<time begin="00:00:00.50"/><clear/>[Music]
<time begin="00:00:15.62"/><clear/>>>> Good evening.
<time begin="00:00:17.22"/><clear/>
<time begin="00:00:18.29"/><clear/>I'm Dan Colley, the

director
of the Center for Tropical
<time begin="00:00:21.86"/><clear/>and Emerging Global Diseases

here at UGA.
<time begin="00:00:24.07"/><clear/>And it's my pleasure to

welcome
each of you to this fourth lecture
<time begin="00:00:29.59"/><clear/>in the series titled

Global
Health: Voices from the Vanguard.
<time begin="00:00:34.86"/><clear/>This series has been put

together
jointly by Professor Pat Thomas
<time begin="00:00:39.07"/><clear/>and me through the

benevolence
of the Knight Chair in Health
<time begin="00:00:43.12"/><clear/>and Medical Journalism, who

is Pat Thomas.
<time begin="00:00:46.36"/><clear/>And the Center for Tropical

and Emerging Global
Diseases and the president's venture fund.
<time begin="00:00:52.06"/><clear/>Pulling this together

with
Pat has really been fun.
<time begin="00:00:56.68"/><clear/>And in large part, that, not

only because of Pat
<time begin="00:01:00.99"/><clear/>but is because of the

extraordinary
assistance that's been provided by Diane Murray
<time begin="00:01:06.47"/><clear/>and Anettra Mapp of the

Grady
College of Journalism and Mass Communications
<time begin="00:01:11.87"/><clear/>with the support of

Tammy
Ambrose from the Center
<time begin="00:01:14.17"/><clear/>for Tropical and Emerging

Global Diseases.
<time begin="00:01:16.61"/><clear/>And if you don't mind, I'd

like to give them
and the rest of the staff that have allowed us
<time begin="00:01:22.33"/><clear/>to do this, a little applause

at this point.

<time begin="00:01:24.51"/><clear/>[Applause]
<time begin="00:01:31.80"/><clear/>>>> Now, some of you know that

this lecture
series, because I've said it several times,
<time begin="00:01:36.51"/><clear/>those of you who have been

before,
is built into the UGA framework
<time begin="00:01:41.74"/><clear/>for global health

proposal
that we've sent to the NIH.
<time begin="00:01:46.91"/><clear/>We don't know whether that's

going
to be funded because it's the NIH
<time begin="00:01:50.67"/><clear/>and it will still be three

months
before it even gets reviewed.
<time begin="00:01:54.69"/><clear/>But we think that the

series
has served as a focus
<time begin="00:01:59.66"/><clear/>for cross-campus interest in

global health.
<time begin="00:02:04.09"/><clear/>And varieties of global

health
activities have come out of it.
<time begin="00:02:09.09"/><clear/>So based on that belief, Pat

and I
are now discussing the likelihood
<time begin="00:02:14.43"/><clear/>of making this an

established
lecture series here at UGA.
<time begin="00:02:18.70"/><clear/>So we hope that you will

continue
next spring to support this notion
<time begin="00:02:23.71"/><clear/>by coming and participating

and attending.
<time begin="00:02:27.51"/><clear/>Tonight Dr. Scott Angle will

introduce
the fourth Voices of the Vanguard lecturer.
<time begin="00:02:34.47"/><clear/>Dr. Angle is dean of the

College of Agricultural
and Environmental Sciences having come
<time begin="00:02:39.99"/><clear/>to UGA last August as did

Professor Thomas,
<time begin="00:02:45.30"/><clear/>which must mean we're

doing
something right in recruiting.
<time begin="00:02:48.44"/><clear/>This has been a very good

year.
 <time begin="00:02:50.52"/><clear/>Dr. Angle is an

internationally known soil
scientist who has over 350 publications,
 <time begin="00:02:58.70"/><clear/>largely in the area of

soil
microbiology and biochemistry
 <time begin="00:03:02.18"/><clear/>as it relates to increased

crop growth.
 <time begin="00:03:05.09"/><clear/>So I'm very pleased that he's

joined us
this evening to introduce the final speaker
 <time begin="00:03:09.75"/><clear/>in this year's Voices from

the
Vanguard series who is Dr. Tony James,
 <time begin="00:03:15.30"/><clear/>and I'll leave it to

Scott
to introduce Dr. James.
 <time begin="00:03:19.51"/><clear/>[Silence]
 <time begin="00:03:28.99"/><clear/>>>> Dr. Scott Angle: Thank

you. It's my pleasure
to be here with you this evening
 <time begin="00:03:32.29"/><clear/>and this is unfortunately the

first time I've
been able to join you for this seminar series.
 <time begin="00:03:38.26"/><clear/>Being in the college of

agriculture,
one of my jobs is not to be on campus
 <time begin="00:03:43.37"/><clear/>and so I spend very little

time here
 <time begin="00:03:45.16"/><clear/>and I've simply not had

the
opportunity to join you for one of these.
 <time begin="00:03:48.84"/><clear/>So I'm very happy I can be

here today
and listen to our wonderful speaker.
 <time begin="00:03:52.87"/><clear/>As I look across the audience

I did want to take
quick poll, I'm just interested in who is here
 <time begin="00:03:57.29"/><clear/>and maybe this will help Dr.

James as well.
 <time begin="00:03:59.73"/><clear/>How many of you are here
because you're interested in insects
 <time begin="00:04:03.17"/><clear/>and other things that fly and

bite?
 <time begin="00:04:06.52"/><clear/>
 <time begin="00:04:08.07"/><clear/>Okay. Versus those of you who

have more of a
public health perspective and are interested
 <time begin="00:04:14.12"/><clear/>in why people get sick

and
how you get them better.
 <time begin="00:04:17.89"/><clear/>There's a little more on that

side.
 <time begin="00:04:19.72"/><clear/>But you've got a pretty good

mix here.
 <time begin="00:04:21.64"/><clear/>I think that's really been

the focus
of much of your career is looking
 <time begin="00:04:24.54"/><clear/>at the intersection of

biology and human health.
 <time begin="00:04:29.78"/><clear/>And because of that you've

absolutely
established just a wonderful reputation
 <time begin="00:04:34.29"/><clear/>for yourself.
 <time begin="00:04:34.80"/><clear/>I, you know, I've been

familiar with
your work for a number of years now
 <time begin="00:04:38.61"/><clear/>because I've had a

personal
interest in this area.
 <time begin="00:04:40.53"/><clear/>But let me go ahead and give

you a little
bit of background on Dr. Tony James. He is a molecular biologist

who
 <time begin="00:04:44.50"/><clear/>got both his undergraduate

and his PhD at
the University of California at Irvine.
 <time begin="00:04:49.74"/><clear/>From there he left the

university and traveled
to the east coast to Harvard University
 <time begin="00:04:53.73"/><clear/>where he had a post-doc in

the med school.
 <time begin="00:04:56.25"/><clear/>He worked for a brief period

of time in
the department of tropical public health
 <time begin="00:05:00.63"/><clear/>at Harvard University and

then he
left there in 1989 to return back to
 <time begin="00:05:07.26"/><clear/> the California coast where

he is
currently the Vice Chair of the Department
 <time begin="00:05:11.18"/><clear/>of Molecular Biology and

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Biochemistry.<br/>
 <time begin="00:05:14.42"/><clear/>As I said, he is quite

distinguished<br/>
in his career.<br/>
 <time begin="00:05:17.61"/><clear/>Many, many publications, many

accolades.<br/>
 <time begin="00:05:20.61"/><clear/>As I went through the long

list which was<br/>
given to me, I noted that he is a fellow<br/>
 <time begin="00:05:25.30"/><clear/>in the American Academy of

Sciences,<br/>
for those of you who don't know,<br/>
 <time begin="00:05:28.77"/><clear/>our highest scientific

achievement and<br/>
the Entomological Society of London.<br/>
 <time begin="00:05:34.08"/><clear/>He's a leading expert on

vector-parasite<br/>
interactions, mosquito molecular biology,<br/>
 <time begin="00:05:39.53"/><clear/>and other problems in

insect<br/>
developmental biology.<br/>
 <time begin="00:05:43.04"/><clear/>The goal of his work has

always<br/>
been to develop and define tools<br/>
 <time begin="00:05:47.42"/><clear/>that would prevent the

transmission of<br/>
parasites from mosquitoes to other hosts.<br/>
 <time begin="00:05:52.45"/><clear/>And he has been working

more<br/>
at the molecular side of trying<br/>
 <time begin="00:05:55.29"/><clear/>to interrupt this

transmission<br/>
than on the pragmatic side.<br/>
 <time begin="00:06:01.96"/><clear/>Dr. James has particular

expertise in<br/>
the study of malaria, which I'm sure many<br/>
 <time begin="00:06:06.12"/><clear/>of you know is one of the

most<br/>
significant diseases on a worldwide basis<br/>
 <time begin="00:06:10.54"/><clear/>and claims more than two

million lives a year.<br/>
 <time begin="00:06:14.63"/><clear/>Today's lecture is sponsored

by the Grady<br/>
College Knight Chair and Health Communication<br/>
 <time begin="00:06:19.80"/><clear/>and the Center for

Tropical<br/>
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and Emerging Global diseases.
 <time begin="00:06:23.49"/><clear/>And with that, Tony, I'd

ask
you to come to the podium.
 <time begin="00:06:26.07"/><clear/>The title of his lecture

today is
Victims, Vectors, and Vaccines.
 <time begin="00:06:30.07"/><clear/>Let's give him a hand

please.
 <time begin="00:06:31.51"/><clear/>[Applause]
 <time begin="00:06:39.26"/><clear/>[Silence]
 <time begin="00:06:47.01"/><clear/>>>> Well thank you Dean

Angle.
 <time begin="00:06:48.60"/><clear/>Can you hear me okay with

this?
 <time begin="00:06:53.82"/><clear/>And I want to thank Dr.

Colley and Professor
Thomas for inviting me to speak to you today.
 <time begin="00:07:00.41"/><clear/>I'm going to speak initially

about malaria
as a disease and teach those of you
 <time begin="00:07:05.90"/><clear/>who don't know anything about

it, a little
bit about it, then spend the last part
 <time begin="00:07:09.85"/><clear/>of the lecture talking about

the work that
we're doing with the experimental aspect of it.
 <time begin="00:07:14.03"/><clear/>Not in too much detail but

enough hopefully so
you'll get the flavor for what we're doing.
 <time begin="00:07:18.42"/><clear/>In this first image, this is

a human
blood smear taken from a child who at the start
 <time begin="00:07:23.62"/><clear/>of the malaria transmission

season.
 <time begin="00:07:25.74"/><clear/>And for those of you who have

never
looked at a human blood smear before,
 <time begin="00:07:30.08"/><clear/>if you stain with Nissl,

which is a stain
 <time begin="00:07:31.15"/><clear/>that turns things

purple,
you shouldn't see anything.
 <time begin="00:07:35.26"/><clear/>It should be a nice

clear
field like you see here.
 <time begin="00:07:37.39"/><clear/>What you see are lots of

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little purple things.<br/>
 <time begin="00:07:39.74"/><clear/>These are the malaria

parasites<br/>
Plasmodium falciparum.<br/>
 <time begin="00:07:42.42"/><clear/>So this is a fairly easy<br/>
thing to diagnose from humans.<br/>
 <time begin="00:07:45.39"/><clear/>It leaves the purple blood

smears because you<br/>
see things that aren't supposed to be there<br/>
 <time begin="00:07:49.97"/><clear/>and this is actually a very

dramatic<br/>
event when done for the first time.<br/>
 <time begin="00:07:55.88"/><clear/>Malaria is a disease that's

actually been known<br/>
 <time begin="00:07:57.69"/><clear/>for a long time even though

it has been<br/>
described, not by the use of the word malaria,<br/>
 <time begin="00:08:02.37"/><clear/>as we'll see in a second, but

the<br/>
symptoms of it described for a long time.<br/>
 <time begin="00:08:05.59"/><clear/>And it's understood that

perhaps Alexander the<br/>
Great may have actually died from this disease.<br/>
 <time begin="00:08:09.66"/><clear/>Several years ago,

excavations in Rome<br/>
uncovered a graveyard that was full of children.<br/>
 <time begin="00:08:15.55"/><clear/>And these children had

died<br/>
apparently all at the same time.<br/>
 <time begin="00:08:18.44"/><clear/>Decomposition said they were

all buried together.<br/>
 <time begin="00:08:20.71"/><clear/>They were also buried with

dogs.<br/>
 <time begin="00:08:22.86"/><clear/>And dogs were the symbol of

the Dog Star Sirius.<br/>
 <time begin="00:08:25.84"/><clear/>Which meant that these

children had died<br/>
sometime in late August because that's<br/>
 <time begin="00:08:29.60"/><clear/>when the star became brightly

evident.<br/>
 <time begin="00:08:31.61"/><clear/>And from the keeper of

epidemiology<br/>
at the [inaudible] it was determined<br/>
 <time begin="00:08:35.97"/><clear/>that these children likely

had<br/>
died of malaria at the time.<br/>
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 <time begin="00:08:39.36"/><clear/>This is a disease that

was<br/>
known a very long time ago.<br/>
 <time begin="00:08:43.50"/><clear/>This is an interesting quote

that gives you some<br/>
idea of the impact of the disease on country.<br/>
 <time begin="00:08:48.34"/><clear/>This is a quote from two

