any pediatrician's office. So those of you who have taken your kids to the pediatrician, you've seen him or her mark down your child's weight on the growth chart and it usually goes along with, I'm sorry, I don't have the pointer here, but it goes along with different percentiles. You see age on the X-axis, in terms of months and weight, on the Y-axis, in terms of weight gain, and you look for children to grow along different percentiles. This is, you see the third percentile, the 10th, the 25th, the 50th, the 70th all the way up to the 97th percentile. But now I'm showing you a child who's plodding along in the red there and what's happened to this child is his growth is flat. He's not growing at all until we intervene. And now we're going to intervene by giving a dose of drugs to expel the worms.
we give that dose of drugs? <br/>
<time begin="00:23:05.85"/>You see this very impressive catch-up growth, <br/>
<time begin="00:23:11.80"/>So what I like to tell my medical students who are interested in the endocrine system, <br/>
<time begin="00:23:16.25"/>Here's the world's leading endocrinopathy, it's parasitic worms. <br/>
<time begin="00:23:19.79"/>Here's the world's leading cause of growth suppression. <br/>
<time begin="00:23:23.02"/>What's the mechanism? <br/>
<time begin="00:23:23.87"/>How do worms suppress growth? <br/>
<time begin="00:23:25.99"/>Anybody have an idea? <br/>
<time begin="00:23:27.99"/>So intuitively you would guess right, intuitively you would guess there's some type of competition between parasite and host for nutrients. <br/>
<time begin="00:23:41.80"/>But the sad truth is nobody knows, why? <br/>
<time begin="00:23:45.41"/>Because nobody studies this. So here's the world's leading cause of growth retardation in the world and you cannot find a single paper in the scientific literature on the mechanism by which worms stunt growth, why is that? <br/>
<time begin="00:23:59.46"/>Well, the problem is who funds this kind of research? <br/>
<time begin="00:24:02.76"/>This is not a problem in the United States. <br/>
<time begin="00:24:12.93"/>It's the leading cause of growth retardation not in Georgia, but it's the leading cause of growth retardation perhaps...
in Central America and there are no agencies that are specifically directed to funding basic mechanism problems in the developing world.

There's a term that those of you who attended Victoria Hale's talk she probably used the term, the 10/90 gap to refer to the fact that less than ten percent of the world's resources go for the research on problems that afflict 90 percent of the diseases in the world and those diseases are those represented by those in developing countries.

It's astonishing, the world's leading cause of growth retardation and there's no scientific literature on the topic.

Now as to that I'm going to direct you to the right-hand panel, this issue of Parasitology Today which I know most of you get at home and this is to show that these worms not only suppress growth and physical development but they also inhibit the ability of kids to learn.

So there are good studies to show that the more worms you have in your intestine, the lower your IQ is. So they have a direct, there's some type of almost direct effect of impairing IQ and tests of school performance. So just like worms are a leading cause,
They're also the leading cause of more psychiatric disturbance in the developing world.

