Good evening. I'm Dan Colley, the director of the Center for Tropical and Emerging Global Diseases here at UGA. And it's my pleasure to welcome each of you to this fourth lecture in the series titled Global Health: Voices from the Vanguard. This series has been put together jointly by Professor Pat Thomas and me through the benevolence of the Knight Chair in Health and Medical Journalism, who is Pat Thomas. And the Center for Tropical and Emerging Global Diseases and the president's venture fund. Pulling this together with Pat has really been fun. And in large part, that, not only because of Pat but is because of the extraordinary assistance that has been provided by Diane Murray and Anettra Mapp of the Grady College of Journalism and Mass Communications with the support of Tammy Ambrose from the Center for Tropical and Emerging Global Diseases. And if you don't mind, I'd like to give them and the rest of the staff that have allowed us to do this, a little applause at this point.
Now, some of you know that this lecture series, because I've said it several times, those of you who have been before, is built into the UGA framework for global health proposal that we've sent to the NIH. We don't know whether that's going to be funded because it's the NIH and it will still be three months before it even gets reviewed. But we think that the series has served as a focus for cross-campus interest in global health. And varieties of global health activities have come out of it. So based on that belief, Pat and I are now discussing the likelihood of making this an established lecture series here at UGA. So we hope that you will continue next spring to support this notion by coming and participating and attending. Tonight Dr. Scott Angle will introduce the fourth Voices of the Vanguard lecturer. Dr. Angle is dean of the College of Agricultural and Environmental Sciences having come to UGA last August as did Professor Thomas, which must mean we're doing something right in recruiting. This has been a very good
Dr. Angle is an internationally known soil scientist who has over 350 publications, largely in the area of soil microbiology and biochemistry as it relates to increased crop growth. So I'm very pleased that he's joined us this evening to introduce the final speaker in this year's Voices from the Vanguard series who is Dr. Tony James, and I'll leave it to Scott to introduce Dr. James. Thank you. It's my pleasure to be here with you this evening and this is unfortunately the first time I've been able to join you for this seminar series. Being in the college of agriculture, one of my jobs is not to be on campus and so I spend very little time here and I've simply not had the opportunity to join you for one of these. So I'm very happy I can be here today and listen to our wonderful speaker. As I look across the audience I did want to take a quick poll, I'm just interested in who is here because you're interested in insects because you're interested in insects and other things that fly and bite? Okay. Versus those of you who...
have more of a public health perspective and are interested in why people get sick and how you get them better. There's a little more on that side. But you've got a pretty good mix here. I think that's really been the focus of much of your career is looking at the intersection of biology and human health. And because of that you've absolutely established just a wonderful reputation for yourself. I, you know, I've been familiar with your work for a number of years now because I've had a personal interest in this area. But let me go ahead and give you a little bit of background on Dr. Tony James. He is a molecular biologist who got both his undergraduate and his PhD at the University of California at Irvine. From there he left the University and traveled to the east coast to Harvard University where he had a post-doc in the med school. He worked for a brief period of time in the department of tropical public health at Harvard University and then he left there in 1989 to return back to the California coast where he is currently the Vice Chair of the Department of Molecular Biology and
James.txt

Biochemistry.<br/>

As I said, he is quite distinguished in his career.<br/>

Many, many publications, many accolades.<br/>

As I went through the long list which was given to me, I noted that he is a fellow in the American Academy of Sciences, for those of you who don't know.<br/>

He's a leading expert on vector-parasite interactions, mosquito molecular biology, and other problems in insect developmental biology.<br/>

The goal of his work has always been to develop and define tools that would prevent the transmission of parasites from mosquitoes to other hosts.<br/>

And he has been working more at the molecular side of trying to interrupt this transmission than on the pragmatic side.<br/>

Dr. James has particular expertise in the study of malaria, which I'm sure many of you know is one of the most significant diseases on a worldwide basis and claims more than two million lives a year.<br/>

Today's lecture is sponsored by the Grady College Knight Chair and Health Communication and the Center for Tropical Page 5
And Emerging Global diseases.<br/>
<time begin="00:06:23.49"/>And with that, Tony, I'd ask<br/>
you to come to the podium.<br/>
<time begin="00:06:26.07"/>The title of his lecture today is<br/>
Victims, Vectors, and Vaccines.<br/>
<time begin="00:06:30.07"/>Let's give him a hand please.<br/>
<time begin="00:06:31.51"/>[ Applause ]<br/>
<time begin="00:06:39.26"/>[ Silence ]<br/>
<time begin="00:06:47.01"/>Well thank you Dean Angle.<br/>
<time begin="00:06:48.60"/>Can you hear me okay with this?<br/>
<time begin="00:06:53.82"/>And I want to thank Dr. Colley and Professor<br/>
Thomas for inviting me to speak to you today.<br/>
<time begin="00:07:00.41"/>I'm going to speak initially<br/>
about malaria as a disease and teach those of you<br/>
who don't know anything about it, a little<br/>
bit about it, then spend the last part of the lecture talking about<br/>
the work that we're doing with the experimental aspect of it.<br/>
<time begin="00:07:14.03"/>Not in too much detail but enough hopefully so<br/>
you'll get the flavor for what we're doing.<br/>
<time begin="00:07:18.42"/>In this first image, this is<br/>
a human blood smear taken from a child who at the start<br/>
of the malaria transmission season.<br/>
<time begin="00:07:25.74"/>And for those of you who have never<br/>
looked at a human blood smear before,<br/>
<time begin="00:07:30.08"/>if you stain with Nissl,<br/>
which is a stain that turns things purple,<br/>
you shouldn't see anything.<br/>
<time begin="00:07:31.15"/>It should be a nice clear field like you see here.<br/>
<time begin="00:07:37.39"/>What you see are lots of
little purple things. These are the malaria parasites Plasmodium falciparum. So this is a fairly easy thing to diagnose from humans. It leaves the purple blood smears because you see things that aren't supposed to be there and this is actually a very dramatic event when done for the first time. Malaria is a disease that's actually been known for a long time even though it has been described, not by the use of the word malaria, as we'll see in a second, but the symptoms of it described for a long time. Perhaps Alexander the Great may have actually died from this disease. Several years ago, excavations in Rome uncovered a graveyard that was full of children. And these children had died apparently all at the same time. Decomposition said they were all buried together. They were also buried with dogs. And dogs were the symbol of the Dog Star Sirius. Which meant that these children had died sometime in late August because that's when the star became brightly evident. And from the keeper of epidemiology at the [inaudible] it was determined that these children likely died of malaria at the time.
This is a disease that was known a very long time ago. This is an interesting quote that gives you some idea of the impact of the disease on country.