Italian members<br/>
of parliament and this is actually 1898,<br/>
 <time begin="00:08:53.57"/><clear/>so this was two centuries ago

now at<br/>
this point and it talks about the impact<br/>
 <time begin="00:08:58.09"/><clear/>of this disease on the

countryside and Italy.<br/>
 <time begin="00:09:01.26"/><clear/>And basically they were

talking<br/>
about the economic impact,<br/>
 <time begin="00:09:04.39"/><clear/>the fact that the disease

itself leaves<br/>
uncultivated, two million hectares of land<br/>
 <time begin="00:09:09.15"/><clear/>and in Italy. And that just

means that<br/>
the farmers who were working<br/>
 <time begin="00:09:12.15"/><clear/>up there were too sick<br/>
to actually do the work.<br/>
 <time begin="00:09:14.55"/><clear/>And it poisons and kills

about two million<br/>
inhabitants at the time this was in Italy.<br/>
 <time begin="00:09:18.66"/><clear/>So this is a large number of

people.<br/>
 <time begin="00:09:20.50"/><clear/>Killed about fifteen thousand

of them.<br/>
 <time begin="00:09:22.79"/><clear/>And at the time they said

there was no<br/>
other health problem so deeply linked<br/>
 <time begin="00:09:26.17"/><clear/>to the prosperity of their

country.<br/>
 <time begin="00:09:27.65"/><clear/>So over a hundred years ago

it was recognized<br/>
 <time begin="00:09:30.93"/><clear/>that this particular disease

has a major<br/>
impact on the economics of a country.<br/>
 <time begin="00:09:36.41"/><clear/>This is a hundred years later

and this was a<br/>
quote by the then director general of the WHO,<br/>
 <time begin="00:09:42.02"/><clear/>Dr. Brundtland who said that
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malaria<br/>
is the single largest disease in Africa<br/>
 <time begin="00:09:46.68"/><clear/>and the primary cause of

poverty.<br/>
 <time begin="00:09:48.45"/><clear/>Every day three thousand

children die from<br/>
malaria, every year there are<br/>
 <time begin="00:09:52.53"/><clear/>five hundred million new

infections<br/>
among children and adults.<br/>
 <time begin="00:09:56.43"/><clear/>And the reason I showed these

two<br/>
slides and these two quotes is<br/>
 <time begin="00:10:00.55"/><clear/>to show you how little has

changed,<br/>
 <time begin="00:10:02.81"/><clear/>at least within over a

hundred years<br/>
of recognition of this disease.<br/>
 <time begin="00:10:07.42"/><clear/>And this is a more recent

quote by Dr.<br/>
Regina Rabinovich who was a then director<br/>
 <time begin="00:10:13.25"/><clear/>of the infectious disease

program of<br/>
the Bill and Melinda Gates Foundation.<br/>
 <time begin="00:10:17.07"/><clear/>And at the time was lamenting

the fact that<br/>
the world has yet to commit resources needed<br/>
 <time begin="00:10:21.58"/><clear/>to control this

preventable<br/>
and treatable disease.<br/>
 <time begin="00:10:24.05"/><clear/>And she was getting to

talking about the<br/>
cause at African Malaria Day.<br/>
 <time begin="00:10:28.64"/><clear/>Well as you perhaps know,

subsequent to that,<br/>
 <time begin="00:10:30.33"/><clear/>the Gates foundation has

made<br/>
a very large investment in the amount<br/>
 <time begin="00:10:35.66"/><clear/>of research infrastructure

and<br/>
direct aid for the development<br/>
 <time begin="00:10:39.97"/><clear/>of vaccines for the malaria

parasites.<br/>
 <time begin="00:10:42.19"/><clear/>So the situation is improving

considerably.<br/>
 <time begin="00:10:45.60"/><clear/>So what we're going to be
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talking about<br/>
today, for those of you who don't know,<br/>
 <time begin="00:10:48.74"/><clear/>is to give you a brief

introduction about<br/>
what is malaria, why is it still a problem,<br/>
 <time begin="00:10:54.23"/><clear/>what's being done to fight

it, and<br/>
what are the prospects for the future.<br/>
 <time begin="00:10:57.45"/><clear/>And I'll talk a little bit

about<br/>
our work in this area as we talk<br/>
 <time begin="00:11:00.52"/><clear/>about what's being done to

fight it.<br/>
 <time begin="00:11:03.31"/><clear/>So what is malaria?<br/>
 <time begin="00:11:04.15"/><clear/>And this is a, almost a

primer<br/>
in the disease here.<br/>
 <time begin="00:11:07.70"/><clear/>The original name comes

from<br/>
the Italian words meaning "bad air."<br/>
 <time begin="00:11:12.27"/><clear/>And this bad air association

came about<br/>
because people realized that people<br/>
 <time begin="00:11:15.99"/><clear/>who lived near marshes

were<br/>
more likely to get the disease<br/>
 <time begin="00:11:20.04"/><clear/>than people who did not live

near marshes.<br/>
 <time begin="00:11:24.32"/><clear/>At the time they didn't make

the connection with<br/>
the fact that, that's where the mosquitoes are<br/>
 <time begin="00:11:28.44"/><clear/>and we'll see that malaria

is<br/>
a mosquito transmitted disease.<br/>
 <time begin="00:11:31.24"/><clear/>And so they just thought

that<br/>
perhaps this is an issue associated<br/>
 <time begin="00:11:33.99"/><clear/>with the bad air associated

with marshes.<br/>
 <time begin="00:11:36.28"/><clear/>And those of you who

have<br/>
been near marshes realize<br/>
 <time begin="00:11:38.26"/><clear/>that on certain nights

they<br/>
smell very bad, right?<br/>
 <time begin="00:11:41.79"/><clear/>Lots of sulfur compound.<br/>
 <time begin="00:11:43.34"/><clear/>So at that, offer half
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established the
issue and the disease got to mean bad air.
<time begin="00:11:48.92"/><clear/>It is an infectious system,

so this just
means that there's an etiological agent,
<time begin="00:11:52.79"/><clear/>something which actually

causes the disease.
<time begin="00:11:56.21"/><clear/>For those of you in biology,

it's
an intercellular protozoan parasite.
<time begin="00:12:00.15"/><clear/>So it's a single celled

organism, eurkaryotic,
that lives within cells.
<time begin="00:12:05.03"/><clear/>It's vector-borne, so it has

a
biological agent of transmission.
<time begin="00:12:09.15"/><clear/>In this case, those are the

mosquitoes.
<time begin="00:12:11.03"/><clear/>And it has a high degree of

host specificity
meaning that there are lots of different species
<time begin="00:12:15.39"/><clear/>of malaria parasite, but they

often have a very precise,
host affiliation.
<time begin="00:12:22.47"/><clear/>So the ones that infect human

beings
for example, won't infect birds.
<time begin="00:12:26.23"/><clear/>And the ones that infect

birds,
won't infect human beings.
<time begin="00:12:29.27"/><clear/>And we see here, the three

major
components in the aspect of malaria disease:
<time begin="00:12:35.65"/><clear/>the parasites themselves, the

mosquitoes that
transmit them, and a diversity in population.
<time begin="00:12:42.25"/><clear/>So in humans, we talk about

the etiological
agents, these are the things that cause disease,
<time begin="00:12:48.14"/><clear/>there are four species that

are significant.
<time begin="00:12:50.44"/><clear/>The most significant is

one
called Plasmodium falciparum.
<time begin="00:12:53.69"/><clear/>And this is the one that

causes
the most disease and death.

<time begin="00:12:56.38"/><clear/>A close runner up is one

called Plasmodium vivax.
<time begin="00:13:00.95"/><clear/>Plasmodium falciparum is the

principal pathogen
that we find in Africa and actually distributed
<time begin="00:13:07.67"/><clear/>through many parts of the

world,
where Plasmodium vivax
<time begin="00:13:10.57"/><clear/>tends to be found in the

Far
East and also in Central America.
<time begin="00:13:15.84"/><clear/>And these two are cause for

significant
disease and mortality in humans.
<time begin="00:13:20.24"/><clear/>And we have two other

species, Plasmodium ovale
and Plasmodium malariae which also infect humans
<time begin="00:13:26.62"/><clear/>but don't create the type of

disease burden that
we see associated with these first two here.
<time begin="00:13:31.78"/><clear/>And it's thought that these

two are
the older ones associated with humans,
<time begin="00:13:35.77"/><clear/>that they've been associated

with
humans much longer than these two
<time begin="00:13:39.24"/><clear/>and as a consequence

their
virulence has been attenuated.
<time begin="00:13:42.98"/><clear/>If you're a parasite, not

that any of you would
be parasites, but if you were a parasite one
<time begin="00:13:49.87"/><clear/>of the most important things

you
could do is not to kill your host,
<time begin="00:13:52.55"/><clear/>okay, because that's where

you live.
<time begin="00:13:54.09"/><clear/>And so we look at close

pathogen interactions
that we find parasites that don't seem
<time begin="00:13:59.35"/><clear/>to affect their host in a

major way,
<time begin="00:14:00.83"/><clear/>you'll see that they've had

a
longer time to adapt to the host.
<time begin="00:14:04.86"/><clear/>This picture you've already

seen, but
this is a really interesting picture
 <time begin="00:14:08.49"/><clear/>of a human red blood cell

without
and with malaria parasites.
 <time begin="00:14:11.97"/><clear/>So you can actually see that

these
parasites live within the red blood cells
 <time begin="00:14:16.15"/><clear/>and they basically spend
 <time begin="00:14:18.82"/><clear/>this portion of their lives

consuming the
materials that are in the red blood cells.
 <time begin="00:14:25.44"/><clear/>Well malaria transmission is

complex.
 <time begin="00:14:29.37"/><clear/>It's transmitted by, at least

to humans,
by mosquitoes of the genus Anopheles.
 <time begin="00:14:33.87"/><clear/>So there's only one genus

that we know
that transmits the human parasite.
 <time begin="00:14:37.41"/><clear/>However, there are over four

hundred species of
Anopheles described and we know that at least sixty eight
 <time begin="00:14:43.12"/><clear/>of them are associated
with malaria transmission.
 <time begin="00:14:46.27"/><clear/>And that forty of them are

main vectors.
 <time begin="00:14:48.86"/><clear/>And so this makes it very

difficult to think
about genetic strategies because each one
 <time begin="00:14:53.26"/><clear/>of these species has a

different
genetic identity.
 <time begin="00:14:55.59"/><clear/>And we'll see how that

complicates
the circumstances in a little bit.
 <time begin="00:14:59.04"/><clear/>What I've listed under here,

which unfortunately
appears to be too small for you to see,
 <time begin="00:15:02.78"/><clear/>are a number of species that

are
major vectors in different areas.
 <time begin="00:15:05.53"/><clear/>Anopheles gambiae is a major

vector in
Africa and Anopheles stephensi is in India
 <time begin="00:15:12.09"/><clear/>and Southeast Asia,

Anopheles
dirus is in Southeast Asia,

<time begin="00:15:15.41"/><clear/>fluviatilis, albimanus,

etcetera.
<time begin="00:15:17.58"/><clear/>These are spread in other

parts of the world.
<time begin="00:15:22.39"/><clear/>Alright. So a few interesting

facts:
<time begin="00:15:25.39"/><clear/>humans are the only natural

reservoirs
of the four species that cause the disease.
<time begin="00:15:30.15"/><clear/>So there are no free living

forms.
<time begin="00:15:32.71"/><clear/>You're not about to get

malaria as
a free living agent in soil
<time begin="00:15:37.72"/><clear/>or in other circumstances

so,
the life cycle is very complex.
<time begin="00:15:43.81"/><clear/>And this is a slide that

I
put up with some hesitation.
<time begin="00:15:46.75"/><clear/>Those of us who work in

parasitology,
there's almost a word, we have no [inaudible].
<time begin="00:15:50.97"/><clear/>I'm not about to walk you

through
this slide, it's not important.
<time begin="00:15:54.98"/><clear/>But just for you to

understand
it, it's highly complex.
<time begin="00:15:57.59"/><clear/>If there are no free living

forms of the
parasite, you either have to be in the mosquito
<time begin="00:16:02.27"/><clear/>which is represented by this

portion
of the life cycle, or in the human.
<time begin="00:16:05.67"/><clear/>And when you think about

it,
that's a pretty tenuous life cycle.
<time begin="00:16:08.67"/><clear/>You have to be in one

organism or the other.
<time begin="00:16:11.05"/><clear/>So the point of this is, is

that well
jeez it would seem fairly straightforward
<time begin="00:16:15.97"/><clear/>if all we have to do is break

this life cycle.
<time begin="00:16:18.84"/><clear/>That would be a fairly easy

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thing to do.<br/>
 <time begin="00:16:20.55"/><clear/>But it turns out it's not for

one very simple<br/>
reason, and that is there are a lot of people,<br/>
 <time begin="00:16:24.66"/><clear/>and there are a lot of

mosquitoes.<br/>
 <time begin="00:16:25.96"/><clear/>And that alone is

sufficient<br/>
to maintain this transmission.<br/>
 <time begin="00:16:28.63"/><clear/>Alright let's talk a

little<br/>
bit about the epidemiology.<br/>
 <time begin="00:16:33.65"/><clear/>Malaria is endemic to

the<br/>
poorest countries in the world.<br/>
 <time begin="00:16:37.24"/><clear/>So this is a disease that's

associated with<br/>
poverty and when we look at the distribution<br/>
 <time begin="00:16:41.74"/><clear/>on this slide, the

countries<br/>
that have malaria, are known<br/>
 <time begin="00:16:45.64"/><clear/>to have malaria cluster

in<br/>
the bright green areas here.<br/>
 <time begin="00:16:49.31"/><clear/>And we can see that's along

the equatorial area here<br/>
and it just happens to be countries<br/>
 <time begin="00:16:54.46"/><clear/>where there's a tremendous

amount of poverty.<br/>
 <time begin="00:16:56.52"/><clear/>But it also happens to be the