What's the mechanism? Who knows. But a very important problem and, so this is one of the reasons why these worm infections are so important is because their ability to cause physical and intellectual growth retardation and physical and intellectual development. Now the problem though is -- as important as that is, the worms generally speaking are not killing. So you might have heard about malaria as one of the leading killers of children in the world, 2 million deaths annually, but what worms are doing is something a little bit different. They're not so much killing kids in the developing world, there's about 100,000 deaths a year from these types of parasitic worms, a few more from the kinds of worms that Dan Colley studies, schistosomiasis which causes about 200 maybe 1,000 deaths per year, but rather they're destroying quality of life. And we've only developed a metric for measuring that over the last two decades and the metric that we use to focus on the ability of something to cause disease and cause disability but not...
necessarily death is a metric known as the DALY, it stands for the Disability Adjusted Life Year. It refers to the number of life years lost either from premature death, something that might kill you in childhood, or premature disability such as worms. And when we use this metric of DALYs, what we find is that these worm infections are enormously important. So not using deaths but using DALYs look at where helminth infections stack up compared to what we sometimes refer to as the big three, H.I.V. AIDS, TB or malaria. So helminth infections are right up there, with hookworm infections among the most important of all the different helminths. The problem for someone like myself is we have Bono beating the drum about AIDS, malaria and TB, you have Angelina Jolie beating her drum about AIDS, malaria and TB but we don't have myself who gets about four people coming to a lecture, and Dan Colley who does a little better gets about ten people coming to his lecture to talk about parasitic worms. And so there's this great disparity in advocacy, but having said that the World Health Organization is very effective in trying to do their best to persuade
ministers of health throughout the developing world to adopt procedures by which children, especially school-age children, would start receiving what we call anthelmintic drugs on a large scale. And in 2001 at the 54th World Health Assembly, see the World Health Assemblies are where major health decisions are made, are actually passed on an international scale, the following resolution was proposed and it was known as Resolution 54.19. With a goal of attaining a minimum target of regular administration of anthelmintic, which was comprised of a benzimidazole anthelmintic, either albendazole or mebendazole, the one that put all those worms in the pan that you just saw, for the soil-transmitted helminths, plus a second drug known as praziquantel which treats another very important helminth infection known as schistosomiasis which Professor Colley studies, to at least 75 percent and up to 100 percent of all school-age children at risk for morbidity by the year 2010. That's a big program, in fact, the estimates are we're talking about the regular treatment of 500 million school children on an annual basis. So, if implemented, this
would become one of the largest health programs ever attempted but for a good reason because of the enormous impact that these worms have on child health in terms of physical growth as well as education vis-a-vis intellectual development. So this was a very exciting resolution, however, it's not as rosy as you might think and the reason we're particularly concerned about it has to do with this. This is a graph of a study that Marco Albonico and his colleagues at WHO did in Pemba Island off the coast of Tanzania and what I'm showing you on the Y-axis is our measurement of number of worms per individual and on the X-axis is days. And what they did is they went into two villages, they went into Village A or Village B or the red village or the blue village and they went in armed with an anthelmitic drug, in this case mebendazole. Now it turns out mebendazole doesn't always work as well as advertised. In some regions the efficacy, the ability of them to cure these worm infections, is only around 21 percent but in this case they did pretty well, and they brought the number of worms on the left-hand side of that graph pretty much down close to zero. And now what they're going
to, what these guys did in Pemba Island is they walked away after anthelmitic deworming. Deworming is a term that we sometimes use to deal with these worms. And now we're going to walk away for 120 to 180 days, four to six months.

What's happened? They're back. They came back because one of the unusual features about these worms is they do not have the ability to stimulate naturally protective immunity. And so what the studies show is that and this is particularly true of all the worms that we're talking about today but it's particularly important for hookworm. This means that hookworm infected patients will reacquire hookworms to pretreatment levels within four to twelve months following a dose of anthelmitic chemotherapy. Practically speaking, unless you're prepared to go back into these villages with your dose of anthelmitic drugs every four to six months for the life of this child, or for the time these children are in school, the kids are going to remain wormy because the worms come right back. So is one of the reasons
why even though we have drugs available to deworm, they're often not effective for purposes of public health control because of this unique feature of the worms to come back. And now there's good data to indicate that the efficacy of these BZAs, these benzimidazoles, as I said, this is point number 3, will diminish with increasing use. In other words, what starts to happen, if you keep on repeating this exercise over and over again, the drugs stop working as well as they used to. And there is concern that this might be the beginning of what we're seeing as anthelmitic drug resistance that the worms are becoming resistant to the drugs and it turns out it only takes a point mutation in one of the nematode tubular alleles to confer this type of resistance. Professor Kaplan in the vet school is actually studying this phenomena not for human worms but for veterinary worms but it's a similar type of phenomena. So this business of the worms coming back and the fact that now maybe we're seeing the tip of resistance occurring makes us think well we might have to come up with something better, that in the long run for these drugs. And this is particularly true for hookworm and let me tell you a few specifics about hookworm before we
go<br/>
<time begin="00:33:39.89"/><clear/>into what we're actually going to propose to do about it. <br/>
<time begin="00:33:42.84"/><clear/>So I don't know how well it shows up here. <br/>
<time begin="00:33:44.49"/><clear/>Is there any way we can get the lights down just for this one slide? <br/>
<time begin="00:33:47.49"/><clear/>If it's not possible, don't sweat it. <br/>
<time begin="00:33:50.91"/><clear/>But what I'm showing you is a scanning electron micrograph of a hookworm on the left-hand side <br/>
<time begin="00:33:58.70"/><clear/>and it's armed with these very ferocious looking teeth or cutting plates that allows it to adhere <br/>
<time begin="00:34:05.93"/><clear/>to the inside layer of the small intestine. <br/>
<time begin="00:34:09.34"/><clear/>And in the middle panel what I'm showing you is a longitudinal section <br/>
<time begin="00:34:13.79"/><clear/>of hookworm intestine with the worm attached <br/>
<time begin="00:34:19.87"/><clear/>and you can see how deeply embedded the worm is <br/>
<time begin="00:34:42.46"/><clear/>so that a person who has large numbers of hookworms is essentially losing blood. <br/>
<time begin="00:34:47.02"/><clear/>He's hemorrhaging through his
intestinal<br/>