This is a quote from two Italian members of parliament and this is actually 1898, so this was two centuries ago now at this point and it talks about the impact of this disease on the countryside and Italy. And basically they were talking about the economic impact, the fact that the disease itself leaves uncultivated, two million hectares of land and in Italy. And that just means that the farmers who were working up there were too sick to actually do the work. And it poisons and kills about two million inhabitants at the time this was in Italy. So this is a large number of people.

Killed about fifteen thousand of them. And at the time they said there was no other health problem so deeply linked to the prosperity of their country. So over a hundred years ago it was recognized that this particular disease has a major impact on the economics of a country. This is a hundred years later and this was a quote by the then director general of the WHO, Dr. Brundtland who said that
malaria is the single largest disease in Africa and the primary cause of poverty. Every day three thousand children die from malaria, every year there are five hundred million new infections among children and adults. And the reason I showed these two slides and these two quotes is to show you how little has changed, at least within over a hundred years of recognition of this disease.

And this is a more recent quote by Dr. Regina Rabinovich who was a then director of the infectious disease program of the Bill and Melinda Gates Foundation. And at the time was lamenting the fact that the world has yet to commit resources needed to control this preventable and treatable disease. And she was getting to talking about the cause at African Malaria Day. Well as you perhaps know, subsequent to that, the Gates foundation has made a very large investment in the amount of research infrastructure and direct aid for the development of vaccines for the malaria parasites. So the situation is improving considerably. So what we're going to be
talking about today, for those of you who don't know, is to give you a brief introduction about what is malaria, why is it still a problem, what's being done to fight it, and what are the prospects for the future. And I'll talk a little bit about our work in this area as we talk about what's being done to fight it. So what is malaria? And this is a, almost a primer in the disease here. The original name comes from the Italian words meaning "bad air." And this bad air association came about because people realized that people who lived near marshes were more likely to get the disease than people who did not live near marshes. At the time they didn't make the connection with the fact that, that's where the mosquitoes are and we'll see that malaria is a mosquito transmitted disease. And so they just thought perhaps this is an issue associated with marshes. And those of you who have been near marshes realize that on certain nights they smell very bad, right? Lots of sulfur compound. So at that, offer half
established the issue and the disease got to mean bad air. It is an infectious system, so this just means that there's an etiological agent, something which actually causes the disease. For those of you in biology, it's an intercellular protozoan parasite. So it's a single celled organism, eukaryotic, that lives within cells. It's vector-borne, so it has a biological agent of transmission. In this case, those are the mosquitoes. And it has a high degree of host specificity meaning that there are lots of different species of malaria parasite, but they often have a very precise host affiliation. So the ones that infect human beings, won't infect birds. And the ones that infect birds, won't infect human beings. And we see here, the three major components in the aspect of malaria disease: the parasites themselves, the mosquitoes that transmit them, and a diversity in population. So in humans, we talk about the etiological agents, these are the things that cause disease, there are four species that are significant. The most significant is one called Plasmodium falciparum. And this is the one that causes the most disease and death.
A close runner up is one called *Plasmodium vivax*. Plasmodium falciparum is the principal pathogen that we find in Africa and actually distributed through many parts of the world, where *Plasmodium vivax* tends to be found in the Far East and also in Central America. And these two are cause for significant disease and mortality in humans. And we have two other species, *Plasmodium ovale* and *Plasmodium malariae* which also infect humans but don't create the type of disease burden that we see associated with these first two here. And it's thought that these two are the older ones associated with humans, that they've been associated with humans much longer than these two. And as a consequence their virulence has been attenuated. If you're a parasite, not that any of you would be parasites, but if you were a parasite one of the most important things you could do is not to kill your host, okay, because that's where you live. And so we look at close pathogen interactions that we find parasites that don't seem to affect their host in a major way. You'll see that they've had a longer time to adapt to the host. This picture you've already
seen, but this is a really interesting picture of a human red blood cell without and with malaria parasites. So you can actually see that these parasites live within the red blood cells and they basically spend this portion of their lives consuming the materials that are in the red blood cells. Well malaria transmission is complex. It's transmitted by, at least to humans, by mosquitoes of the genus Anopheles. So there's only one genus that we know that transmits the human parasite. However, there are over four hundred species of Anopheles described and we know that at least sixty eight of them are associated with malaria transmission. And that forty of them are main vectors. And so this makes it very difficult to think about genetic strategies because each one of these species has a different genetic identity. And we'll see how that complicates the circumstances in a little bit. What I've listed under here, which unfortunately appears to be too small for you to see, are a number of species that are major vectors in different areas. Anopheles gambiae is a major vector in Africa and Anopheles stephensi is in India, Anopheles dirus is in Southeast Asia,
fluviatilis, albimanus, etcetera. These are spread in other parts of the world. Alright. So a few interesting facts:

humans are the only natural reservoirs of the four species that cause the disease. So there are no free living forms. You're not about to get malaria as a free living agent in soil or in other circumstances, so, the life cycle is very complex. And this is a slide that I put up with some hesitation. Those of us who work in parasitology, there's almost a word, we have no inaudible. I'm not about to walk you through this slide, it's not important. But just for you to understand it, it's highly complex. If there are no free living forms of the parasite, you either have to be in the mosquito, which is represented by this portion of the life cycle, or in the human. And when you think about it, that's a pretty tenuous life cycle. You have to be in one organism or the other. So the point of this is, is that well jeez it would seem fairly straightforward if all we have to do is break this life cycle. That would be a fairly easy
one very simple reason, and that is there are a lot of people, and there are a lot of mosquitoes. And that alone is sufficient to maintain this transmission.

Alright let's talk a little bit about the epidemiology. Malaria is endemic to the poorest countries in the world. So this is a disease that's associated with poverty and when we look at the distribution on this slide, the countries that have malaria are known to have malaria cluster in the bright green areas here.

And we can see that's along the equatorial area here and it just happens to be countries where there's a tremendous amount of poverty. But it also happens to be the places where the mosquitoes are.

So if we think about some of the statistics of malaria, they're output the standards. Alright? We have three hundred to five hundred million clinical cases a year. And these are cases where people have been diagnosed, they come into a clinical setting and are diagnosed with symptoms. There are greater than a million deaths each year. So this, you'll hear statistics about...
The point here is that it's very difficult to get very good statistics about the number of people who have been dying of this disease because they're often in areas where there are other diseases. But we know it's at least a million. And when you work this out it's somewhere on the average of two persons per million averaged over a year. And most of these deaths occur in Sub-Saharan Africa. One of the interesting things about the epidemiology of the disease is that when you're first exposed to this through the bite of a mosquito, I mean it's often as a child and we see what's called age related prevalence. In terms of mortality here, we see that the deaths are in people who are usually under five years old. Okay? And what this means is that children are the most susceptible to this disease. And if they can make it through the first year of infection, then they develop what's called specific antibodies, the parasite rates go down, and they become protected. So what's important is that...
there's a natural protection to this disease if you can survive the first infection.