places<br/>
where the mosquitoes are.<br/>
 <time begin="00:16:59.01"/><clear/>So if we think about some of

the statistics<br/>
of malaria, they're output the standards.<br/>
 <time begin="00:17:05.82"/><clear/>Alright? We have three

hundred to five<br/>
hundred million clinical cases a year.<br/>
 <time begin="00:17:09.14"/><clear/>And these are cases where

people have<br/>
been diagnosed,they come<br/>
 <time begin="00:17:12.26"/><clear/>into a clinical setting<br/>
and are diagnosed with symptoms.<br/>
 <time begin="00:17:15.09"/><clear/>There are greater than a<br/>
million deaths each year.<br/>
 <time begin="00:17:18.00"/><clear/>So this, you'll hear

statistics about<br/>
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one million, two million, three million,
 <time begin="00:17:23.28"/><clear/>the point here is that it's

very difficult
to get very good statistics about the number
 <time begin="00:17:27.58"/><clear/>of people who have been dying

of
this disease because they're often
 <time begin="00:17:29.96"/><clear/>in areas where there are

other diseases.
 <time begin="00:17:31.69"/><clear/>But we know it's at least a

million.
 <time begin="00:17:33.35"/><clear/>And when you work this

out
it's somewhere on the average
 <time begin="00:17:35.84"/><clear/>of two persons per million

averaged over a year.
 <time begin="00:17:38.24"/><clear/>And most of these deaths
occur in Sub-Saharan Africa.
 <time begin="00:17:41.10"/><clear/>One of the interesting things

about
the epidemiology of the disease is
 <time begin="00:17:46.77"/><clear/>that when you're first

exposed to
this through the bite of a mosquito,
 <time begin="00:17:50.85"/><clear/>I mean it's often as a child

and we see
what's called age related prevalence.
 <time begin="00:17:55.87"/><clear/>In terms of mortality here,

we
see that the deaths are in people
 <time begin="00:18:00.31"/><clear/>who are usually under five

years old.
 <time begin="00:18:03.05"/><clear/>Okay? And what this means is

that children
are, and the example that we're using here,
 <time begin="00:18:09.32"/><clear/>the children are the

most
susceptible to this disease.
 <time begin="00:18:11.84"/><clear/>And if they can make it

through
the first year of infection,
 <time begin="00:18:14.78"/><clear/>then they develop what's

called
specific antibodies, the parasite rates
 <time begin="00:18:18.27"/><clear/>go down, and they become

protected.
 <time begin="00:18:20.31"/><clear/>So what's important is that

there's
a natural protection to this disease
 <time begin="00:18:23.89"/><clear/>if you can survive the first

infection.
 <time begin="00:18:26.50"/><clear/>A little information about

the
clinical stuff, as we said before,
 <time begin="00:18:33.62"/><clear/>children are the most

vulnerable to this
particular pathogen, but so are pregnant women.
 <time begin="00:18:38.03"/><clear/>You have somebody on campus

here,
Julie Moore who's been working
 <time begin="00:18:41.13"/><clear/>on this aspect of the

disease.
 <time begin="00:18:42.94"/><clear/>But the symptoms of the

uncomplicated
malaria involve fever, malaise,
 <time begin="00:18:46.49"/><clear/>fatigue, anemia, headache and

myalgia.
 <time begin="00:18:49.21"/><clear/>And these are symptoms that

overlap
tremendously with other infectious diseases.
 <time begin="00:18:53.48"/><clear/>There's a more severe and

complicated
form of malaria, it's often associated
 <time begin="00:19:01.35"/><clear/>with this once issued

Plasmodium
falciparum, and it's characterized
 <time begin="00:19:04.94"/><clear/>by what's called cerebral

malaria, which
leads to seizures, coma and convulsions,
 <time begin="00:19:08.97"/><clear/>it's more what we imagine,

the more
classical of a severe disease to be like.
 <time begin="00:19:13.81"/><clear/>And then a number of

other
symptoms associated with that.
 <time begin="00:19:17.87"/><clear/>And people had at one point

thought
 <time begin="00:19:20.27"/><clear/>that they knew the reason why

malaria
would become dangerous and not have to deal
 <time begin="00:19:24.72"/><clear/>with the fact that the

parasite will have
the ability to cause cells to sequester

<time begin="00:19:29.32"/><clear/>in vasculature and that the

consequences will
be conditions that lead to seizures and coma.
<time begin="00:19:35.71"/><clear/>This clearly happens with

Plasmodium falciparum,
but there's some debate now as to whether
<time begin="00:19:40.50"/><clear/>or not this is the thing

that
actually ends up causing people to die.
<time begin="00:19:44.63"/><clear/>The economic impact, we've

now
gone through the introductory part,
<time begin="00:19:47.96"/><clear/>the economic impact is

significant.
<time begin="00:19:50.24"/><clear/>It's estimated that malaria

as a
disease slows economic growth by as much
<time begin="00:19:56.82"/><clear/>as 1.3% per
year, which is highly significant.
<time begin="00:20:00.10"/><clear/>And that people who live in

malaria-
free areas have a gross domestic product
<time begin="00:20:05.59"/><clear/>which is 3 times higher

than
those who live in other regions.
<time begin="00:20:08.93"/><clear/>So there's an interesting

association
where we realize that if we spent anywhere
<time begin="00:20:14.60"/><clear/>from one dollar to eight

dollars on malaria
treatments per year, we could have tremendous impact
<time begin="00:20:19.47"/><clear/>on the economics of a

particular area.
<time begin="00:20:23.81"/><clear/>Unfortunately the

countries
that are most plagued
<time begin="00:20:26.18"/><clear/>by these diseases do not

have
access to this kind of funding.
<time begin="00:20:30.99"/><clear/>And we'll get into this a

little bit when
we talk about the drugs that are used
<time begin="00:20:34.65"/><clear/>to treat malaria and the cost

of those
drugs and why this becomes, why this becomes really

important.
<time begin="00:20:39.41"/><clear/>But I want you to somehow, in

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your mind<br/>
if you can, remember how much you spent<br/>
 <time begin="00:20:43.45"/><clear/>on your last bottle of Advil,

because<br/>
that'll be important in just a little bit.<br/>
 <time begin="00:20:47.14"/><clear/>I can remember that

twenty<br/>
tablets is like, what,<br/>
 <time begin="00:20:49.51"/><clear/>6 or 7 dollars, something

like that?<br/>
 <time begin="00:20:52.27"/><clear/>Remember? No, no, somebody

buys that for you.<br/>
 <time begin="00:20:54.67"/><clear/>Alright, well, Advil's

expensive.<br/>
 <time begin="00:20:59.29"/><clear/>And if you look at total

public health spending<br/>
and some of the countries we're talking about,<br/>
 <time begin="00:21:06.38"/><clear/>it's ten dollars per person

per year.<br/>
 <time begin="00:21:08.78"/><clear/>And that's for

everything.<br/>
 <time begin="00:21:10.47"/><clear/>And that includes

maternal,<br/>
prenatal care, etcetera.<br/>
 <time begin="00:21:14.09"/><clear/>So when we talk about drugs

being<br/>
expensive that's going to be important.<br/>
 <time begin="00:21:19.97"/><clear/>Okay. So we have a standard

economic model<br/>
<br/>
 <time begin="00:21:26.41"/><clear/>which talks about the fact

that<br/>
if we have economic improvements<br/>
 <time begin="00:21:29.45"/><clear/>in a society, this will lead

to better health.<br/>
 <time begin="00:21:32.14"/><clear/>But the way this is being

viewed in more<br/>
modern terms, we're starting to understand<br/>
 <time begin="00:21:36.45"/><clear/>that if we have, that the new

economic<br/>
model actually feeds in both directions.<br/>
 <time begin="00:21:41.48"/><clear/>That if we increase the

health standards,<br/>
 <time begin="00:21:44.64"/><clear/>of people, we'll

actually<br/>
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have better economic growth.<br/>
 <time begin="00:21:47.32"/><clear/>And there's a lot of work

being done by a<br/>
economist and public health professor<br/>
 <time begin="00:21:53.51"/><clear/>Jeffery Sacks, who's actually

looking at this.<br/>
 <time begin="00:21:55.81"/><clear/>And so the new models of

what's going on in<br/>
terms of malaria and its impact on economics,<br/>
 <time begin="00:22:01.92"/><clear/>suggests that it's a two way

street here.<br/>
 <time begin="00:22:05.52"/><clear/>So why is malaria still a

problem?<br/>
 <time begin="00:22:08.75"/><clear/>Well it's a problem because

the<br/>
traditional approaches that we've been using<br/>
 <time begin="00:22:11.93"/><clear/>to control it are no longer

working<br/>
as effectively as they used to.<br/>
 <time begin="00:22:17.38"/><clear/>In the old days, the old days

being<br/>
twenty years ago and maybe longer than that,<br/>
 <time begin="00:22:22.52"/><clear/>going back to the beginning

of the last century,<br/>
we had a very powerful anti-vector measures.<br/>
 <time begin="00:22:29.49"/><clear/>And these measures

involved<br/>
applications of insecticides.<br/>
 <time begin="00:22:34.50"/><clear/>These are toxic

chemicals<br/>
that will kill the mosquitoes.<br/>
 <time begin="00:22:37.72"/><clear/>We understood that mosquitoes

were<br/>
vectors, we learned that in 1897 and ever<br/>
 <time begin="00:22:44.60"/><clear/>since then there've been

efforts to<br/>
control mosquitoes with the idea being<br/>
 <time begin="00:22:48.57"/><clear/>that if you had fewer bites

you would<br/>
have fewer cases of malaria occurring.<br/>
 <time begin="00:22:53.84"/><clear/>And as a consequence

then,<br/>
reducing morbidity and mortality.<br/>
 <time begin="00:22:57.12"/><clear/>And this turned out to be

true.<br/>  START START START START
 <time begin="00:22:58.86"/><clear/>And the application of
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insecticides<br/>
 <time begin="00:23:00.55"/><clear/>and controlling mosquito<br/>
breeding sites was very important.<br/>
 <time begin="00:23:04.95"/><clear/>We've had here demonstrated

two different<br/>
approaches and I put this up here as a lesson<br/>
 <time begin="00:23:10.05"/><clear/>because this particular

approach here is<br/>
totally ineffective for controlling malaria<br/>
 <time begin="00:23:14.43"/><clear/>which is driving around

neighborhoods spraying<br/>
insecticides into the open neighborhood.<br/>
 <time begin="00:23:19.98"/><clear/>And the reason it doesn't

work is because the<br/>
mosquitoes aren't flying around on the streets.<br/>
 <time begin="00:23:25.46"/><clear/>That old joke about why you

rob banks because<br/>
that's where the money is, well mosquitoes go<br/>
 <time begin="00:23:31.32"/><clear/>into houses because that's

where the<br/>
people are, that's who they feed on.<br/>
 <time begin="00:23:34.64"/><clear/>And so malaria control has

to<br/>
focus on actually going into houses<br/>
 <time begin="00:23:39.49"/><clear/>and controlling

mosquitoes<br/>
that are in the houses.<br/>
 <time begin="00:23:41.45"/><clear/>And there was a technique

called indoor residual<br/>
spraying which this gentleman here is doing.<br/>
 <time begin="00:23:47.24"/><clear/>He's spraying the inside of a

house with DDT.<br/>
 <time begin="00:23:50.73"/><clear/>And the reason that this

works is that<br/>
mosquitoes, when they come to feed on you or me<br/>
 <time begin="00:23:55.92"/><clear/>or anybody who's in a house,

it's<br/>
only the females that feed on blood.<br/>
 <time begin="00:23:59.74"/><clear/>And what the female does is

she takes this<br/>
enormous blood meal, it's enormous in her sense,<br/>
 <time begin="00:24:05.17"/><clear/>because she's a very small,

the blood meal<br/>
is about four or five times her body weight.<br/>
 <time begin="00:24:09.66"/><clear/>And she can't fly very well

after that.<br/>
 <time begin="00:24:11.94"/><clear/>And so what she does is she
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flies to the nearest<br/>
wall and undergoes a process of dieresis.<br/>
 <time begin="00:24:17.24"/><clear/>And when she dieresis, she

loses<br/>
the fluid associated with the blood.<br/>
 <time begin="00:24:22.55"/><clear/>And so you'll have this

mosquito come in flying,<br/>
be inside the house, flying pretty accurately,<br/>
 <time begin="00:24:27.61"/><clear/>working pretty good here,

land on<br/>
somebody, bite them, and then kind of whoa,<br/>
 <time begin="00:24:32.78"/><clear/>fly over and hang out on the

wall.<br/>
 <time begin="00:24:35.61"/><clear/>So if you coat the wall with

insecticide,<br/>
alright, this will kill the mosquito.<br/>
 <time begin="00:24:39.96"/><clear/>And this is a very, very

powerful technique<br/>
for controlling transmission of malaria<br/>
 <time begin="00:24:46.00"/><clear/>and we'll talk about

this<br/>
again in just a second.<br/>
 <time begin="00:24:49.74"/><clear/>The problem with this is<br/>
that, well it's two fold.<br/>
 <time begin="00:24:52.35"/><clear/>One is that the principal

insecticide<br/>
that worked very well is DDT.<br/>
 <time begin="00:24:56.86"/><clear/>And DDT as we all know, has

significant<br/>
impact on non-target organisms.<br/>
 <time begin="00:25:04.60"/><clear/>So it accumulates in the food

chain and<br/>
is particularly detrimental to birds<br/>
 <time begin="00:25:10.11"/><clear/>who will accumulate DDT, it

makes their<br/>
egg shells soft and as a consequence,<br/>
 <time begin="00:25:15.60"/><clear/>does damage to the

reproduction of raptors<br/>
particularly, birds that feed on other animals.<br/>
 <time begin="00:25:23.96"/><clear/>But the main problem with