tract and the result is<br/>

that an individual who

is<br/>

so affected with large numbers<br/>

of hookworm is losing enough

blood to cause<br/>

iron loss sufficient to cause iron deficiency<br/>

because blood is rich in iron

and protein<br/>

loss because blood is very rich in protein.<br/>

So it's causing iron deficiency and protein<br/>

malnutrition and here's a major cause of it.<br/>

So 40 hookworms will cause about 1.0 mLs of<br/>

blood loss per day so here is a kid walking<br/>

around in developing country with 40 worms loosing 1.0 mLs of blood per day, <br/>

may not seem like a huge amount but<br/>

it's about .6 milligrams of iron<br/>

but that's their daily iron requirement.<br/>

So these worms are robbing kids<br/>

of their daily iron requirements and the consequences then are, there's<br/>

some good epidemiologic studies to show<br/>

that 37 percent of the iron deficiency<br/>

anemia in Brazil is due to hookworm.<br/>

in Zanzibar 35 percent and up to 73 percent of <br/>

severe anemia in Africa is due to hookworms.<br/>

We saw that many parts of Africa hookworm is as important as a cause of anemia,<br/>

the consequence of the anemia has a lot to do, the chronic anemia in kids, <br/>

with child growth retardation, child intellectual and cognitive impairments<br/>

and then very important
It's also a problem in pregnant women. So pregnant women are another very vulnerable population and now there's good studies to show that hookworm results in adverse maternal, fetal outcomes, increased maternal mortality, low birthrate and increased infant mortality. All right. I did something bad. So, now the question is well, what can we do about this. Well, I wonder if you can take me one step back, one slide back. We looked at this and said well, this is how I really got started in the hookworm business. I said well, the problem if the hookworm keep coming back, what can we do that's preventive. What can we do to prevent the hookworms from coming back? And the answer is can you make a vaccine, can you make an anti-worm vaccine? And the answer turns out is yes we think we can. And let me tell you how we think we can go about doing that. So I'm going to start you at the bottom of this chart where you see worms. And I'm sorry, I don't have the pointer. Worms are attached to the inside of an intestine they're feeding on blood. What happens is the worms are
mating, and they're producing eggs and, when eggs exit the body in feces, those feces get deposited on ground that has lots of moisture and shade in the absence of sanitation and this, these will allow the eggs to hatch and will give rise to small larvae stages which will feed on organic debris and bacteria in the ground and then what they'll do is they'll undergo a spontaneous molt to which is sometimes known as the L3 or the third infected larvae stage and that's shown on the upper left-hand panel where I'm trying to show you blades of grass and clusters of worms are standing on the blades of grass and they're waving like this and it's a behavior that's called questing and you know what they're questing for? They're questing for you, of course, to come into contact with them and these larvae have the ability to directly penetrate human skin and these larvae have the swallowed in the case of another species of hookworm. These worms will go through a one- to two-month sojourn through the body. They'll go through the lungs and eventually make their way to the intestinal tract where they'll grow up to be adult worms that are about a centimeter long and feed on blood. So what is it that makes
anything about this that makes me think we can make a vaccine? Well, it turns out that a group at John Hopkins School of Public Health in the 1930's actually did make a vaccine. And what they showed is that they took those L3, those third stage infected larvae, and started taking small doses of that and immunized taking laboratory animals. And so that's what I mean by at the top there success vaccinating dogs against canine dog hookworm infection using the dog hookworm, and it was taken one step further in the 1960's so that by 1970 you could buy a bottle of dog hookworm vaccine, and you could buy it in Florida in 1973 and the eastern half of United States by 1974, and it was comprised of living larvae, they're about 600 microns in size, so about a little less than half a millimeter, zapped with x-rays. And you need to zap them with x-rays just enough so that they would stay alive but not so much that they would develop after you gave them to the animal. So you could march in with your dog in Florida in 1973, say I want to immunize the dog against hookworm, your
A veterinarian would take those x-ray zapped larvae, he'd have a bottle on the shelf of x-ray zapped larvae and then he would inject your dog and, twice, and you'd get a pretty good immune response that protected your animal against infection. The problem was, there were multiple problems, one of them was, when those x-ray zapped larvae started to die, they stopped secreting something that they needed to stimulate a protective immunity. There was something the larvae were secreting, they were actually spitting out, that was stimulating the protective immune response. So although the vaccine worked commercially it was a failure because the poor veterinarian couldn't keep the stuff on the shelf long enough. Once he let it go for more than a few weeks, the larvae started to die on the shelf and they were no longer secreting something that was protective. So we came up with the idea, well, what if we don't do the larvae, we just collect enough worm spit from the larvae in order to elicit a protective immune response? The problem was you can't get enough hookworms, so we have to make it ultimately by genetic engineering. And so we went on this very
arduous journey in the late '80's and early 1990's to undertake the worm spit program to actually identify what these larvae were making that were stimulating the protective immune response. And so I had gotten my first NIH grant in the late 1980's to start looking at this and it was very distressing to me because, after getting my grant, I realized that they weren't making anything. This was not good, this was my first NIH grant. I told the NIH what I was going to do. I was going to identify what the worms spit and use it to make a vaccine and there was really nothing in the spit. So this was of great concern to me until I had recruited a postdoc to my lab named John Hardin who had an interest in worm physiology and he had found that, if you take larval stages of worms and incubate them with serum from a laboratory animal, that you can trick them into thinking they were in people. And that was, so I said well, maybe that's what we need to do. We need to first trick the larvae into thinking they're in the person and that's what will cause them to start spitting out something.
that is protective and indeed that was the case.