A little information about the clinical stuff, as we said before, children are the most vulnerable to this particular pathogen, but so are pregnant women. You have somebody on campus here, Julie Moore who's been working on this aspect of the disease.

But the symptoms of the uncomplicated malaria involve fever, malaise, fatigue, anemia, headache and myalgia. And these are symptoms that overlap tremendously with other infectious diseases.

There's a more severe and complicated form of malaria, it's often associated with this once issued Plasmodium falciparum, and it's characterized by what's called cerebral malaria, which leads to seizures, coma and convulsions.

It's more what we imagine, the more classical of a severe disease to be like. And then a number of other symptoms associated with that. And people had at one point thought that they knew the reason why malaria would become dangerous and not have to deal with the fact that the parasite will have the ability to cause cells to sequester.
in vasculature and that the consequences will be conditions that lead to seizures and coma. This clearly happens with Plasmodium falciparum, but there's some debate now as to whether or not this is the thing that actually ends up causing people to die.

The economic impact, we've now gone through the introductory part, the economic impact is significant. It's estimated that malaria as a disease slows economic growth by as much as 1.3% per year, which is highly significant. And that people who live in malaria-free areas have a gross domestic product which is 3 times higher than those who live in other regions. So there's an interesting association where we realize that if we spent anywhere from one dollar to eight dollars on malaria treatments per year, we could have tremendous impact on the economics of a particular area. Unfortunately the countries that are most plagued have access to this kind of funding. And we'll get into this a little bit when we talk about the drugs that are used to treat malaria and the cost of those drugs and why this becomes, why this becomes really important.
your mind
if you can, remember how much you spent on your last bottle of Advil, because that'll be important in just a little bit.

I can remember that twenty tablets is like, what, 6 or 7 dollars, something like that?
Remember? No, no, somebody buys that for you. Alright, well, Advil's expensive.

And if you look at total public health spending and some of the countries we're talking about, it's ten dollars per person per year.

And that's for everything. And that includes maternal, prenatal care, etcetera. So when we talk about drugs being expensive that's going to be important.

Okay. So we have a standard economic model which talks about the fact that if we have economic improvements in a society, this will lead to better health. But the way this is being viewed in more modern terms, we're starting to understand that if we have, that the new economic model actually feeds in both directions. That if we increase the health standards, of people, we'll actually
have better economic growth. And there's a lot of work being done by a economist and public health professor Jeffery Sacks, who's actually looking at this. And so the new models of what's going on in terms of malaria and its impact on economics, suggests that it's a two way street here. So why is malaria still a problem? Well it's a problem because the traditional approaches that we've been using to control it are no longer working as effectively as they used to. In the old days, the old days twenty years ago and maybe longer than that, going back to the beginning of the last century, we had a very powerful anti-vector measures. These measures involved applications of insecticides. These are toxic chemicals that will kill the mosquitoes. We understood that mosquitoes were vectors, we learned that in 1897 and ever since then there've been efforts to control mosquitoes with the idea being that if you had fewer bites you would have fewer cases of malaria occurring. And as a consequence then, reducing morbidity and mortality. And this turned out to be true.
insecticides and controlling mosquito breeding sites was very important. We've had here demonstrated two different approaches and I put this up here as a lesson because this particular approach here is totally ineffective for controlling malaria which is driving around neighborhoods spraying insecticides into the open neighborhood. And the reason it doesn't work is because the mosquitoes aren't flying around on the streets. That old joke about why you rob banks because that's where the money is, well mosquitoes go into houses because that's where the people are, that's who they feed on. And so malaria control has to focus on actually going into houses and controlling mosquitoes that are in the houses. And there was a technique called indoor residual spraying which this gentleman here is doing. He's spraying the inside of a house with DDT. And the reason that this works is that mosquitoes, when they come to feed on you or me or anybody who's in a house, it's only the females that feed on blood. And what the female does is she takes this enormous blood meal, it's enormous in her sense, because she's a very small, the blood meal is about four or five times her body weight. And she can't fly very well after that. And so what she does is she
flies to the nearest wall and undergoes a process of dieresis. And when she dieresis, she loses the fluid associated with the blood. And so you'll have this mosquito come in flying, be inside the house, flying pretty accurately, working pretty good here, land on somebody, bite them, and then kind of whoa, fly over and hang out on the wall. So if you coat the wall with insecticide, alright, this will kill the mosquito. And this is a very, very powerful technique for controlling transmission of malaria and we'll talk about this again in just a second. The problem with this is that, well it's two fold. One is that the principal insecticide that worked very well is DDT. And DDT as we all know, has significant impact on non-target organisms. So it accumulates in the food chain and is particularly detrimental to birds who will accumulate DDT, it makes their egg shells soft and as a consequence, does damage to the reproduction of raptors. Particularly, birds that feed on other animals. But the main problem with DDT is actually DDT resistance. Alright? And that is the mosquitoes became resistant to it and it could no longer be used. Now there's interesting issues associated with DDT.
The fact that it was used in tons per acre in agricultural use, was actually responsible for the accumulation of DDT in the environment.

The public health uses of DDT were so minimal that they did not have a negative impact. And indeed now the only sanctioned usage of DDT left in the world as we exist now, is for malaria control, and we actually need it as a powerful tool.

One of the other things that came up of why malaria's still a problem, is drug resistance. We knew from very early on that there were various plant extracts that could be used to treat the disease, the oldest one being quina which is a nice additive obviously for gin and tonics.

But that developed out of the fact that in South America, the natives had understood that there was the bark of a tree called a Cinchona that when made into an emulsion would counteract the effects of the actual malaria disease.