DDT<br/>
is actually DDT resistance.<br/>
 <time begin="00:25:28.07"/><clear/>Alright? And that is the

mosquitoes became<br/>
resistant to it and it could no longer be used.<br/>
 <time begin="00:25:33.96"/><clear/>Now there's interesting

issues<br/>
associated with DDT.<br/>
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 <time begin="00:25:37.91"/><clear/>The fact that it was used in

tons per acre
in agricultural use, was actually responsible
 <time begin="00:25:45.81"/><clear/>for the accumulation of DDT

in the environment.
 <time begin="00:25:48.30"/><clear/>The public health uses of DDT

were so minimal
that they did not have a negative impact.
 <time begin="00:25:53.24"/><clear/>And indeed now the only

sanctioned usage
of DDT left in the world as we exist now,
 <time begin="00:25:59.08"/><clear/>is for malaria control, and

we
actually need it as a powerful tool.
 <time begin="00:26:03.83"/><clear/>One of the other things that

came up of why
malaria's still a problem, is drug resistance.
 <time begin="00:26:11.39"/><clear/>We knew from very early on

that there were
various plant extracts that could be used
 <time begin="00:26:16.66"/><clear/>to treat the disease,

the
oldest one being quinai
 <time begin="00:26:19.84"/><clear/>which is a nice additive
obviously for gin and tonics.
 <time begin="00:26:24.40"/><clear/>But that developed out of the

fact that in
South America, the natives had understood
 <time begin="00:26:29.59"/><clear/>that there was the bark of a

tree
called a Cinchona that when made
 <time begin="00:26:32.34"/><clear/>into an emulsion would

counteract the
effects of the actual malaria disease.
 <time begin="00:26:38.22"/><clear/>When this was discovered

by
Europeans coming to the new world,
 <time begin="00:26:44.73"/><clear/>it was a highly guarded

secret, alright?
 <time begin="00:26:47.18"/><clear/>There were groups of priests

who were
part of the colonial infrastructure
 <time begin="00:26:54.42"/><clear/>who brought this secret back

to them in
Europe and the reason it was powerful was
 <time begin="00:26:57.58"/><clear/>that we showed, we'd seen

before,

there was malaria in Europe.
 <time begin="00:27:00.87"/><clear/>And for them to bring back a

cure to the
new, from the new world to the old world,
 <time begin="00:27:05.43"/><clear/>was very important and very

wealthy patrons
would pay to have their children treated
 <time begin="00:27:10.59"/><clear/>by these people who held this

secret.
 <time begin="00:27:12.41"/><clear/>There's a very interesting

story behind the
fact that this drug was brought to the old world
 <time begin="00:27:17.56"/><clear/>and that there was an effort

to
control it so that the people
 <time begin="00:27:20.81"/><clear/>who had it would have a

lot
of influence and power.
 <time begin="00:27:24.24"/><clear/>However after it became

widely available,
resistance started to develop to it and a series
 <time begin="00:27:30.30"/><clear/>of new drugs were developed,

chloroquine,
mefloquine, fansidar and doxycycline
 <time begin="00:27:35.01"/><clear/>and the issues associated

with
this are the fact that we use them
 <time begin="00:27:39.93"/><clear/>for awhile and then we see

resistance.
 <time begin="00:27:42.12"/><clear/>And there's an interesting

set of
slides here which shows the use
 <time begin="00:27:46.51"/><clear/>of various new drugs as they

came out.
 <time begin="00:27:49.16"/><clear/>Chloroquine, just after World

War
II and until the late sixties.
 <time begin="00:27:53.59"/><clear/>It was sixteen years before

we saw significant
resistance to Chloroquine develop.
 <time begin="00:27:58.25"/><clear/>As a consequence to that

though, we needed new
drugs and the drug fansidar was introduced,
 <time begin="00:28:04.19"/><clear/>but it was only six years

before
we saw resistance to that.
 <time begin="00:28:09.35"/><clear/>And mefloquine came on in

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the<br/>
late seventies, early eighties,<br/>
 <time begin="00:28:13.90"/><clear/>but it was only four

years<br/>
before we saw resistance to that.<br/>
 <time begin="00:28:17.21"/><clear/>And the last one on here is

atovaquone<br/>
 <time begin="00:28:20.51"/><clear/>and it was only six

months<br/>
before we saw resistance to that.<br/>
 <time begin="00:28:23.24"/><clear/>So this is a very disturbing

trend for<br/>
this particular disease and that is,<br/>
 <time begin="00:28:27.24"/><clear/>the drugs we have

invariably<br/>
resulted in resistance.<br/>
 <time begin="00:28:31.18"/><clear/>But the period of time

that<br/>
it took for that resistance<br/>
 <time begin="00:28:33.69"/><clear/>to become evident has grown

shorter and shorter.<br/>
 <time begin="00:28:36.81"/><clear/>If I have the next

slide.<br/>
 <time begin="00:28:40.46"/><clear/>It's been estimated that we

need a new<br/>
drug every five years if we're going<br/>
 <time begin="00:28:45.10"/><clear/>to just treat malaria alone

by using drugs.<br/>
 <time begin="00:28:47.78"/><clear/>So this causes a tremendous

burden on the<br/>
people who are attempting to develop these drugs.<br/>
 <time begin="00:28:51.46"/><clear/>There are other contributing

factors to<br/>
why malaria is still a problem in addition<br/>
 <time begin="00:28:56.61"/><clear/>to insecticide resistance and

drug resistance.<br/>
 <time begin="00:28:59.51"/><clear/>And these include, well this

is a painful one,<br/>
little private sector or commercial interest.<br/>
 <time begin="00:29:06.86"/><clear/>Okay? Noone's going to get

rich<br/>
off of making malaria drugs.<br/>
 <time begin="00:29:11.17"/><clear/>Alright, so this is

something<br/>
which is an impediment.<br/>
 <time begin="00:29:13.89"/><clear/>What it means is that drug
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companies are<br/>
unwilling to invest the amount of resources<br/>
 <time begin="00:29:20.40"/><clear/>that are necessary to come up

with new drugs<br/>
because they just won't get the kind of payback<br/>
 <time begin="00:29:24.46"/><clear/>that they're used to getting

for the<br/>
types of drugs that they develop.<br/>
 <time begin="00:29:29.45"/><clear/>Once again the Gates

Foundation is trying<br/>
to take a step in this direction by working<br/>
 <time begin="00:29:35.63"/><clear/>with drug companies to

guarantee them some<br/>
kind of payback on their initial investments,<br/>
 <time begin="00:29:40.80"/><clear/>but that's not a very

productive<br/>
business model for making this work.<br/>
 <time begin="00:29:44.66"/><clear/>Decay in healthcare

infrastructure, it's a<br/>
painful fact that as societies have transitioned<br/>
 <time begin="00:29:49.78"/><clear/>from colonial to

post-colonial, which they ought<br/>
to, there have been decreases in the way some<br/>
 <time begin="00:29:57.07"/><clear/>of the societies have been

organized.<br/>
 <time begin="00:29:58.86"/><clear/>And as a consequence of that,

the<br/>
healthcare structure has fallen apart.<br/>
 <time begin="00:30:02.66"/><clear/>This is a tragic situation

considering<br/>
that the benefits of democracy, etcetera,<br/>
 <time begin="00:30:08.90"/><clear/>to certain societies is

obviously<br/>
very important, okay.<br/>
 <time begin="00:30:12.10"/><clear/>But as a consequence of

that<br/>
some of the type of management<br/>
 <time begin="00:30:14.59"/><clear/>of healthcare infrastructure

has fallen<br/>
apart and as a consequence of that,<br/>
 <time begin="00:30:18.24"/><clear/>we've seen resurgence of the

disease.<br/>
 <time begin="00:30:20.24"/><clear/>Then political turmoil is

always a<br/>
recipe for something bad to happen.<br/>
 <time begin="00:30:24.55"/><clear/>If you have a healthcare
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infrastructure
 <time begin="00:30:27.04"/><clear/>and you have political

turmoil,
that is often interrupted.
 <time begin="00:30:31.63"/><clear/>And I've had a few pictures

here
that are supposed to exemplify that.
 <time begin="00:30:35.69"/><clear/>Okay. So the next sort of

area
we want to talk a little bit
 <time begin="00:30:39.15"/><clear/>about is what's being done to

fight it.
 <time begin="00:30:40.84"/><clear/>So I've kind of painted a

negative
picture about malaria at this point,
 <time begin="00:30:44.28"/><clear/>it's a very nasty disease, it

kills a lot of
people and there are some things that we used
 <time begin="00:30:49.15"/><clear/>to have that worked, don't

work so well anymore.
 <time begin="00:30:52.83"/><clear/>Do we just throw up our hands

and walk away?
 <time begin="00:30:54.57"/><clear/>And the answer is no.
 <time begin="00:30:55.19"/><clear/>Alright, we continue to try

to do things with
it and so I'm going to quickly review some
 <time begin="00:31:00.69"/><clear/>of the areas of the types of

things that
are being done to currently fight it.
 <time begin="00:31:05.63"/><clear/>And all infectious diseases,

when
people work with infectious diseases,
 <time begin="00:31:08.83"/><clear/>there are three main areas

that one works in.
 <time begin="00:31:11.37"/><clear/>The first one is

diagnostics.
 <time begin="00:31:13.07"/><clear/>And we'll talk a little

bit
more in details in just a second.
 <time begin="00:31:18.07"/><clear/>But diagnostics basically

deals with trying
 <time begin="00:31:21.34"/><clear/>to determine what it is

that's
causing a particular disease.
 <time begin="00:31:24.78"/><clear/>And when we go back to the

symptoms of malaria,

 <time begin="00:31:26.97"/><clear/>we talk about headaches,
fevers, muscle aches, etcetera.
 <time begin="00:31:30.65"/><clear/>Most of you who have had

the
flu or a bad cold will recognize
 <time begin="00:31:33.41"/><clear/>that those symptoms overlap

bad
colds and bad flu's, etcetera.
 <time begin="00:31:37.96"/><clear/>Alright? So infectious

disease,
the types of symptoms that one has
 <time begin="00:31:42.18"/><clear/>with infectious diseases
overlap one another quite a bit.
 <time begin="00:31:45.58"/><clear/>Alright? Unless you can go in

and make
a definitive diagnosis and say, yes,
 <time begin="00:31:49.60"/><clear/>there is this particular

pathogen there,
or this particular parasite there,
 <time begin="00:31:53.10"/><clear/>it's very difficult

sometimes
to figure out what's going on.
 <time begin="00:31:56.43"/><clear/>So diagnostics becomes very

important.
 <time begin="00:31:58.91"/><clear/>And if you talk to your

colleagues or your
professors or members of the community talk
 <time begin="00:32:03.70"/><clear/>with some of the scientists

who work on
the campus here, and talk to them about some
 <time begin="00:32:07.65"/><clear/>of the efforts they have,

diagnostics is
very important and they will attest to that.
 <time begin="00:32:13.15"/><clear/>One of the reasons that

diagnostics is important
is because one wants to administer therapeutics.
 <time begin="00:32:19.51"/><clear/>These are drugs that either

cure you
 <time begin="00:32:22.21"/><clear/>by eliminating the

pathogen
or alleviate the symptoms.
 <time begin="00:32:26.59"/><clear/>So they may not

necessarily
cure you, but they may make it
 <time begin="00:32:29.37"/><clear/>so that the symptoms aren't

quite so severe.
 <time begin="00:32:31.98"/><clear/>And if the therapeutics are

highly
specific, meaning that the drug works
 <time begin="00:32:36.13"/><clear/>for a particular organism,

it's really important
to know what that organism is, alright?
 <time begin="00:32:40.35"/><clear/>So we can see this logical

flow from having
good diagnostics to good therapeutics.
 <time begin="00:32:46.26"/><clear/>It turns out for some of the

things that you
can get, etiological agents, nasty organisms,
 <time begin="00:32:53.71"/><clear/>that the drugs that are

available
for them are pretty bad.
 <time begin="00:32:58.27"/><clear/>I mean you take these drugs,

they make you sick.
 <time begin="00:33:00.33"/><clear/>They have a very strong

effect on your
own physiology and so you don't want
 <time begin="00:33:05.98"/><clear/>to be giving people drugs

willy
nilly without knowing what they are.
 <time begin="00:33:09.73"/><clear/>So diagnostics is very

important and leads
into the application of therapeutics.
 <time begin="00:33:14.59"/><clear/>Ideally if we had good

therapeutics, you
would take a pill and you would be cured.
 <time begin="00:33:18.65"/><clear/>Alright, but very often we

don't
get that kind of circumstance.
 <time begin="00:33:21.71"/><clear/>What we get is a circumstance

where we're just
trying to control the disease symptoms, alright.
 <time begin="00:33:26.00"/><clear/>We're not necessarily trying

to
cure the person of the disease,
 <time begin="00:33:28.74"/><clear/>because we don't have

anything that works.
 <time begin="00:33:31.11"/><clear/>
 <time begin="00:33:32.33"/><clear/>See what else I can tell you

about that.
 <time begin="00:33:33.74"/><clear/>That's enough.
 <time begin="00:33:34.87"/><clear/>Alright prevention.
 <time begin="00:33:36.23"/><clear/>Well prevention turns out

to
be the most cost effective way
 <time begin="00:33:40.27"/><clear/>to deal with these infectious

diseases.
 <time begin="00:33:44.60"/><clear/>If you never get the

infectious disease,
then you don't have to be diagnosed
 <time begin="00:33:49.57"/><clear/>or very expensive diagnostic