So our strategy became then to reproduce the effect of what we call an attenuated larval L3 vaccine by substituting a genetically engineered recombinant antigen because you would never get enough of the molecules in the spit to make it yourself. You had to make it by genetic engineering and this one slide took us almost a decade to get. This slide because it's hard to get enough of the material in an abundance in order to identify the molecules that the worms are secreting number one, and then you have to go through the arduous task of making what are known as [inaudible] from the parasites in order to clone the genes for these and then genetically engineer them into something else like a bacteria or a yeast. And so these are the three major proteins that we identified from those larvae and one of them is called ancylostoma secreted protein one, ancylostoma secreted protein two and astacin metalloprotease 1, so ASP1, ASP2 and ASP3, and this was a decade of work that John Hawdon, H-a-w-d-o-n, and I came up with and we decided that these were the vaccine candidates we were going to pursue. Now I don't have time to, unfortunately, go into the science and the science is kind of fun.
but and quirky and interesting but to make a long story short, we identified of those three molecules one of them in particular looked particularly promising as a vaccine candidate and it became the protein in the middle there known as ASP2. This is a crystal structure of the protein which we ultimately solved in collaboration with [inaudible] Sojo at the University of Nebraska and I'm sorry to say to this day we know everything about this protein except what it does for the parasite. But what we have shown is a number of important things, one of them is first of all that the, if you take antibodies to this protein, it blocks the ability of larvae to move. It impairs their ability to migrate. It impairs their ability to go from A to B. So it's doing something, so an antibody response, so the proteins needed for the larvae to know where it's going in the world and secondly, we found that, if you go into regions of Brazil or China where there is endemic hookworm and we found that same result in two countries, that there is a subset of the population that naturally seems to learn how to make the antibodies to this protein which is very unusual. So about a fifth, so if you go into any hookworm endemic area,
You'll find about 15 percent of the population naturally has antibodies to this protein and that 15 percent is protected from getting heavy hookworm infection. So we have this interesting laboratory observation on antibody inhibiting the ability of the larvae to migrate with human immunological evaluation and then, when we tested it as a protected vaccine in laboratory animals, it worked. It elicited an immune response that inhibited, that would greatly reduce the number of adult hookworms compared to laboratory control animals. As I say, I don't have time to go into it today but the mechanism then is that these antibodies to this ASP2 protein inhibit the ability of the L3s to migrate through the tissues. It reduces the number of adult hookworms and then this will then reduce the amount of intestinal blood loss, reduce the number of egg counts and ultimately reduce malnutrition and anemia. So after almost 25 years of work, we had come up with what we thought was a viable strategy for making a vaccine. The problem came when I realized that we had just done the easy part. Why do I say that? Well, because hookworm is,
it belongs to a group of what are known as 13 neglected tropical diseases, so what do I mean by these neglected tropical diseases, these are, at least 13 infections which include things like river blindness which is caused by onchocerca volvulus on the left, Guinea worm in the middle lymphatic filariasis on the right, leprosy is another one of these neglected diseases represent a group of that parasitic and bacterial infections that occur in rural areas of low-income countries almost exclusively. So they are diseases that have the exclusive purview of the estimated 2 to 3 billion people who live on less than $2 a day. They not only occur in a setting of poverty but they also promote poverty and another interesting feature about them is you've heard of things like emerging infection, like Avian Flu or West Nile or SARS, these are diseases which we never knew but suddenly they kind of appear, well, they don't just appear but they appear over a period of years, and maybe you read about them in the newspaper and they're diseases of great concern. Well, these are just the opposite, these are not emerging at all, these have burdened humanity for centuries so much so that