When this was discovered by Europeans coming to the new world, it was a highly guarded secret, alright? There were groups of priests who were part of the colonial infrastructure who brought this secret back to them in Europe and the reason it was powerful was that we showed, we'd seen before,
there was malaria in Europe. And for them to bring back a
cure to the new, from the new world to the old world, was very important and very
wealthy patrons would pay to have their children treated by these people who held this
secret. There's a very interesting story behind the fact that this drug was brought to the old world and that there was an effort
to control it so that the people who had it would have a lot of influence and power. However after it became widely available, resistance started to develop to it and a series of new drugs were developed, chloroquine, mefloquine, fansidar and doxycycline and the issues associated with this are the fact that we use them for awhile and then we see resistance. And there's an interesting set of slides here which shows the use of various new drugs as they came out. Chloroquine, just after World War II and until the late sixties, it was sixteen years before we saw significant resistance to Chloroquine develop. As a consequence to that, however, we needed new drugs and the drug fansidar was introduced but it was only six years before we saw resistance to that. And mefloquine came on in
The late seventies, early eighties, but it was only four years before we saw resistance to that. And the last one on here is atovaquone and it was only six months before we saw resistance to that. So this is a very disturbing trend for this particular disease and that is, the drugs we have invariably resulted in resistance. But the period of time that it took for that resistance to become evident has grown shorter and shorter. If I have the next slide. It's been estimated that we need a new drug every five years if we're going to just treat malaria alone by using drugs. So this causes a tremendous burden on the people who are attempting to develop these drugs. There are other contributing factors to why malaria is still a problem in addition to insecticide resistance and drug resistance. And these include, well this is a painful one, little private sector or commercial interest. Okay, no one's going to get rich off of making malaria drugs. Alright, so this is something which is an impediment. What it means is that drug
companies are unwilling to invest the amount of resources that are necessary to come up with new drugs because they just won't get the kind of payback that they're used to getting for the types of drugs that they develop. Once again the Gates Foundation is trying to take a step in this direction by working with drug companies to guarantee them some kind of payback on their initial investments, but that's not a very productive business model for making this work. Decay in healthcare infrastructure, it's a painful fact that as societies have transitioned from colonial to post-colonial, which they ought to, there have been decreases in the way some of the societies have been organized. And as a consequence of that, the healthcare structure has fallen apart. This is a tragic situation considering that the benefits of democracy, etcetera, to certain societies is obviously very important, okay. But as a consequence of that some of the type of management of healthcare infrastructure has fallen apart and as a consequence of that, we've seen resurgence of the disease. Then political turmoil is always a recipe for something bad to happen. If you have a healthcare
infrastructure and you have political turmoil, that is often interrupted. And I've had a few pictures here that are supposed to exemplify that. Okay. So the next sort of area we want to talk a little bit about is what's being done to fight it. So I've kind of painted a negative picture about malaria at this point, it's a very nasty disease, it kills a lot of people and there are some things that we used to have that worked, don't work so well anymore. Do we just throw up our hands and walk away? And the answer is no. Alright, we continue to try to do things with it and so I'm going to quickly review some of the areas of the types of things that are being done to currently fight it. And all infectious diseases, when people work with infectious diseases, there are three main areas that one works in. The first one is diagnostics. And we'll talk a little bit more in details in just a second. But diagnostics basically deals with trying to determine what it is that's causing a particular disease. And when we go back to the symptoms of malaria,
we talk about headaches, fevers, muscle aches, etcetera. Most of you who have had the flu or a bad cold will recognize that those symptoms overlap bad colds and bad flu’s, etcetera. Alright? So infectious disease, the types of symptoms that one has with infectious diseases overlap one another quite a bit. Alright? Unless you can go in and make a definitive diagnosis and say, yes, there is this particular pathogen there, or this particular parasite there, it’s very difficult to figure out what’s going on. So diagnostics becomes very important. And if you talk to your colleagues or your professors or members of the community talk with some of the scientists who work on the campus here, and talk to them about some of the efforts they have, diagnostics is very important and they will attest to that. One of the reasons that diagnostics is important is because one wants to administer therapeutics. These are drugs that either cure you or alleviate the symptoms. So they may not necessarily cure you, but they may make it so that the symptoms aren’t quite so severe. And if the therapeutics are
highly specific, meaning that the drug works for a particular organism,
it’s really important to know that organism is alright?
So we can see this logical flow from having good diagnostics to good therapeutics.
It turns out for some of the things that you can get, etiological agents, nasty organisms,
that the drugs that are available for them are pretty bad. I mean you take these drugs, they make you sick.
They have a very strong effect on your own physiology and so you don’t want to be giving people drugs willy nilly without knowing what they are.
So diagnostics is very important and leads into the application of therapeutics.
Ideally if we had good therapeutics, you would take a pill and you would be cured.
Alright, but very often we don’t get that kind of circumstance.
What we get is a circumstance where we’re just trying to control the disease symptoms, alright.
We’re not necessarily trying to cure the person of the disease.
because we don’t have anything that works.
See what else I can tell you about that.
That’s enough.
Alright prevention.
Well prevention turns out to be the most cost effective way to deal with these infectious
If you never get the infectious disease, then you don't have to be diagnosed or very expensive diagnostic techniques or you don't have to spend money on drugs. And prevention, when working with infectious agents, is as simple as not coming in contact with that infectious agent. So all these things that tell you to avoid certain circumstances where you won't get certain diseases, I'm talking to the students now, alright. That actually makes sense. No one's trying to cut out you having a lot of fun and everything. But if you don't come in contact with the infectious agent, you won't get the disease, alright? So that's really simple, it's straightforward, something to keep in mind, okay? And it works, alright. It's called the dependency clause. You have to be in the same place. You know, the pathogens aren't going to fall out of the sky kind of thing or be on a doorknob or anything like that. Alright. So prevention is actually very useful. And we're going to talk about two aspects.
of prevention in just a little bit. One of them dealing with not coming in contact with the infectious agent and the other one dealing with what happens if you do come in contact with the infectious agent and the deployment of vaccine. So something gives you a pre-exposure that allows your body to build up a resistance. How am I doing here? Alright. Alright. So, there are three very recent milestone efforts as we segue into the type of work that's going on in my lab that are then important for thinking and developing novel ways to deal with malaria. And all of these are based on dealing with genes and the genome. Alright, and there are lots of different reasons why this is important. But I told you before that malaria parasites have a very strong host specificity. That the types of parasites that infect human beings, only infect human beings, they don't infect birds, they don't infect lizards, primates or other models, or mice that have been used. And that suggests that genes are somehow involved. Both the genes of the host, so the genetic makeup of the human makes it particularly
susceptible to a group of parasites, and the genetic makeup of those parasites. Alright, there's something about them that allows them to grow in humans. And so the sequencing of the human genome and the sequencing of the parasite genome are major steps in trying to get our hands on those pieces of discreet information that allow this type of host parasite interaction to take place.

In addition, we have the genome sequence of the vector. In this case the Anopheles mosquito, specifically Anopheles gambiae. And a similar sort of argument applies here. The fact that only Anopheles mosquitoes transmit human malaria, and that the malaria can infect these parasites, suggests that there's some genetic aspect to this, some inheritable aspect. And we're starting to see the impact of genetics and genetic tools and the sequencing of these genomes, knowing all the things that are there on the development of new strategies to control malaria.

In diagnostics it's as straightforward as asking the question, if you have malaria parasites, they're ought to be malaria DNA there, alright? So that makes the diagnostics more straightforward and so people are...
developing techniques that distinguish malaria parasites from other things based on DNA.

distinction that would cause what are called febrile diseases, diseases that give you those symptoms headaches, fever, etcetera.

Alright. If that's caused by influenza virus, you ought to find evidence of the influenza gene on there.

If it's caused by malaria parasites, you ought to be able to find evidence for that.

And so this is being developed there.

And there are a number of different tests that people are trying to develop. Most of, those of you who are undergraduates have done laboratories where you've looked at DNA, this is a gel, electrophoresis of DNA, you can see it. This is a dipstick test they found out.