techniques
or you don't have to spend money on drugs.
 <time begin="00:33:54.19"/><clear/>And prevention, when working

with
infectious agents, is as simple as not coming
 <time begin="00:33:59.93"/><clear/>in contact with that

infectious agent.
 <time begin="00:34:02.14"/><clear/>So all these things that tell

you
to avoid certain circumstances
 <time begin="00:34:05.73"/><clear/>where you won't get certain

diseases,
I'm talking to the students now, alright.
 <time begin="00:34:09.99"/><clear/>That actually makes sense,

alright.
 <time begin="00:34:11.92"/><clear/>No one's trying to cut out

you
having a lot of fun and everything.
 <time begin="00:34:14.65"/><clear/>But if you don't come in

contact
with the infectious agent,
 <time begin="00:34:17.80"/><clear/>you won't get the disease,

alright?
 <time begin="00:34:19.70"/><clear/>So that's really simple, it's

straightforward,
something to keep in mind, okay?
 <time begin="00:34:25.48"/><clear/>And it works, alright.
 <time begin="00:34:28.48"/><clear/>It's called the dependency

clause.
 <time begin="00:34:30.59"/><clear/>You have to be in the same

place.
 <time begin="00:34:32.63"/><clear/>You know, the pathogens

aren't going
to fall out of the sky kind of thing
 <time begin="00:34:35.97"/><clear/>or be on a doorknob or

anything like that.
 <time begin="00:34:38.91"/><clear/>Alright. So prevention is

actually very useful.
 <time begin="00:34:41.63"/><clear/>And we're going to talk about

two aspects

of prevention in just a little bit.
 <time begin="00:34:45.15"/><clear/>One of them dealing with not

coming
in contact with the infectious agent
 <time begin="00:34:49.24"/><clear/>and the other one dealing

with what
happens if you do come in contact
 <time begin="00:34:52.42"/><clear/>with the infectious agent

and
the deployment of vaccine.
 <time begin="00:34:55.21"/><clear/>So something gives you a

pre-exposure that
allows your body to build up a resistance.
 <time begin="00:35:00.25"/><clear/>How am I doing here?
 <time begin="00:35:01.24"/><clear/>Alright. Alright.
 <time begin="00:35:06.16"/><clear/>So, there are three very

recent milestone
efforts as we segue into the type
 <time begin="00:35:10.60"/><clear/>of work that's going on in my

lab
that are then important for thinking
 <time begin="00:35:15.37"/><clear/>and developing novel ways to

deal with malaria.
 <time begin="00:35:19.92"/><clear/>And all of these are based

on
dealing with genes and the genome.
 <time begin="00:35:24.68"/><clear/>Alright, and there are lots

of
different reasons why this is important.
 <time begin="00:35:29.25"/><clear/>But I told you before that

malaria parasites
have a very strong host specificity.
 <time begin="00:35:35.68"/><clear/>That the types of parasites

that infect
human beings, only infect human beings,
 <time begin="00:35:40.17"/><clear/>they don't infect birds,
they don't infect lizards,
 <time begin="00:35:42.70"/><clear/>primates or other

models,
or mice that have been used.
 <time begin="00:35:46.44"/><clear/>And that suggests that

genes
are somehow involved.
 <time begin="00:35:50.22"/><clear/>Both the genes of the

human
host, so the genetic makeup
 <time begin="00:35:54.34"/><clear/>of the human makes it

particularly

susceptible to a group of parasites,
 <time begin="00:35:58.46"/><clear/>and the genetic makeup of

those parasites.
 <time begin="00:36:00.80"/><clear/>Aright, there's something

about them
that allows them to grow in humans.
 <time begin="00:36:05.59"/><clear/>And so the sequencing of the

human genome and the
sequencing of the parasite genome are major steps
 <time begin="00:36:12.14"/><clear/>in trying to get our hands on

those pieces
of discreet information that allow this type
 <time begin="00:36:18.25"/><clear/>of host parasite interaction

to take place.
 <time begin="00:36:21.25"/><clear/>In addition, we have the
genome sequence of the vector.
 <time begin="00:36:24.49"/><clear/>In this case the Anopheles

mosquito,
specifically Anopheles gambiae.
 <time begin="00:36:28.33"/><clear/>And a similar sort of

argument applies here.
 <time begin="00:36:30.75"/><clear/>The fact that only

Anopheles
mosquitoes transmit human malaria,
 <time begin="00:36:34.47"/><clear/>and that the malaria can

infect these parasites,
suggests that there's some genetic aspect
 <time begin="00:36:39.65"/><clear/>to this, some inheritable

aspect.
 <time begin="00:36:41.45"/><clear/>And we're starting to see the

impact of
genetics and genetic tools and the sequencing
 <time begin="00:36:47.55"/><clear/>of these genomes, knowing all

the things
that are there on the development
 <time begin="00:36:50.93"/><clear/>of new strategies to control

malaria.
 <time begin="00:36:54.34"/><clear/>In diagnostics it's as

straightforward as asking
the question, if you have malaria parasites,
 <time begin="00:37:01.14"/><clear/>they're ought to be malaria

DNA there, alright?
 <time begin="00:37:03.53"/><clear/>So that makes the

diagnostics
more straightforward
 <time begin="00:37:06.22"/><clear/>and so people are

developing
techniques that disting-, based on DNA,
<time begin="00:37:12.55"/><clear/>that distinguish malaria
parasites from other things
<time begin="00:37:15.72"/><clear/>that would cause what are

called febrile
diseases, diseases that give you those symptoms
<time begin="00:37:19.05"/><clear/>that I talked about, the
headaches, fever, etcetera.
<time begin="00:37:21.61"/><clear/>Alright. If that's caused by

influenza virus,
<time begin="00:37:24.01"/><clear/>you ought to find evidence

of
the influenza gene on there.
<time begin="00:37:26.84"/><clear/>If it's caused by malaria

parasites, you
ought to be able to find evidence for that.
<time begin="00:37:31.29"/><clear/>And so this is being

developed there.
<time begin="00:37:33.93"/><clear/>And there are a number of

different
tests that people are trying to develop.
<time begin="00:37:37.33"/><clear/>And they're called rapid,

development of rapid
diagnostic tests, RDTs and basically a number
<time begin="00:37:44.60"/><clear/>of different assays are being

developed.
<time begin="00:37:48.35"/><clear/>Most of, those of you who are

undergraduates
have done laboratories where you've looked
<time begin="00:37:52.05"/><clear/>at DNA, this is a gel,

electrophoresis
of DNA, you can see it.
<time begin="00:37:55.77"/><clear/>This is a dipstick test they

found out.
<time begin="00:37:57.69"/><clear/>And the idea is to see if you

could come up with
a rapid way to tell if a person has malaria.
<time begin="00:38:05.67"/><clear/>The gold standard is that

blood smear that
we've been seeing over and over and over again.
<time begin="00:38:10.78"/><clear/>If you take a blood smear

and
you see those parasites there,
<time begin="00:38:13.53"/><clear/>then you know a person is