you can find vivid descriptions of these in ancient text and you can pick up the Bible or the Talmud or the Bible by Giza or the writings of Hippocrates or the Egyptian papyrus and find references, very clear cut vivid references to these diseases and one of the reasons is they have notorieties being deforming and, therefore, they have an intense stigma associated with them, and then of course, the attention of the Bonos, the Angelina Jolies, not to mention the attention of the United States public health community and as you can imagine you make products for these things you can. What's the commercial market for them? This is bad, this is viral that's, imagine I'm going to make a hookworm vaccine for the 3 billion people in the world who live on less than $2 a day. I mean, this is the biomedical equivalent of the Producers. You know the movie The Producers, they make a Broadway show that deliberately flops. well this, for this you basically have to convince people to back your guaranteed money-losing company. So that was of great concern for us but we took great inspiration from the work of Gandhi who once said: My experience has taught me
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that no movement ever stops or languishes for want of funds. This does not mean that any movement can go on without money but it does mean that wherever it has good men and all of that and good women and true at its helm, it is bound to attract to itself the requisite funds. So we figured we had that going for us. Well, what we did was, we realized that we were never going to make a, get a pharmaceutical company interested and we decided we're just going to have to do the damn thing ourselves. So what we did was set-up in association with a non-governmental organization called the Sabine Vaccine Institute with the logo on the right and that's named after Albert Sabine who discovered the polio vaccine, joined with the laboratory at GW, we would set-up what we called our guaranteed money-losing company, and if you go to the seventh floor of our building, it looks just like a bio-tech company. It has fermenters whirring. It has quality control units, it's just, I can promise you we're never going to turn a profit and the reason we're going to do this, of course, is because of the
backing of the Bill and Melinda Gates Foundation that gave us that funding in order to take this all the way through from the laboratory observation such as what I just presented, to the point where we're going to make a bottle of vaccines. So the hookworm vaccine that was manufactured is a recombinant protein expressed in yeast and then absorbed to an aluminium compound known as a hydrogel to help it stimulate an immune response and these are the list of the milestones. And it's getting late so I want to finish up and there at the bottom right is our first bottle of hookworm vaccine. One of the problems for doing this is we thought it was very important early on that even though this vaccine would never be licensed in the United States we wanted to not bypass the usual routes of drug development that one would have to do let's say if you were a Merck or a Pfizer so we wanted to go through the U.S. Food and Drug Administration which means filing what's known as an investigational or a new drug application. The problem there is FDA doesn't really care if you're Merck or Pfizer or whether you're a guaranteed money-losing company called the Human Hookworm Vaccine Initiative and Sabine Vaccine Institute, you still have the same, pass the same amount of
rigorous tests and that's why you need something like a large scale Gates funding because it is very expensive. You have to bring in quality control experts, quality assurance experts and people with industrial experience and that requires a fairly high salary so we chose to do instead is we took faculty members, research faculty members, research professors, research associate professors and got them trained in industry practices so it's kind of a hybrid culture of academia and industry and we were greatly helped by a group of consultants from an organization known as Science Applications International that was very helpful in teaching us how to go about doing those industry practices. So we've now completed our phase one study in 36 adult healthy human volunteers. We give doses of ten 1500 micrograms of doses of zero, two and four months for safety and immunogenicity, and I'm not yet supposed to disclose the results of that study other than the fact that it's safe and immunogenic and so, and now what we're doing is based on the results of this which we hope to reveal fairly soon, we want to now see if the thing works. So where are we going to do