And the idea is to see if you could come up with a rapid way to tell if a person has malaria.

The gold standard is that blood smear that we've been seeing over and over and over again. If you take a blood smear and you see those parasites there, then you know a person is infected.

So this isn't perfect,
okay?<br/><br/>But it's a start in this direction.<br/><br/>Therapeutic, this is that quote I talked about,<br/>that a new drug must be available every five years.<br/>Genomics has actually been very useful here because we can study biological pathways that are present in the parasite that we don't find in the human and then we can ask the question, can we find drugs that will affect those biochemical pathways that exist only in the parasite and therefore won't have an impact on the human. And so there's been quite a bit of work in this particular area and I have two citations here specifically relating to new biochemical pathways that have been found that are targets for this. Alright. So we're going to talk a little bit about prevention and finish off here talking about some of the work that's going on in our lab. We do, do work on vaccines, alright? So the, for those of you who don't know, the principal behind a vaccine is to expose your body to an infectious agent in a circumstance where that infectious
agent
won't cause severe disease.
This allows your body to
amount an immune response against that.
so when you see the real thing,
you're ready to fight it off, alright?
You've got a chance because your body's already been primed.
And there's been a tremendous effort to develop vaccines and, for malaria and we'll see.
in just a second how those work out.
And then I'm going to tell you about some new anti-vector measures.
the work that's going on in our lab.
Alright. I put this slide in here just to show you that vaccines can be highly efficacious.
and this is a slide that I got from one of our principle vaccinologists, Victor Nussenzweig. I mean he put this together in a talk he gave.
It talks about the power of prevention, the impact of vaccines in the US.
and these are vaccines from a number of different diseases, poliomyelitis, diphtheria,
measles, rubella, mumps and pertussis.
And what happens to cases per one thousand after the introduction of the vaccine.
And you can see for polio that the number drops very rapidly.
In fact for all of these the numbers go down.
Measles is experiencing a rebirth here.
But for the majority of them, the cases per one hundred thousand go way down to the point where most of the students in the room have no idea what a polio case actually looks like. Alright? I'm actually old enough to have had classmates that got polio and as a consequence were confined to crutches for the rest of their lives. Alright? So this is something only the senior members in this group know about. And that's a direct impact of the vaccine. So there's a whole major, what used to be a major disease here that's no longer part of the spectrum of your life as a consequence of the development of vaccine. So the whole point of this is to tell you that if we had a vaccine for malaria, we would expect to have the similar type of dramatic impact. And for malaria we've got a number of possible imaginable vaccines. We've got a vaccine that, this is a mosquito here, it doesn't look like much. Just magnification. But this is a mosquito that is feeding on the arm of a human and infecting a particular stage called the sporozoite. This is the infectious form of the parasite.
And so a good vaccine would be a vaccine that blocks these parasites from infecting us. Alright? That would be, in fact, probably be the best vaccine we could get. It's a complete protection here. If we could get that. But this alone isn't sufficient a cause disease. So disease is not the same thing as being infected. Most of you know that. Because right now everyone you is infected with e coli. You've got all these bacteria growing in your gut. But they don't cause a disease, okay? You can have an infection without having disease. Where we see the disease is once the parasite gets into the liver and starts growing in the liver, it makes these forms which get out and start eating the red blood cells. We saw that picture and this is where the disease actually manifests and where people start getting symptoms. So it's possible to develop a vaccine that protects against the forms that actually cause disease. So this is one type that people are looking at. They're looking at the one that blocks.
infection, one that prevents disease and then there's another group of people that are looking to prevent transmission because I told you before that this parasite lives only in the humans and only in the mosquitoes and has to go back and forth between the mosquitoes and the humans. So if we could actually make a vaccine that prevents the mosquito from taking up the stages that infects it, then we could block transmission this way. Well the good news is that people are working on all three of these. And it's a competition, sometimes friendly. And the idea would be that one would have a vaccine that would combine elements of all three of these blocking strategies and have something that works really well. Alright, insecticide nets work really well. Very, very, very well. It's a very curious thing about the mosquitoes that transmit malaria, at least in Africa. They usually bite from like midnight to maybe three or four o'clock in the morning. Which is when you're asleep, alright. Alright? They've adapted to feeding on humans at a time when humans are least able.
to protect themselves. So it's these early hours in the morning. So if you ever have a chance to go to Africa and you're worried about malaria, the one thing you don't want to be doing is running around in the middle of the night. Alright. The other thing you do want is sleeping under a net. Alright. Because this prevents the mosquitoes from getting to you. Alright. And you can sleep under this net and they can't bite you and it will protect you. And in fact, they've done studies and they've shown that you can actually reduce total malaria by about 17 percent and severe disease by as much as 50 percent when using bed nets. So these actually work, alright?

So more advice for you, for those of you who are going into the field. It's important to have a net that doesn't have holes in it, alright?

Now that may sound not like a big deal, but remember the mosquito has all night, or at least the hours between midnight and say four or five in the morning and then she can come back the next night, to find that hole in the net. And they will do that, alright?

If there are holes in the net, they'll just hang around there until one actually gets in. So you want to make sure that...
there are no<br/>
holes in the net and you want to make sure<br/>
that you don't sleep up<br/>
again<br/>
the net, alright?<br/>
So that it's right up against<br/>
your skin.<br/>
Because believe it or not,<br/>
they'll land<br/>
on the net, and they'll just bite through.<br/>
And one of the most<br/>
interesting, if you're a<br/>
scientist and creepy if you're not a scientist,<br/>
things that you can do is<br/>
wake up in the<br/>
middle of the night, turn your flashlight on<br/>
and look at the outside of<br/>
the net.<br/>
It will convince you to<br/>
stay<br/>
inside the net, that's for sure.<br/>
At least it did for me.<br/>
Alright. But these work,<br/>
and<br/>
they work very, very well.<br/>
Alright so let's talk a<br/>
little bit about what we do in our laboratory.<br/>
The research in our<br/>
laboratory is<br/>
stimulated, I'm going to be talking only<br/>
about this side here which is<br/>
genetic<br/>
control of vector born diseases,<br/>
is stimulated by two<br/>
things<br/>
that I haven't told you yet.<br/>
But turn out to be fairly<br/>
interesting, I think.<br/>
That's why we work on it of<br/>
course.<br/>
The first is that not<br/>
mosquito can transmit every pathogen.<br/>
We've already talked about<br/>
that.
We talked about the fact that Anopheles mosquitoes transmit malaria. Well you know about other vector born diseases, you’ve heard about West Nile Virus, you may have even heard about Dengue viruses, you’ve probably heard about Encephalitis, the various types of Encephalitis. Well the Anopheles mosquitoes don’t transmit those viruses. Alright? There’s a whole other group of mosquitoes that transmit those. And those whole other group that transmit those don’t transmit the human malaria, alright? So where am I going with this?