infected.
<time begin="00:38:16.24"/><clear/>So this isn't perfect,

```
okay?<br/>
 <time begin="00:38:18.69"/><clear/>But it's a start in this

direction.<br/>
 <time begin="00:38:22.25"/><clear/>Therapeutic, this is that

quote I talked about,<br/>
 <time begin="00:38:25.45"/><clear/>that a new drug must be

available<br/>
every five years.<br/>
 <time begin="00:38:28.37"/><clear/>Genomics has actually been

very useful here<br/>
because we can study biological pathways<br/>
 <time begin="00:38:33.05"/><clear/>that are present in the

parasite<br/>
that we don't find in the human<br/>
 <time begin="00:38:36.86"/><clear/>and then we can ask the

question,<br/>
can we find drugs<br/>
 <time begin="00:38:39.97"/><clear/>that will affect those

biochemical<br/>
pathways that exist only in the parasite<br/>
 <time begin="00:38:44.88"/><clear/>and therefore won't have an

impact on the human.<br/>
 <time begin="00:38:47.49"/><clear/>And so there's been quite a

bit<br/>
of work in this particular area<br/>
 <time begin="00:38:50.89"/><clear/>and I have two citations here

specifically<br/>
relating to new biochemical pathways<br/>
 <time begin="00:38:56.20"/><clear/>that have been found that are

targets for this.<br/>
 <time begin="00:38:59.19"/><clear/>
 <time begin="00:39:00.98"/><clear/>Alright. So we're going to

talk a little bit<br/>
about prevention and finish off here talking<br/>
 <time begin="00:39:04.83"/><clear/>about some of the work

that's<br/>
going on in our lab.<br/>
 <time begin="00:39:09.62"/><clear/>We do, do work on vaccines,

alright?<br/>
 <time begin="00:39:11.76"/><clear/>So the, for those of you who

don't<br/>
know, the principal behind a vaccine is<br/>
 <time begin="00:39:15.61"/><clear/>to expose your body to

an<br/>
infectious agent in a circumstance<br/>
 <time begin="00:39:20.04"/><clear/>where that infectious
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agent<br/>
won't cause severe disease.<br/>
 <time begin="00:39:23.02"/><clear/>This allows your body to

amount<br/>
an immune response against that,<br/>
 <time begin="00:39:26.31"/><clear/>so when you see the real

thing,<br/>
you're ready do fight it off, alright?<br/>
 <time begin="00:39:29.85"/><clear/>You've got a chance

because<br/>
your body's already been primed.<br/>
 <time begin="00:39:33.02"/><clear/>And there's been a tremendous

effort to<br/>
develop vaccines and, for malaria and we'll see<br/>
 <time begin="00:39:38.65"/><clear/>in just a second how those

work out.<br/>
 <time begin="00:39:41.01"/><clear/>And then I'm going to tell

you<br/>
about some new anti-vector measures,<br/>
 <time begin="00:39:43.77"/><clear/>the work that's going on in

our lab.<br/>
 <time begin="00:39:45.28"/><clear/>Alright. I put this slide in

here just to show<br/>
you that vaccines can be highly efficacious<br/>
 <time begin="00:39:51.57"/><clear/>and this is a slide that I

got from<br/>
one of our principle vaccinologists,<br/>
 <time begin="00:39:58.12"/><clear/>Victor Nussenzweig, I<br/>
mean he put this together in a talk he gave.<br/>
 <time begin="00:40:01.48"/><clear/>It talks about the power of

prevention,<br/>
the impact of vaccines in the US<br/>
 <time begin="00:40:05.65"/><clear/>and these are vaccines from a

number of<br/>
different diseases, poliomyelitis, diphtheria,<br/>
 <time begin="00:40:09.88"/><clear/>measles, rubella, mumps and

pertussis.<br/>
 <time begin="00:40:13.38"/><clear/>And what happens to cases per

one hundred<br/>
thousand after the introduction of the vaccine.<br/>
 <time begin="00:40:19.75"/><clear/>And you can see for polio

that<br/>
the number drops very rapidly.<br/>
 <time begin="00:40:23.88"/><clear/>In fact for all of these the

numbers go down.<br/>
 <time begin="00:40:26.12"/><clear/>Measles is experiencing a

rebirth here.<br/>
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<time begin="00:40:28.80"/><clear/>But for the majority of them,

the cases per
one hundred thousand go way down to the point
<time begin="00:40:34.30"/><clear/>where most of the students in

the room have
no idea what a polio case actually looks like.
<time begin="00:40:41.63"/><clear/>Alright? I'm actually old

enough to
have had classmates that got polio
<time begin="00:40:47.13"/><clear/>and as a consequence were

confined to
crutches for the rest of their lives.
<time begin="00:40:51.02"/><clear/>Alright? So this is something

only the
senior members in this group know about.
<time begin="00:40:55.67"/><clear/>But it's something which is

not even on
the horizon of the younger people here.
<time begin="00:41:00.20"/><clear/>And that's a direct impact of

the vaccine.
<time begin="00:41:02.35"/><clear/>So there's a whole major,

what used to be
a major disease here that's no longer part
<time begin="00:41:07.38"/><clear/>of the spectrum of your life

as a
consequence of the development of vaccine.
<time begin="00:41:11.39"/><clear/>So the whole point of this is

to tell
you that if we had a vaccine for malaria,
<time begin="00:41:14.74"/><clear/>we would expect to have

the
similar type of dramatic impact.
<time begin="00:41:19.28"/><clear/>And for malaria we've got a

number
of possible imaginable vaccines.
<time begin="00:41:23.36"/><clear/>We've got a vaccine that,

this is a
mosquito here, it doesn't look like much.
<time begin="00:41:26.74"/><clear/>Just magnification.
<time begin="00:41:28.74"/><clear/>But this is a mosquito that

is
feeding on the arm of a human
<time begin="00:41:31.49"/><clear/>and infecting a

particular
stage called the sporozoite.
<time begin="00:41:34.54"/><clear/>This is the infectious form

of the parasite.

<time begin="00:41:37.03"/><clear/>And so a good vaccine would

be a vaccine that
blocks these parasites from infecting us.
<time begin="00:41:43.11"/><clear/>Alright? That would be, in

fact, that would
probably be the best vaccine we could get.
<time begin="00:41:46.89"/><clear/>It's a complete protection

here.
<time begin="00:41:48.29"/><clear/>If we could get that.
<time begin="00:41:50.39"/><clear/>But this alone isn't

sufficient a cause disease.
<time begin="00:41:53.83"/><clear/>So disease is not the

same
thing as being infected.
<time begin="00:41:56.27"/><clear/>Most of you know that.
<time begin="00:41:57.15"/><clear/>Because right now every one

of
you is infected with e coli.
<time begin="00:42:01.67"/><clear/>You've got all these

bacteria
growing in your gut.
<time begin="00:42:04.41"/><clear/>But they don't cause a

disease, okay?
<time begin="00:42:06.68"/><clear/>So you can have an

infection
without having disease.
<time begin="00:42:10.71"/><clear/>Where we see the disease is

once the parasite
gets into the liver and starts growing
<time begin="00:42:14.61"/><clear/>in the liver, it makes these

forms which get
out and start eating the red blood cells.
<time begin="00:42:18.98"/><clear/>We saw that picture and this

is
where the disease actually manifests
<time begin="00:42:22.05"/><clear/>and where people start

getting symptoms.
<time begin="00:42:23.98"/><clear/>So it's possible to

develop
a vaccine that protects
<time begin="00:42:27.88"/><clear/>against the forms that

actually cause disease.
<time begin="00:42:30.60"/><clear/>So this is one type that

people are looking at.
<time begin="00:42:33.05"/><clear/>They're looking at the one

that blocks

infection, one that prevents disease
 <time begin="00:42:36.43"/><clear/>and then there's another

group of people
that are looking to prevent transmission
 <time begin="00:42:40.39"/><clear/>because I told you before

that this
parasite lives only in the humans and only
 <time begin="00:42:45.65"/><clear/>in the mosquitoes and has to

go back and
forth between the mosquitoes and the humans.
 <time begin="00:42:50.60"/><clear/>So if we could actually make

a vaccine that
prevents the mosquito from taking up the stages
 <time begin="00:42:54.74"/><clear/>that infects it, then we

could
block transmission this way.
 <time begin="00:42:58.37"/><clear/>Well the good news is that

people
are working on all three of these.
 <time begin="00:43:01.93"/><clear/>And it's a competition,

sometimes friendly.
 <time begin="00:43:05.61"/><clear/>And the idea would be that

one would have a
vaccine that would combine elements of all three
 <time begin="00:43:11.14"/><clear/>of these blocking strategies

and have
something that works really well.
 <time begin="00:43:16.17"/><clear/>
 <time begin="00:43:18.08"/><clear/>As corny as it sounds,

alright,
insecticide nets work really well.
 <time begin="00:43:24.93"/><clear/>Very, very, very well.
 <time begin="00:43:26.79"/><clear/>It's a very curious thing

about the mosquitoes
that transmit malaria, at least in Africa.
 <time begin="00:43:32.34"/><clear/>They usually bite from like

midnight to
maybe three or four o'clock in the morning.
 <time begin="00:43:38.11"/><clear/>Which is when you're asleep,

alright.
 <time begin="00:43:40.56"/><clear/>Which is when it's easiest to

bite you.
 <time begin="00:43:42.68"/><clear/>Alright? They've adapted

to
feeding on humans at a time
 <time begin="00:43:45.90"/><clear/>when humans are least

able

to protect themselves.
 <time begin="00:43:48.84"/><clear/>So it's these early hours in

the morning.
 <time begin="00:43:50.89"/><clear/>So if you ever have a chance

to go to
Africa and you're worried about malaria,
 <time begin="00:43:54.68"/><clear/>the one thing you don't want

to be doing is
running around in the middle of the night.
 <time begin="00:43:58.01"/><clear/>Alright. The other thing you

do want
to be doing is sleeping under a net.
 <time begin="00:44:02.09"/><clear/>Alright. Because this

prevents the
mosquitoes from getting to you.
 <time begin="00:44:05.12"/><clear/>Alright. And you can sleep

under this net and
they can't bite you and it will protect you.
 <time begin="00:44:09.84"/><clear/>And in fact, they've done

studies and they've
shown that you can actually reduce total malaria
 <time begin="00:44:16.88"/><clear/>by about 17 percent and

severe disease by
as much as 50 percent when using bed nets.
 <time begin="00:44:22.85"/><clear/>So these actually work,

alright?
 <time begin="00:44:26.50"/><clear/>So more advice for you, for

those
of you who are going into the field.
 <time begin="00:44:29.35"/><clear/>It's important to have a net

that
doesn't have holes in it, alright?
 <time begin="00:44:32.41"/><clear/>Now that may sound not like a

big deal,
but remember the mosquito has all night,
 <time begin="00:44:38.79"/><clear/>or at least the hours between

midnight
and say four or five in the morning
 <time begin="00:44:42.23"/><clear/>and then she can come back

the next
night, to find that hole in the net.
 <time begin="00:44:46.09"/><clear/>And they will do that,

alright?
 <time begin="00:44:47.36"/><clear/>If there are holes in the

net, they'll just
hang around there until one actually gets in.
 <time begin="00:44:50.84"/><clear/>So you want to make sure that

there are no
holes in the net and you want to make sure
 <time begin="00:44:54.24"/><clear/>that you don't sleep up

against
the net, alright?
 <time begin="00:44:56.72"/><clear/>So that it's right up against

your skin.
 <time begin="00:44:58.70"/><clear/>Because believe it or not,

they'll land
on the net, and they'll just bite through.
 <time begin="00:45:02.67"/><clear/>And one of the most

interesting, if you're a
scientist and creepy if you're not a scientist,
 <time begin="00:45:08.52"/><clear/>things that you can do is

wake up in the
middle of the night, turn your flashlight on
 <time begin="00:45:12.33"/><clear/>and look at the outside of

the net.
 <time begin="00:45:14.62"/><clear/>It will convince you to

stay
inside the net, that's for sure.
 <time begin="00:45:18.53"/><clear/>At least it did for me.
 <time begin="00:45:20.52"/><clear/>Alright. But these work,

and
they work very, very well.
 <time begin="00:45:23.62"/><clear/>Alright so let's talk a

little bit
about what we do in our laboratory.
 <time begin="00:45:28.54"/><clear/>The research in our

laboratory is
stimulated, I'm going to be talking only
 <time begin="00:45:32.76"/><clear/>about this side here which is

genetic
control of vector born diseases,
 <time begin="00:45:37.47"/><clear/>is stimulated by two

things
that I haven't told you yet.
 <time begin="00:45:42.65"/><clear/>But turn out to be fairly

interesting, I think.
 <time begin="00:45:46.09"/><clear/>That's why we work on it of

course.
 <time begin="00:45:48.25"/><clear/>The first is that not

every
mosquito can transmit every pathogen.
 <time begin="00:45:53.78"/><clear/>We've already talked about

that.

<time begin="00:45:54.95"/><clear/>We talked about the fact

that
Anopheles mosquitoes transmit malaria.
<time begin="00:45:59.02"/><clear/>Well you know about other

vector born
diseases, you've heard about West Nile Virus,
<time begin="00:46:03.10"/><clear/>you may have even heard about

Dengue
viruses, you've probably heard
<time begin="00:46:06.00"/><clear/>about Encephalitis, the

various
types of Encephalitis.
<time begin="00:46:09.61"/><clear/>Well the Anopheles

mosquitoes
don't transmit those viruses.
<time begin="00:46:12.70"/><clear/>Alright? There's a whole

other group
of mosquitoes that transmit those.
<time begin="00:46:15.62"/><clear/>And those whole other group

that transmit those
don't transmit the human malaria, alright?
<time begin="00:46:19.83"/><clear/>So where am I going with

this?
<time begin="00:46:21.87"/><clear/>Once again, genetics seems to

be involved.
<time begin="00:46:24.27"/><clear/>There's a genetic makeup of a

particular
mosquito that allows it to be a hospitable host
<time begin="00:46:29.96"/><clear/>for a particular set of

pathogens
and therefore can transmit that.
<time begin="00:46:33.26"/><clear/>So that's the first

observation, that not
every blood sucking mosquito has the ability
<time begin="00:46:37.54"/><clear/>to transmit every disease and

that's
likely a consequence of genetics.
<time begin="00:46:41.94"/><clear/>But it turns out to even

be
more interesting than that,
<time begin="00:46:45.60"/><clear/>and that is that you can take

a population
of mosquitoes or you can take a species
<time begin="00:46:49.68"/><clear/>of mosquitoes that normally

transmit,
so say this Anopheles gambiae
<time begin="00:46:53.61"/><clear/>that normally transmits human

malaria.
 <time begin="00:46:55.76"/><clear/>With a little bit of work,

you can feed that
on a source where it can become infected.
 <time begin="00:47:03.69"/><clear/>What do I mean by that?
 <time begin="00:47:05.19"/><clear/>We can culture these

malaria
parasites in a dish and if we're lucky,
 <time begin="00:47:09.19"/><clear/>there'll be both of the types

that
eat the red blood cells and you've got
 <time begin="00:47:11.51"/><clear/>to constantly give them red

blood cells.
 <time begin="00:47:13.69"/><clear/>So when you're around a

malaria lab it's kind of
nervous because there's all these people walking
 <time begin="00:47:17.26"/><clear/>around with sixty ml syringes

which are
the big ones looking for blood, you know.
 <time begin="00:47:21.32"/><clear/>So, you want to be careful

around them.
 <time begin="00:47:25.21"/><clear/>They're shameless in their

pursuit.
 <time begin="00:47:27.85"/><clear/>But they'll take your red

blood cells, they'll
prepare them, they'll put them in this dish
 <time begin="00:47:31.28"/><clear/>and the malaria parasites

will live on them,
they'll feed on them, they can keep as cultured.
 <time begin="00:47:35.79"/><clear/>Well certain cultures will

make the forms of
the parasite that can infect the mosquito.
 <time begin="00:47:40.03"/><clear/>And so you can take this

blood from
this dish then and feed it to a mosquito
 <time begin="00:47:44.29"/><clear/>and the mosquitoes will get

the parasite.
 <time begin="00:47:46.59"/><clear/>Alright that's a long way of

telling you that
we don't infect the people in our lab, okay?
 <time begin="00:47:50.74"/><clear/>You needed to know that.
 <time begin="00:47:54.25"/><clear/>So when you do that you can

actually select
those mosquitoes that become infected
 <time begin="00:47:58.24"/><clear/>and mate them all together

and you can

take the ones that don't become infected,
 <time begin="00:48:01.68"/><clear/>mate them together and

you
do that for a little while.
 <time begin="00:48:04.25"/><clear/>And pretty soon you have two

populations,
you have one population that's really easy
 <time begin="00:48:09.12"/><clear/>to infect, and another

population
that's not so easy to infect.
 <time begin="00:48:13.09"/><clear/>Now you can do genetics.
 <time begin="00:48:14.52"/><clear/>You can cross them

together
and say, how does it behave?
 <time begin="00:48:17.14"/><clear/>Is it like a dominant

trait?
 <time begin="00:48:18.60"/><clear/>Is it a recessive trait?
 <time begin="00:48:20.24"/><clear/>How many genes are

involved?
 <time begin="00:48:21.77"/><clear/>You can actually start to map

out the genetics
of susceptibility, that is those that become infected
 <time begin="00:48:26.78"/><clear/>from resistance, those

that
are resistant to that.
 <time begin="00:48:29.09"/><clear/>And you say, hey there

are
genes that are involved.
 <time begin="00:48:31.68"/><clear/>Indeed there's a lot of

science going on
right now trying to identify those genes
 <time begin="00:48:37.13"/><clear/>that make it possible for a

mosquito to
become infected and therefore transmit it.
 <time begin="00:48:42.94"/><clear/>When we first started doing

this work, we
weren't in the position to identify those genes.
 <time begin="00:48:47.88"/><clear/>We started this work a long

time ago.
 <time begin="00:48:49.54"/><clear/>We didn't have the human
genome all available to us,
 <time begin="00:48:51.82"/><clear/>we didn't have the

malaria
parasite genome available to us
 <time begin="00:48:54.90"/><clear/>and we didn't have the

mosquito
genome available to us.
 <time begin="00:48:57.58"/><clear/>And we thought it would be

very difficult for us
to identify just exactly what these genes are.
 <time begin="00:49:02.74"/><clear/>So we came up with a strategy

which
is going to sound kind of crazy,
 <time begin="00:49:06.95"/><clear/>but we decided we would just

make a gene.
 <time begin="00:49:09.69"/><clear/>Alright? So instead of

relying on naturally
occurring genes that confer resistance
 <time begin="00:49:14.90"/><clear/>to malaria parasites, this

was
in the late nineties, you know,
 <time begin="00:49:19.40"/><clear/>or actually early nineties,

you know.
 <time begin="00:49:21.16"/><clear/>The arrogance of the nineties

as we call
it, why not just make a gene, alright?
 <time begin="00:49:25.22"/><clear/>And we can actually put

it
together and we thought, okay,
 <time begin="00:49:27.61"/><clear/>that sounds like an

interesting idea.
 <time begin="00:49:29.67"/><clear/>If we're going to make a

gene
though, what's it going to look like?
 <time begin="00:49:32.31"/><clear/>So a simple molecular biology

lesson for you is
a gene can be thought of as having two parts.
 <time begin="00:49:38.06"/><clear/>One part which is the

control
sequence, the part that tells it when,
 <time begin="00:49:41.50"/><clear/>where, how much to make,

alright?
 <time begin="00:49:43.73"/><clear/>So that controls it.
 <time begin="00:49:44.93"/><clear/>And the other part is

the
part that's actually made.
 <time begin="00:49:47.47"/><clear/>Alright? The part that is

the
product or the gene so to speak.
 <time begin="00:49:51.51"/><clear/>So we thought, well why not

just use this
very simple model, define circumstances
 <time begin="00:49:56.48"/><clear/>where we have control

sequences that we want

and make something that kills malaria parasites.
 <time begin="00:50:02.00"/><clear/>So that's what we did.
 <time begin="00:50:03.78"/><clear/>And I'll show you how that

works.
 <time begin="00:50:06.24"/><clear/>Alright, well the first

thing
is this control sequence stuff,
 <time begin="00:50:11.08"/><clear/>this is actually turns out to

be important.
 <time begin="00:50:13.70"/><clear/>And so we have a little more

life cycle stuff
here, but it's actually pretty straightforward.
 <time begin="00:50:18.93"/><clear/>I'm going to fast forward one

because
I think this is the picture we want.
 <time begin="00:50:22.50"/><clear/>It wasn't immediately obvious

to most
of you that what you were looking
 <time begin="00:50:25.69"/><clear/>at was a schematic

representation of a mosquito.
 <time begin="00:50:28.39"/><clear/>This looks a little bit more

like it.
 <time begin="00:50:29.99"/><clear/>So this is a schematic

representation
of a mosquito.
 <time begin="00:50:33.10"/><clear/>And what happens is, this is

a mosquito as
if she had been opened up and you're kind
 <time begin="00:50:38.69"/><clear/>of looking inside of her

and
there's a lot of stuff in there
 <time begin="00:50:42.38"/><clear/>and it's not important

to
memorize what this stuff is.
 <time begin="00:50:44.94"/><clear/>But she's got a long

proboscis which
comes off the field of view here.
 <time begin="00:50:49.06"/><clear/>And she'll land on you and

she'll probe.
 <time begin="00:50:50.82"/><clear/>Alright, and that's a whole

other lecture
that Dr. Champaign here can talk about,
 <time begin="00:50:55.43"/><clear/>what is involved in actually

getting a blood
meal out of a host because it's not easy.
 <time begin="00:51:00.59"/><clear/>But when she gets that blood

meal it
ends up here in what's called the midgut.
 <time begin="00:51:04.47"/><clear/>So this is the first

encounter of the
malaria parasite with the mosquito.
 <time begin="00:51:08.54"/><clear/>And if you think about it,

it's a very
different change to what it was used to.
 <time begin="00:51:14.22"/><clear/>It was used to living in the

human being
that's a nice thirty seven degrees,
 <time begin="00:51:17.93"/><clear/>ninety eight point six

Fahrenheit,
temperature, the Ph, the acid concentration
 <time begin="00:51:22.87"/><clear/>in the blood is very

specific,
it's in that nice environment
 <time begin="00:51:25.99"/><clear/>where it's living in and

eating red blood cells.
 <time begin="00:51:28.57"/><clear/>Everything's great.
 <time begin="00:51:29.68"/><clear/>And all of a sudden it finds

itself in
the digestive system of an insect, okay?
 <time begin="00:51:34.25"/><clear/>This is about as alien as

you
can possibly get it seems.
 <time begin="00:51:38.91"/><clear/>So the first site of

interaction
then is this midgut and if we want to go
 <time begin="00:51:44.56"/><clear/>after the malaria parasites

why
not put the gene that we're making,
 <time begin="00:51:48.54"/><clear/>why not put its product in

the midgut here?
 <time begin="00:51:51.43"/><clear/>Why not put it in the

place
where the parasites are?
 <time begin="00:51:54.09"/><clear/>So that actually turns out to

be a
good place to go after the parasite.
 <time begin="00:51:59.99"/><clear/>And indeed when you look at

the naturally
occurring resistance to malaria parasites many
 <time begin="00:52:06.21"/><clear/>of the resistance genes have

as
their phenotype, the way they look,
 <time begin="00:52:10.18"/><clear/>the inability of the

parasite
to ever get out of the midgut.
 <time begin="00:52:13.42"/><clear/>The mosquitos basically

ingest
them and they can't get out, okay?
 <time begin="00:52:17.73"/><clear/>So this is something

which
is reflected in nature.
 <time begin="00:52:19.90"/><clear/>But once they get out, they

get into this
open circulatory system and they have
 <time begin="00:52:25.00"/><clear/>to migrate to the salivary

glands.
 <time begin="00:52:27.25"/><clear/>Well this open circulatory

system is very much
like yours and I in a certain way and that is
 <time begin="00:52:32.63"/><clear/>that the immune aspects of

the mosquito often
play out here in this open circulatory system.
 <time begin="00:52:38.20"/><clear/>So we have the possibility

of
going after the malaria parasite
 <time begin="00:52:42.57"/><clear/>where it's in this open

circulatory system.
 <time begin="00:52:46.38"/><clear/>And then all of them have to

make their way back
 <time begin="00:52:48.22"/><clear/>to the salivary glands

before
they're transmitted on to a new host.
 <time begin="00:52:51.81"/><clear/>Because what happens is the

parasites get into
the salivary gland, the mosquito lands on you,
 <time begin="00:52:56.23"/><clear/>salivates into the wound site

and
then delivers the pathogens that way.
 <time begin="00:53:00.53"/><clear/>So basically we look at these

various tissues
and we say well here are our opportunities
 <time begin="00:53:06.05"/><clear/>to interrupt the development

of this parasite.
 <time begin="00:53:08.24"/><clear/>We have the midgut, the open

circulatory
system, and the salivary glands.
 <time begin="00:53:12.68"/><clear/>So to go back to this

synthetic
gene we're going to make,
 <time begin="00:53:16.37"/><clear/>what we need to do is find a

control sequences
of a gene that will allow us to put something
 <time begin="00:53:21.79"/><clear/>in the midgut, the hemolymph

or
the salivary glands, alright?
 <time begin="00:53:25.86"/><clear/>So that's strategy one is to

identify
the appropriate control sequences.
 <time begin="00:53:29.83"/><clear/>And our hypothesis then is

that we have
these in the appropriate effector molecule,
 <time begin="00:53:35.24"/><clear/>if we get this gene into a

population of vectors
and we spread this gene through that population,
 <time begin="00:53:44.58"/><clear/>we should see a decrease in

the
transmission of that pathogen,
 <time begin="00:53:47.19"/><clear/>in this case the malaria

parasite, okay?
 <time begin="00:53:50.04"/><clear/>And so that's what we try to

do.
 <time begin="00:53:54.09"/><clear/>Alright. So when we

recognized this, we realized
that we had several major areas of research
 <time begin="00:53:59.92"/><clear/>and we're only going to

talk
about this one right now, okay?
 <time begin="00:54:04.03"/><clear/>I have got to give another

talk tomorrow
and for those of you who are interested
 <time begin="00:54:06.93"/><clear/>in this next step, we can

talk
about it then, but this has to deal
 <time begin="00:54:09.99"/><clear/>with how we can actually make

this mosquito.
 <time begin="00:54:13.40"/><clear/>Okay. And so the first thing

we need to be able
to do is we're talking about making a gene,
 <time begin="00:54:17.68"/><clear/>well we ought to be able
to put that gene back in.
 <time begin="00:54:20.01"/><clear/>So we have to develop

transgenesis technology.
 <time begin="00:54:22.56"/><clear/>And this took a long time, it

took
a long, long time for us to do.
 <time begin="00:54:27.68"/><clear/>But the idea here is if

you're going to
have a gene that you want to be able to put
 <time begin="00:54:31.08"/><clear/>that gene back into the

insect in
the way that it's stably integrated,
 <time begin="00:54:35.75"/><clear/>meaning it goes into that

mosquito
and it's passed on to the progeny.
 <time begin="00:54:39.46"/><clear/>And that means that it can

actually
be spread to the population.
 <time begin="00:54:43.36"/><clear/>We talked already about

identifying control
sequences that can express the effector molecule
 <time begin="00:54:48.62"/><clear/>and then we have the actual

effector molecule,
 <time begin="00:54:51.07"/><clear/>the molecule that will

interfere
with the parasite.
 <time begin="00:54:55.81"/><clear/>Alright. We have transgenesis

technology,
it works wonderfully with mosquitoes.
 <time begin="00:54:59.15"/><clear/>This is just a little review

slide and it
shows all these great mosquitoes with glow
 <time begin="00:55:02.58"/><clear/>in the dark eyes, which you

might
think might be an advantage.
 <time begin="00:55:06.27"/><clear/>But probably is not.
 <time begin="00:55:08.96"/><clear/>And we have control

sequences.
 <time begin="00:55:10.42"/><clear/>This is a slide which talks

about the various
kinds of control sequences that we have
 <time begin="00:55:15.29"/><clear/>that would work with the

parasites and this is
a genomics display of genes that are turned on,
 <time begin="00:55:21.77"/><clear/>fourteen thousand genes that

are turned
on and off and so we have lots of things
 <time begin="00:55:25.07"/><clear/>that we can actually work

with as a
consequence of the genomics effort.
 <time begin="00:55:29.27"/><clear/>But I want to spend time

talking about the
effector molecules for malaria parasites.
 <time begin="00:55:34.78"/><clear/>Now you want to build a gene

that
interferes with the malaria parasite.
 <time begin="00:55:39.99"/><clear/>How would you go about doing

that?
 <time begin="00:55:41.88"/><clear/>Well you already know that

the parasite has to
live inside the mosquito and we already know
 <time begin="00:55:46.62"/><clear/>that it invades certain

tissues, it
invades the midgut when it's ingested,
 <time begin="00:55:49.85"/><clear/>it gets into the hemolymph

and
invades the salivary glands.
 <time begin="00:55:53.25"/><clear/>Well the question is you've

got a single
celled organism, how does it know where to go?
 <time begin="00:55:58.75"/><clear/>Alright. What does it mean to

know where to go?
 <time begin="00:56:01.77"/><clear/>So this is a single cell, it

doesn't have
a brain, it doesn't even have a neuron.
 <time begin="00:56:06.37"/><clear/>It can't think about

where
it's going in the organism.
 <time begin="00:56:10.31"/><clear/>So we think about, well what

are
honing devices for cells and stuff.
 <time begin="00:56:15.02"/><clear/>You know we think about

the
concept of having receptors.
 <time begin="00:56:18.30"/><clear/>Alright, and I can

translate
that very easily for you.
 <time begin="00:56:21.71"/><clear/>Receptors are molecules that

are on the surface
of the tissue where the pathogen has to go
 <time begin="00:56:27.06"/><clear/>and they somehow say

that
this is where you want to be,
 <time begin="00:56:29.55"/><clear/>it's a molecule that's on the

surface.
 <time begin="00:56:31.61"/><clear/>And you have a ligand which

is another molecule
which is on the surface of the parasite
 <time begin="00:56:35.66"/><clear/>that interacts specifically

with that receptor.
 <time begin="00:56:38.24"/><clear/>And when those two come