What you need to do clinical trials in a developing country, you can't just march into villages in a developing country. You really have to go where there's a good scientific infrastructure, and we really searched for a long time before we found the right mix where there's both a lot of endemic hookworm infection and yet at the same time there was the capacity to, there was a scientific expertise and capacity to help pull off a clinical trial of a product under what they call GCP, Good Clinical Practices, that is you will adhere to all the standards that you would want to use in the United States and the reason I was so thrilled to come down here to the University of Georgia is to publicly thank Dan Colley because one of the things that Dan's been doing over the last 20 years is he has done all the hard work that saved us from all doing all the hard work by establishing this extraordinary infrastructure in the State of Brazil called Minas Gerais by over years and years going to this laboratory called Rene Rachou Research Center which is part of the Oswaldo Cruz Foundation building up the capacity that made it possible for us to then walk in and then
work with this very well-trained team,
trained to go in and now see if it works against hookworm.
And that's where we're at right now which is now that we've shown that it's safe and immunogenic,
meaning it will elicit some immune response, we're at the point now to see over the next few years whether it actually protects against human hookworm infection and so the idea is, I don't know how well it shows up here but rather than getting reinfection, we'd have that flat line.
I think there will be some reinfection and that's why we think we're ultimately going to have to add a second component to the vaccine which we're now working on which is not just the L3 antigen ASP2 but an adult antigen as well to further reduce the blood loss.
And I know it's late but I'll just show you a couple of slides.
I'll just show you a couple of slides. Can I get the lights down again, is that possible?
We've also found another very interesting class of protein from the adult parasite and as the adult parasite is feeding on blood what happens is it starts swallowing blood, then blood gets digested, the hemoglobin that's...
inside red cells gets digested allowing the parasite to feed on that digested blood as a source of nutrition. Well, Alex Lucas in our group found this very interesting class of enzymes that the worm uses to degrade blood as it feeds and what we found was that if we immunize an animal with those enzymes, it elicits an antibody response to these proteins that line the gut of the worm. So as the worm is feeding on the blood the antibodies localize to it almost like a Trojan Horse and grind up the gut of the worm and make it unable to use that blood effectively so the two proteins together we think are going to be additive in terms of their effect. Now, as I said, so that's still the easy part so making the vaccine, as hard as it was, is the easy part. Now clinically testing it as hard as that's going to be, that's still going to be the easy part and why do I say that? Well, it's based on our experience that we've had with other high-tech recombinant vaccines such as the Hepatitis B vaccine. So this is a vaccine that many of us have gotten. I would argue that most
of us have gotten in this room. It's the only licensed recombinant vaccine and so for all that 40 years of genetic engineering and biotechnology we still only have one licensed recombinant vaccine and that's for Hepatitis B. So there was a 20 to 30 year period before wide scale availability was achieved with that Hepatitis B following proof of principle that the vaccine actually works, and it was 10 to 15 years from the time of licensure. So what the Gates Foundation is very concerned about this and they've asked us to say, well, Peter, it's great that you're doing this but give us a plan. We don't want to wait 20, 30 years before this vaccine is widely used, and we're not the only ones they're telling this to some of their other grantees. We now have to come up with a plan to shorten that 20 to 30 years time horizon to say to five to ten. And I will end by telling you a couple of interesting things that we have done. First of all there's a lot of challenges to what the term that we use is global access for this vaccine, the
enormous magnitude of scale of the human hookworm problem, the 740 million people infected with hookworm, insuring that it's used in high transmission communities which tend to be occurring in remote and rural areas of the developing world, it's neglected disease status meaning impoverished people are the lowest priority commercial markets, there's no market for travelers or for the military and all of the current massive funding schemes are all focused on the big three. We have worms have not, have yet to hit the radar screen and we also don't have good health delivery systems. We want to make this a school-based vaccine because that's the target population almost all the vaccines given in developing countries are used in the infant period. So that's going to be a standing program of immunization. Well, one of the ways we want to overcome this is first of all not have all the vaccine made in Washington D.C. What we're trying to do is build in sustainability so that the vaccine can be made overseas. So what I'm showing you is a list, a ranking of countries, 1 through 25, and ranked by very unusual metric which is not just looking at the number of patents and they've produced or loaded.