Once again, genetics seems to be involved. There’s a genetic makeup of a particular mosquito that allows it to be a hospitable host for a particular set of pathogens and therefore can transmit that. So that’s the first observation, that not every blood sucking mosquito has the ability to transmit every disease and that’s likely a consequence of genetics. But it turns out to even be more interesting than that, and that is that you can take a population of mosquitoes or you can take a species of mosquitoes that normally transmit, so say this Anopheles gambiae.
With a little bit of work, you can feed that on a source where it can become infected. What do I mean by that? We can culture these malaria parasites in a dish and if we're lucky, there'll be both of the types that eat the red blood cells and you've got to constantly give them red blood cells. So when you're around a malaria lab it's kind of nervous because there's all these people walking around with sixty ml syringes which are the big ones looking for blood, you know. So, you want to be careful around them. They're shameless in their pursuit. But they'll take your red blood cells, they'll prepare them, they'll put them in this dish and the malaria parasites will live on them, they can keep as cultured. Well certain cultures will make the forms of the parasite that can infect the mosquito. And so you can take this blood from this dish then and feed it to a mosquito and the mosquitoes will get the parasite. Alright that's a long way of telling you that we don't infect the people in our lab, okay? You needed to know that. So when you do that you can actually select those mosquitoes that become infected and mate them all together and you can...
take the ones that don't become infected, and mate them together and do that for a little while. And pretty soon you have two populations.

You have one population that's really easy to infect, and another population that's not so easy to infect. Now you can do genetics. You can cross them together and say, how does it behave? Is it like a dominant trait? Is it a recessive trait? How many genes are involved? You can actually start to map out the genetics of susceptibility, that is those that become infected from resistance, those that are resistant to that. And you say, hey there are genes that are involved. Indeed there's a lot of science going on right now trying to identify those genes that make it possible for a mosquito to become infected and therefore transmit it. When we first started doing this work, we weren't in the position to identify those genes. We started this work a long time ago. We didn't have the human genome all available to us, we didn't have the malaria parasite genome available to us, and we didn't have the mosquito genome available to us. And we thought it would be
very difficult for us to identify just exactly what these genes are. So we came up with a strategy which is going to sound kind of crazy, but we decided we would just make a gene. Alright? So instead of relying on naturally occurring genes that confer resistance to malaria parasites, this was in the late nineties, you know, or actually early nineties, you know. The arrogance of the nineties as we call it, why not just make a gene, alright? And we can actually put it together and we thought, okay, that sounds like an interesting idea. If we're going to make a gene though, what's it going to look like? So a simple molecular biology lesson for you is a gene can be thought of as having two parts. One part which is the control sequence, the part that tells it when, where, how much to make, alright? So that controls it. And the other part is the part that's actually made. Alright? The part that is the product or the gene so to speak. So we thought, well why not just use this very simple model, define circumstances where we have control sequences that we want.
and make something that kills malaria parasites.<br/>
And that's what we did.<br/>
And I'll show you how that works.<br/>
Alright, well the first thing is this control sequence stuff,<br/>
this is actually turns out to be important.<br/>
And so we have a little more life cycle stuff here, but it's actually pretty straightforward. I'm going to fast forward one because I think this is the picture we want. It wasn't immediately obvious to most of you that what you were looking at was a schematic representation of a mosquito. This looks a little bit more like it. So this is a schematic representation of a mosquito. And what happens is, this is a mosquito as if she had been opened up and you're kind of looking inside of her and there's a lot of stuff in there and it's not important to memorize what this stuff is. But she's got a long proboscis which comes off the field of view here. And she'll land on you and she'll probe. Alright, and that's a whole other lecture that Dr. Champaign here can talk about, what is involved in actually getting a blood meal out of a host because it's not easy.
meal it ends up here in what’s called the midgut. So this is the first encounter of the malaria parasite with the mosquito. And if you think about it, it’s a very different change to what it was used to. It was used to living in the human being that’s a nice thirty seven degrees, ninety eight point six Fahrenheit, the acid concentration in the blood is very specific. It’s in that nice environment where it’s living in and eating red blood cells. Everything’s great. And all of a sudden it finds itself in the digestive system of an insect, okay? This is about as alien as you can possibly get it seems. So the first site of interaction then is this midgut and if we want to go after the malaria parasites why not put the gene that we’re making, why not put its product in the midgut here? Why not put it in the place where the parasites are? So that actually turns out to be a good place to go after the parasite. And indeed when you look at the naturally occurring resistance to malaria parasites many of the resistance genes have their phenotype, the way they look, the inability of the
parasite to ever get out of the midgut.
The mosquitos basically ingest them and they can't get out, okay?
So this is something which is reflected in nature.
But once they get out, they get into this open circulatory system and they have to migrate to the salivary glands.
Well this open circulatory system is very much like yours and I in a certain way and that is that the immune aspects of the mosquito often play out here in this open circulatory system.
So we have the possibility of going after the malaria parasite where it's in this open circulatory system. And then all of them have to make their way back to the salivary glands before they're transmitted on to a new host.
Because what happens is the parasites get into the salivary gland, the mosquito lands on you, salivates into the wound site and then delivers the pathogens that way.
So basically we look at these various tissues and we say well here are our opportunities to interrupt the development of this parasite.
We have the midgut, the open circulatory system, and the salivary glands.
So to go back to this synthetic gene we're going to make, what we need to do is find a
of a gene that will allow us to put something in the midgut, the hemolymph or the salivary glands, alright?
So that's strategy one is to identify the appropriate control sequences. And our hypothesis then is that we have these in the appropriate effector molecule, if we get this gene into a population of vectors and we spread this gene through that population, we should see a decrease in the transmission of that pathogen, in this case the malaria parasite, okay?
And so that's what we try to do.
Alright. So when we recognized this, we realized that we had several major areas of research and we're only going to talk about this one right now, okay?
I have got to give another talk tomorrow and for those of you who are interested, we can talk about it then, but this has to do with how we can actually make this mosquito. Okay. And so the first thing we need to be able to do is we're talking about making a gene, well we ought to be able to put that gene back in. So we have to develop transgenesis technology. And this took a long time, it took a long, long time for us to do. But the idea here is if
you're going to have a gene that you want to be able to put that gene back into the insect in the way that it's stably integrated, meaning it goes into that mosquito and it's passed on to the progeny. And that means that it can actually be spread to the population. We talked already about identifying control sequences that can express the effector molecule and then we have the actual effector molecule, the molecule that will interfere with the parasite. Alright. We have transgenesis technology, it works wonderfully with mosquitoes. This is just a little review slide and it shows all these great mosquitoes with glow in the dark eyes, which you might think might be an advantage. But probably is not. And we have control sequences. This is a slide which talks about the various kinds of control sequences that we have that would work with the parasites and this is a genomics display of genes that are turned on, fourteen thousand genes that are turned on and off and so we have lots of things that we can actually work with as a consequence of the genomics effort. But I want to spend time talking about the effector molecules for malaria parasites. Now you want to build a gene
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that interferes with the malaria parasite.<br/>
<time begin="00:55:39.99"/>How would you go about doing that? <br/>
<time begin="00:55:41.88"/>Well you already know that the parasite has to live inside the mosquito and we already know that it invades certain tissues, it invades the midgut when it's ingested, it gets into the hemolymph and invades the salivary glands.<br/>
<time begin="00:55:53.25"/>Well the question is you've got a single celled organism, how does it know where to go?<br/>
<time begin="00:55:58.75"/>Alright. What does it mean to know where to go?<br/>
<time begin="00:56:01.77"/>So this is a single cell, it doesn't have a brain, it doesn't even have a neuron.<br/>
<time begin="00:56:06.37"/>It can't think about where it's going in the organism.<br/>
<time begin="00:56:10.31"/>So we think about, well what are honing devices for cells and stuff.<br/>
<time begin="00:56:15.02"/>You know we think about the concept of having receptors.<br/>
<time begin="00:56:18.30"/>Alright, and I can translate that very easily for you.<br/>
<time begin="00:56:21.71"/>Receptors are molecules that are on the surface of the tissue where the pathogen has to go.<br/>
<time begin="00:56:27.06"/>And they somehow say that this is where you want to be.<br/>
<time begin="00:56:29.55"/>It's a molecule that's on the surface.<br/>
<time begin="00:56:31.61"/>And you have a ligand which is another molecule which is on the surface of the parasite.<br/>
<time begin="00:56:35.66"/>That interacts specifically with that receptor.<br/>
<time begin="00:56:38.24"/>And when those two come
together, the parasite knows I've got to go here. Alright? So you have this parasite in the middle of a mosquito or somewhere in the mosquito. It's fishing around for a target tissue, when it finds that, it will engage. So if I want to build a mosquito that's resistant to this parasite, one of the things I can do is interfere with the ligand, alright? I can interfere with this ability to detect that specific tissue. The other thing I can do is I can knock out these receptors, alright? Nobody home so to speak. Alright? I can somehow map the target tissue so this parasite doesn't know where to go. So this simple slide here, hopefully simple slide, talks about if I want to make a mosquito that is resistant to a malaria parasite, one of the things I can do is get rid of this piece or I can get rid of a lot. So I can interfere with the receptors or I can interfere with the ligand. So that's one approach and I'll talk about that quickly. The other one is to induce an insect immune response. It turns out that the parasites are susceptible to the innate immune response of the insect. So this simple slide here, hopefully simple slide, talks about if I want to make a mosquito that is resistant to a malaria parasite, one of the things I can do is get rid of this piece or I can get rid of a lot. So I can interfere with the receptors or I can interfere with the ligand. So that's one approach and I'll talk about that quickly. The other one is to induce an insect immune response. It turns out that the parasites are susceptible to the innate immune response of the insect.
fight off infection.
Now if we can somehow elevate it, that might work.
Another way is to interfere with parasite gene expression.
We talked about the fact that when the parasite leaves the human host and goes into the mosquito it's a very different world, alright?
And as a consequence of that, the mosquito turns on, sorry the parasite turns on new genes.
Well if we could somehow interfere with those genes being turned on, we might be able to effect parasite development.
And the other one is just to secrete a toxin, alright, a poison.
So the mosquito's flying around with this poison in it when the parasite gets into it, it dies off.
That's actually not such a bad idea, but it's very difficult to find poisons that discriminate between the parasite and the mosquito.
Now some of you think, well that's not such a bad idea because you want to kill the mosquitoes anyway, but the idea is we're going after the parasite now and if we have something that kills off the mosquito, then the strategy will work in a very different way.
Okay. Next slide.
So what we did in our limited approach at the time, was we figured if we could block parasites
from getting into the salivary glands, that is we could prevent them from getting in here, they would not be transmitted. And we used a model system that dealt with this one mosquito called Aedes aegypti, a Plasmodium gallinaceum that actually infects birds, and Galliform birds. We actually used chickens, so the guinea fowl there look kind of neat. And the parasite molecule that we went after is something called the Circumsporozoite protein. And this is a lot of technical information about it but the most important thing here are these pictures of the parasites here and they're stained with a stain that shows us where this protein is and it's all on the surface of the parasite. And some people think that this is a ligand for the parasite to recognize specific tissues in the mosquito. So we did a really interesting trick based on the fact that not all malaria parasites infect all the different kinds of species. Alright? So we took a bird parasite and we put it into a mouse and the mouse just laughed it off, alright? It's not about to get chicken.
malaria, I mean it's a mouse, alright.