```
together, the<br/>
parasite knows I've got to go here.<br/>
 <time begin="00:56:41.96"/><clear/>Alright? So you have this

parasite in the<br/>
middle of a mosquito or somewhere in the mosquito,<br/>
 <time begin="00:56:47.26"/><clear/>it's got this ligand,<br/>
it's fishing around for a target tissue,<br/>
 <time begin="00:56:50.83"/><clear/>when it finds that, it will

engage.<br/>
 <time begin="00:56:53.54"/><clear/>So if I want to build a

mosquito<br/>
that's resistant to this parasite,<br/>
 <time begin="00:56:57.06"/><clear/>one of the things I can do

is<br/>
interfere with the ligand, alright?<br/>
 <time begin="00:57:00.22"/><clear/>I can interfere with this

ability<br/>
to detect that specific tissue.<br/>
 <time begin="00:57:05.14"/><clear/>The other thing I can do is I

can<br/>
knock out these receptors, alright?<br/>
 <time begin="00:57:08.46"/><clear/>Nobody home so to speak.<br/>
 <time begin="00:57:10.16"/><clear/>Alright? I can somehow map

the target tissue<br/>
so this parasite doesn't know where to go.<br/>
 <time begin="00:57:16.72"/><clear/>So this simple slide here,

hopefully<br/>
simple slide, talks about if I want<br/>
 <time begin="00:57:21.25"/><clear/>to make a mosquito that

is<br/>
resistant to a malaria parasite,<br/>
 <time begin="00:57:24.69"/><clear/>one of the things I can do is

get rid<br/>
of this piece or I can get rid of a lot.<br/>
 <time begin="00:57:29.79"/><clear/>So I can interfere with the

receptors<br/>
or I can interfere with the ligand.<br/>
 <time begin="00:57:33.77"/><clear/>So that's one approach

and<br/>
I'll talk about that quickly.<br/>
 <time begin="00:57:37.62"/><clear/>The other one is to

induce<br/>
and insect immune response.<br/>
 <time begin="00:57:40.62"/><clear/>It turns out that the

parasites are susceptible<br/>
to the innate immune response of the insect,<br/>
 <time begin="00:57:46.79"/><clear/>the ability of this insect to
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fight off infection.
 <time begin="00:57:49.23"/><clear/>Now if we can somehow

elevate
it, that might work.
 <time begin="00:57:52.04"/><clear/>Another way is to

interfere
with parasite gene expression.
 <time begin="00:57:55.97"/><clear/>We talked about the fact that

when the
parasite leaves the human host and goes
 <time begin="00:57:59.71"/><clear/>into the mosquito it's a

very
different world, alright?
 <time begin="00:58:03.97"/><clear/>And as a consequence of that,

the mosquito
turns on, sorry the parasite turns on new genes.
 <time begin="00:58:09.64"/><clear/>Well if we could somehow

interfere
with those genes being turned on,
 <time begin="00:58:12.68"/><clear/>we might be able to effect

parasite development.
 <time begin="00:58:15.73"/><clear/>And the other one is just

to
secrete a toxin, alright, a poison.
 <time begin="00:58:19.09"/><clear/>So the mosquito's flying
around with this poison in it
 <time begin="00:58:22.02"/><clear/>when the parasite gets into

it, it dies off.
 <time begin="00:58:24.90"/><clear/>That's actually not such a

bad idea, but it's
very difficult to find poisons that discriminate
 <time begin="00:58:29.89"/><clear/>between the parasite and the