going on the top right, the number of U.S. patents, or the GDP per capita by looking at the number of U.S. patents per GDP per capita. What do I mean by that? What it means is I'm interested in countries that have high output based on divided by the wealth of the country. So we look at countries like the United States and Japan, they're very wealthy countries and they produce a lot of patents and they're at the top of the list, no surprise there. But there's a group of countries in the gray such as India, China, Brazil, South Africa, Thailand, Malaysia, Indonesia, Argentina, which do very poorly economically but yet are overachievers in terms of their ability to make patents and other metrics of high innovations such as peer reviewed papers and making health products, drugs, vaccines and diagnostics, and when you look at the metric of U.S. patents per GDP per capita, some of those countries come up unexpectedly high such as India, China, Brazil and the terms used for these countries are IDC or Innovative Developing Countries. They've somehow learned to do something very extraordinary in terms of their ability to handle biotechnology. So a key part of our global access now is we're going to these countries and teaching them how to make the NAASP2.
it's called, hookworm vaccine. And the first one we started out with is called Instituto Butantan on the upper left is their symbol there which has a snake and the reason is because it started out as a snake farm. It used to collect snakes from all over Latin America and take the venom from the snake after detoxifying it to make snake antivenoms for all the Americas. Now starting in the 1980's they put in a national program for self-sufficiency immunobiologics, now they produce at this snake farm 86 percent of the vaccines for Brazil. So they made 400, in 2005 they made 483 million doses of vaccines such as DPGBTG and they make their own recombinant Hepatitis B vaccine. Now we're working on a process of technology transfer, so they are going to make the vaccine for the Americas and the idea will be the same in India and China and elsewhere. And then, lastly, we're very concerned about the fact that we want to make this a school age vaccine. It turns out from the lessons learned from Hepatitis B you want to be able
to use the vaccine in a program that's actually that involves a health delivery mechanism that will actually be used. And so now we have this great instruction process by which we're working with developing countries to buy into the idea that we're going to use this hookworm vaccine in the schools possibly even administered by nonhealth care professionals which is still a little bit controversial and we're trying to build on some other school-based vaccine programs that are being considered including this very interesting cervical cancer vaccine for human papillomavirus that was developed recently by Merck and Glaxo-SmithKline. They're also looking at a school-based vaccine program to immunize school-age girls before they become sexually active and get exposed to human papillomavirus, so maybe there will be some tie-in between hookworm vaccine and human papillomavirus vaccine program. These are kind of some of the things that we're trying to do to shorten that timeframe from 30 years down to 5 or 10. So it takes more than a village to make a hookworm vaccine. It takes quite a group of scientists in order.
to create our guaranteed money losing company. Maria Elena Bottazzi at the
top is our project manager. We get a lot of advice from
the Sabine Vaccine Institute especially Phil Russell who's a former major general in the
army. Turns out Walter Reed Army
researchers, enormous amount of expertise in vaccine development. They have a team of
mathematical modelers from the London School of Hygiene and Tropical Medicine
and experts in clinical trials. FIOCRUZ we're working with
extensively and that's a group headed by Rodrigo Correa-Oliveira as well as these two
Butantan which is headed by Isiasis Raw,
Queensland Institute of Medical Research and finally Science Application
International Corporation that provides some of the consultant advice.
NIH funded some of the early part of this work. NIH funded some of the March of Dimes Birth
Defects Foundation was also helpful but it was really the Bill and Melinda Gates Foundation
that provided that big, big dollars that we need to actually fashion something in the laboratory into a product. So I'll stop there. I don't know if there are any questions.
I really appreciate your patience in listening to me this evening.

Thank you.

[Applause]

[Music]