So what it meant was the mouse immune system was able to react to these bird parasites and take it out. So we said to ourselves why not identify what component of the mouse immune system is actually doing that. Alright. And of course it was antibodies, and this is a picture of an antibody molecule here that's got a heavy chain. It's not important. It's got a heavy chain and a light chain. We were able to take the fragments of this gene that are responsible for recognizing that surface protein and clone them as a single product, it's called a single chain antibody. And what we've done is we make a very complex system fairly simple. We've taken something that requires two genes and we made it into something that now works with only a single gene. And we put it into the mosquito. So you need to think about what we've done. We've just taken a part of the mouse immune system and put it into a mosquito.
mosquito that is now resistant to a malaria parasite as a consequence of being mouse-like so to speak. A true chimera. And it worked. Alright? And so I just want to show you one data slide and it’s real easy to follow through here. The experimental one are these yellow bars here, I hope they look yellow to you here. And the rest of these are controlled. And what we have here are the percent of mosquitoes going from zero to one hundred percent that have a certain number of parasites. So zero to ten, eleven to one hundred, a hundred and one to a thousand and greater than a thousand. And these three here, the white, the blue and the green, are controlled. So the important thing you can see here if you look carefully is that there are, of the control mosquitoes, a lot of mosquitoes that have a lot of parasites. Alright? So most of the mosquitoes have greater than a thousand parasites. A few have zero to ten, a few have in these ranges here, but most of them have a lot. But in the one where we put the mouse immune system, we see that very few have greater than a thousand and most of them are down in this area here. So if we look at this curve
for the controls, most of them are way up here looking like this, and when we look at the experimentals that we made, made ourselves, alright, they look like this. So this actually has shifted the number of parasitides from being a lot to being very few. Alright? And this is the consequence of putting in this mouse gene against chicken malaria into this mosquito. Okay. So the question then is, does this work? And here's where reality tends to exert its influence on a very clever set of ideas we think. Alright? When we asked if these mosquitoes then could transmit, we found this interesting result which is that mosquitoes with as few as ten parasites in their glands were sufficient to infect chickens, alright? So the inoculum is very, very low. And this turns out to be highly significant for this whole strategy because the question is, how good do we have to be in order to make this work, alright? And here's our answer. We need to have zero parasites in the salivary glands if we're going to save chickens at least. Okay? So how does this translate to humans? We'll turn out that likely the same kind of target is there. And this comes from a very
interesting set of experiments that would never be done today. It turns out a long time ago that one of the ways of treating syphilis was to give people malaria infections because the high temperatures that people would get when they became infected with malaria was sufficient to kill the bacteria that causes syphilis. So before the use of antibiotics and unfortunately long after the use of antibiotics in some portions of the world, people were actually infected with malaria strain to cure them of this disease. It says eleven patients requiring malaria therapy. Alright so what does it mean to require a malaria therapy? Alright these are patients, are they signing off on this? Anyway, were inoculated with Plasmodium vivax. Doses were 10 sporozoites in four patients, a hundred, etcetera. The bottom line is the minimum dose that they gave them was ten of these parasites. Parasitaemia this is actually the blood
infection, was detected in all patients. So what we saw with our animal model with the chicken malaria, is identical to what we can expect in the human condition here which is that our target is zero parasites. We have to get this down to the point where there are no parasites in the salivary glands. Now as difficult as that may seem it's also comforting because we know what our end point is on this. Okay. So that's unfortunately a quick jump into the science and back out again. But that's all we have time for today. So the future directions now that we're working in our laboratory is we want to move from these animal models which is the aim in malaria parasite, that chicken malaria to the human pathogens. If we're going to work another five years we don't really want chicken, alright? It's the, despite all the wonderful things that might come of the consequences of that, our real object is to work on the human parasites. So we're working with the human parasites now. This is something which I can talk about tomorrow, I have to give a talk in
in entomology or maybe it's biochemistry, that it's great to have built these genes in the laboratory and obviously more work needs to be done to make these highly efficacious. But what we really need to do is conceive of how we're actually going to get them out into the field and so this becomes extremely important. And indeed we have a very large project that's trying to figure out how we're going to get these genes into the field. We're very much interested in the transmission dynamics of malaria in the field. We have this really crazy circumstance for example, in some places in Africa the vector, that is the mosquito that's transmitting malaria is different between the rainy season and the dry season. So it's a completely different mosquito species. And when you're talking about a genetic control strategy you have to then develop that from both species during that, in that particular area. And we need to know what these specific targets are so our work is moving out of the laboratory and into the field. There's a larger agenda which is not particularly ours but which is one, it's ours in a sense that our work overlaps.
that, but it's one that's been mandated by the Roll Back Malaria program by CDC and this brings into play then the various things we learned about earlier on. The fact that we should have insecticide treated bed nets available to people, we should concentrate on developing strategies for dealing with malaria in pregnant women, we should continue to develop the drug and hopefully try to develop some kind of technologies where we can forecast the types of conditions that are going to lead to malaria outbreak. And these are some big picture challenges that I think, how do I say this? You don't want to leave things for the next generation because that means you haven't done your job right. Does that make sense? However should we not be successful, there are some things that are probably likely to be available to those of you who are considering getting into the field. And as that, I think we should consider development of a live vaccine. So any of you who are interested in this kind of stuff, we can talk about that. Because live vaccines tend to work very well. Alright? As you can imagine, I work with genetically engineered organisms and the talk about and thoughts of release of genetically modified organisms into the field is enough
to stimulate very lively discussion. So I have a tremendous attack, but we have a tremendous obligation to educate people what we're about, what we're talking about when we're talking about genetically modified organisms and so we can bring the public up to speed on why we don't, as scientists don't think they're a threat. But why we're also in a position, why we can't forcefully advocate their use, that this is work that has to be left with public health officials. I've had this discussion with a number of people. We talked about the development of various avenues, vaccines, drug development, etcetera, to control malaria. And bed nets are also a good example. And right now we have successes in those areas, but they're not complete, We get thirty percent efficacy here, we get a fifty percent efficacy here, but none of them are complete to the point where we're seeing elimination of malaria. And this is the consequence of the fact that people who work in bed nets, work in drugs and work in vaccines don't often talk amongst one another.
So the one thing that would unite them is some concept that they're trying to approach eradication of malaria as a goal. Now most people will tell you, this is highly unlikely to be achieved. However I think the idea conceptualizing it is something that will bring groups of people together who normally don't talk with one another and perhaps we can get an additive effect out of all these different approaches. And this was written on the slide before we got our Gates funding, but basically the funding that is available for malaria research now is still insufficient. People have made the comment that, well you can't just throw money at a problem and expect a solution to occur. But I would like to point out that that's not necessarily true and this visualization of throwing money at a problem is incorrect, alright? H, and I use HIV as an example of this, alright? When HIV was first started to be researched in the mid eighties, it was recognized that it was going to be a serious challenge to people and it was going to be a serious public health problem. The National Institutes of Health also
recognized that and invested a tremendous amount of money in trying to develop approaches to dealing with HIV.

Now it is true that in the first series of grants and the first rounds of grants there was a lot of bad science. Alright? There's no question about it. However those grants don't get renewed, so there's a five year period where some bad stuff was done, bad meaning that it was just, you know not bad that people were hurt, but it was just bad science, bad ideas kind of stuff. You know, really things that just weren't going to get worked out. But those don't survive the first round. I mean, well they survived the first round but they don't get refunded. So you have a bad idea, you know, and it's something that's really important, there's a lot of money there. You'll get that first grant, but when it comes time to renew it, it won't happen. So very quickly this idea that you're throwing money out there and you're getting bad sciences as a consequence of that, just throwing it out there, there's a mechanism for regulating that and that's the renewal period, alright? So considerable money was put...
And what did we get? So this is actually something really important and that is that you know, HIV, I'm no way encouraging anybody to experiment with it in any fashion. Stay as far away from it as you can. But I will say it's no longer the death sentence that it was fifteen years ago. Alright? For those of you old enough to remember what the environment was like fifteen years ago, twenty years ago at this point now, diagnostic or diagnosis of HIV was essentially that, it was a death sentence. Alright? And it's no longer that way. As a consequence of the fact that we have drug regimens now that can control the disease. So this idea that you can't put money into a problem and expect that alone to solve it, it's not necessarily true. If you put the money into a problem, you recruit good scientists to that and you'll get something good out of it. And I would like to argue that the same kind of investment in malaria will give us the same kind of results. Jeffery Sacks someone I mentioned earlier, has estimated the debt somewhere between 1.3 and
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3 billion dollars a year.<br/>
Which sounds like a lot of<br/>
money and if it was just coming to my lab it would be a lot<br/>
of money, but it's not that much money at all.<br/>
For that meager amount of investment we could expect, I think, probably significant results.<br/>
So this little line here still counts.<br/>
And I think that's it.<br/>
Thank you.<br/>