mosquito.
 <time begin="00:58:32.16"/><clear/>Now some of you think, well

that's
not such a bad idea because you want
 <time begin="00:58:34.90"/><clear/>to kill the mosquitoes

anyway, but the
idea is we're going after the parasite now
 <time begin="00:58:39.10"/><clear/>and if we have something
that kills off the mosquito,
 <time begin="00:58:41.27"/><clear/>then the strategy will

work
in a very different way.
 <time begin="00:58:46.51"/><clear/>Okay. Next slide.
 <time begin="00:58:49.05"/><clear/>So what we did in our limited

approach at the
time, was we figured if we could block parasites

<time begin="00:58:54.91"/><clear/>from getting into the

salivary glands,
that is we could prevent them from getting
<time begin="00:58:59.13"/><clear/>in here, they would not be

transmitted.
<time begin="00:59:02.66"/><clear/>And we used a model system

that dealt with
this one mosquito called Aedes aegypti,
<time begin="00:59:07.79"/><clear/>a Plasmodium gallinaceum that

actually
infects birds, and Galliform birds.
<time begin="00:59:12.35"/><clear/>We actually used chickens, so

the
guinea fowl there look kind of neat.
<time begin="00:59:16.72"/><clear/>And the parasite molecule

that we went after is
something called the Circumsporozoite protein.
<time begin="00:59:22.48"/><clear/>And this is a lot of

technical
information about it
<time begin="00:59:24.89"/><clear/>but the most important thing

here are
these pictures of the parasites here
<time begin="00:59:29.11"/><clear/>and they're stained with a

stain
that shows us where this protein is
<time begin="00:59:32.60"/><clear/>and it's all on the surface

of the parasite.
<time begin="00:59:35.97"/><clear/>And some people think that

this
is a ligand for the parasite
<time begin="00:59:39.44"/><clear/>to recognize specific tissues

in the mosquito.
<time begin="00:59:42.17"/><clear/>So we did a really

interesting
trick based on the fact
<time begin="00:59:45.04"/><clear/>that not all malaria

parasites infect
all the different kinds of species.
<time begin="00:59:50.09"/><clear/>Alright? So we took a

bird
parasite and we put it into a mouse
<time begin="00:59:54.52"/><clear/>and the mouse just laughed it

off, alright?
<time begin="00:59:56.82"/><clear/>It's not about to get

chicken

malaria, I mean it's a mouse, alright.
 <time begin="01:00:00.49"/><clear/>So what it meant was the

mouse immune system
was able to react to these bird parasites
 <time begin="01:00:06.81"/><clear/>and amount an immune response

and take it out.
 <time begin="01:00:09.22"/><clear/>So we said to ourselves

why
not identify what component
 <time begin="01:00:13.08"/><clear/>of the mouse immune

system
is actually doing that.
 <time begin="01:00:16.06"/><clear/>And so we did.
 <time begin="01:00:18.41"/><clear/>
 <time begin="01:00:19.72"/><clear/>Alright. And of course it

was
antibodies, and this is a picture
 <time begin="01:00:22.70"/><clear/>of an antibody molecule

here
that's got a heavy chain,
 <time begin="01:00:25.78"/><clear/>this is technical stuff but

it's not important.
 <time begin="01:00:27.67"/><clear/>It's got a heavy chain and a

light chain.
 <time begin="01:00:29.40"/><clear/>We were able to take the

fragments of this
gene that are responsible for recognizing
 <time begin="01:00:35.99"/><clear/>that surface protein and

clone them as a single
product, it's called a single chain antibody.
 <time begin="01:00:41.28"/><clear/>And what we've done is we

make a
very complex system fairly simple.
 <time begin="01:00:45.59"/><clear/>We've taken something that

requires
two genes and we made it into something
 <time begin="01:00:49.12"/><clear/>that now works with only a

single gene.
 <time begin="01:00:52.09"/><clear/>And we put it into the

mosquito.
 <time begin="01:00:54.18"/><clear/>So you need to think about

what we've done.
 <time begin="01:00:56.55"/><clear/>We've just taken a part of

the mouse
immune system and put it into a mosquito.
 <time begin="01:01:00.91"/><clear/>So we actually have a

mosquito that
is now resistant to a malaria parasite
 <time begin="01:01:06.07"/><clear/>as a consequence of

being
mouse-like so to speak.
 <time begin="01:01:09.77"/><clear/>A true chimera.
 <time begin="01:01:10.89"/><clear/>And it worked.
 <time begin="01:01:13.47"/><clear/>Alright? And so I just want

to show you one data
slide and it's real easy to follow through here.
 <time begin="01:01:20.57"/><clear/>The experimental one are

these yellow bars
here, I hope they look yellow to you here.
 <time begin="01:01:25.68"/><clear/>And the rest of these are

controlled.
 <time begin="01:01:27.34"/><clear/>And what we have here are

the
percent of mosquitoes going from zero
 <time begin="01:01:31.02"/><clear/>to one hundred percent that

have
a certain number of parasites.
 <time begin="01:01:35.25"/><clear/>So zero to ten, eleven to one

hundred,
 <time begin="01:01:38.06"/><clear/>a hundred and one to a

thousand
and greater than a thousand.
 <time begin="01:01:42.08"/><clear/>And these three here, the

white, the
blue and the green, are controlled.
 <time begin="01:01:46.18"/><clear/>So the important thing you

can see here
if you look carefully is that there are,
 <time begin="01:01:49.53"/><clear/>of the control mosquitoes,

there are, a lot
of mosquitoes that have a lot of parasites.
 <time begin="01:01:55.54"/><clear/>Alright? So most of the

mosquitoes
have greater than a thousand parasites.
 <time begin="01:01:59.46"/><clear/>A few have zero to ten, a few

have in these
ranges here, but most of them have a lot.
 <time begin="01:02:04.96"/><clear/>But in the one where we put

the mouse immune
system, we see that very few have greater
 <time begin="01:02:09.37"/><clear/>than a thousand and most

of
them are down in this area here.
 <time begin="01:02:13.52"/><clear/>So if we look at this curve

for the controls,
most of them are way up here looking like this,
 <time begin="01:02:18.38"/><clear/>and when we look at the

experimentals
that we made,
 <time begin="01:02:21.13"/><clear/>made ourselves, alright, they

look like this.
 <time begin="01:02:24.02"/><clear/>So this actually has shifted

the number of
parasites from being a lot to being very few.
 <time begin="01:02:30.35"/><clear/>Alright? And this is the

consequence
of putting in this mouse gene
 <time begin="01:02:33.94"/><clear/>against chicken malaria into

this mosquito.
 <time begin="01:02:37.90"/><clear/>Okay. So the question then

is, does this work?
 <time begin="01:02:41.36"/><clear/>And here's where reality
tends to exert its influence
 <time begin="01:02:45.03"/><clear/>on a very clever set of ideas

we think.
 <time begin="01:02:48.84"/><clear/>Alright? When we asked if

these mosquitoes then
could transmit, we found this interesting result
 <time begin="01:02:56.85"/><clear/>which is that mosquitoes
with as few as ten parasites
 <time begin="01:02:59.79"/><clear/>in their glands were

sufficient
to infect chickens, alright?
 <time begin="01:03:03.51"/><clear/>So the inoculums is very,

very low.
 <time begin="01:03:05.97"/><clear/>And this turns out to be

highly significant for
this whole strategy because the question is,
 <time begin="01:03:10.75"/><clear/>how good do we have to be

in
order to make this work, alright?
 <time begin="01:03:14.40"/><clear/>And here's our answer.
 <time begin="01:03:15.50"/><clear/>We need to have zero

parasites in the salivary
glands if we're going to save chickens at least.
 <time begin="01:03:20.95"/><clear/>Okay? So how does this

translate to humans?
 <time begin="01:03:24.13"/><clear/>Well it turns out that

likely
the same kind of target is there.
 <time begin="01:03:28.34"/><clear/>And this comes from a very

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interesting set of<br/>
experiments that would never be done today.<br/>
 <time begin="01:03:33.89"/><clear/>It turns out a long time ago

that one<br/>
of the ways of treating syphilis was<br/>
 <time begin="01:03:39.32"/><clear/>to give people malaria

infections because<br/>
the high temperatures that people would get<br/>
 <time begin="01:03:44.56"/><clear/>when they became

infected<br/>
with malaria was sufficient<br/>
 <time begin="01:03:48.03"/><clear/>to kill the bacteria that

causes syphilis.<br/>
 <time begin="01:03:52.71"/><clear/>So before the use of

antibiotics and<br/>
unfortunately long after the use of antibiotics<br/>
 <time begin="01:03:58.81"/><clear/>in some portions of the

world,<br/>
people were actually infected<br/>
 <time begin="01:04:01.66"/><clear/>with malaria strain to

cure<br/>
them of this disease.<br/>
 <time begin="01:04:04.96"/><clear/>So this is, I'm going to walk

you through<br/>
this because this is a remarkable set<br/>
 <time begin="01:04:08.30"/><clear/>of language that you'll never

see again.<br/>
 <time begin="01:04:11.06"/><clear/>It says eleven patients

requiring<br/>
malaria therapy.<br/>
 <time begin="01:04:14.59"/><clear/>Alright so what does it

mean<br/>
to require a malaria therapy?<br/>
 <time begin="01:04:17.86"/><clear/>Alright these are

patients,<br/>
are they signing off on this?<br/>
 <time begin="01:04:21.56"/><clear/>Anyway, were inoculated with

Plasmodium vivax.<br/>
 <time begin="01:04:24.46"/><clear/>Doses were 10 sporozoites in

four<br/>
patients, a hundred, etcetera.<br/>
 <time begin="01:04:29.38"/><clear/>The bottom line is the

minimum dose that<br/>
they gave them was ten of these parasites.<br/>
 <time begin="01:04:33.82"/><clear/>Parasitaemia this is actually

the blood<br/>
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infection, was detected in all patients.
 <time begin="01:04:38.93"/><clear/>So what we saw with our

animal
model with the chicken malaria,
 <time begin="01:04:42.10"/><clear/>is identical to what we can

expect
in the human condition here which is
 <time begin="01:04:47.17"/><clear/>that our target is zero

parasites.
 <time begin="01:04:49.34"/><clear/>We have to get this down to

the point where
there are no parasites in the salivary glands.
 <time begin="01:04:53.49"/><clear/>Now as difficult as that

may
seem it's also comforting
 <time begin="01:04:56.15"/><clear/>because we know what our end

point is on this.
 <time begin="01:04:59.98"/><clear/>Okay. So that's unfortunately

a quick
jump into the science and back out again.
 <time begin="01:05:05.60"/><clear/>But that's all we have time

for today.
 <time begin="01:05:08.18"/><clear/>So the future directions now

that we're
working in our laboratory is we want to move
 <time begin="01:05:11.94"/><clear/>from these animal models

which
is the aim in malaria parasite,
 <time begin="01:05:14.87"/><clear/>that chicken malaria to the

human pathogens.
 <time begin="01:05:17.35"/><clear/>If we're going to work

another
five years we don't really want
 <time begin="01:05:19.91"/><clear/>to improve the world for the

chicken, alright?
 <time begin="01:05:21.79"/><clear/>It's the, despite all the

wonderful things
that might come of the consequences of that,
 <time begin="01:05:26.98"/><clear/>our real object is to

work
on the human parasites.
 <time begin="01:05:29.86"/><clear/>So we're working with the

human parasites now.
 <time begin="01:05:33.69"/><clear/>This is something which I can

talk about
tomorrow, I have to give a talk in I think it's

<time begin="01:05:37.60"/><clear/>in entomology or maybe it's

biochemistry,
that it's great to have built these genes
<time begin="01:05:43.87"/><clear/>in the laboratory and

obviously more work needs
to be done to make these highly efficacious.
<time begin="01:05:48.72"/><clear/>But what we really need to do

is conceive
of how we're actually going to get them
<time begin="01:05:51.85"/><clear/>out into the field and so

this
becomes extremely important.
<time begin="01:05:55.16"/><clear/>And indeed we have a very

large project
that's trying to figure out how we're going
<time begin="01:06:00.73"/><clear/>to get these genes into the

field.
<time begin="01:06:03.29"/><clear/>We're very much interested in

the
transmission dynamics of malaria in the field.
<time begin="01:06:06.82"/><clear/>We have this really crazy

circumstance for
example, in some places in Africa the vector,
<time begin="01:06:12.67"/><clear/>that is the mosquito

that's
transmitting malaria is different
<time begin="01:06:15.27"/><clear/>between the rainy season and

the dry season.
<time begin="01:06:18.10"/><clear/>So it's a completely

different mosquito species.
<time begin="01:06:20.10"/><clear/>And when you're talking about

a genetic
control strategy you have to then develop
<time begin="01:06:23.92"/><clear/>that from both species

during
that, in that particular area.
<time begin="01:06:28.36"/><clear/>And we need to know what

these specific
targets are so our work is moving
<time begin="01:06:33.31"/><clear/>out of the laboratory and

into the field.
<time begin="01:06:37.18"/><clear/>There's a larger agenda which

is not
particularly ours but which is one,
<time begin="01:06:42.16"/><clear/>it's ours in a sense that our

work overlaps

that, but it's one that's been mandated
 <time begin="01:06:47.18"/><clear/>by the Roll Back Malaria
program by CDC and this brings
 <time begin="01:06:52.23"/><clear/>into play then the various

things
we learned about earlier on.
 <time begin="01:06:55.21"/><clear/>The fact that we should have

insecticide
treated bed nets available to people,
 <time begin="01:06:59.47"/><clear/>we should concentrate on

developing strategies
for dealing with malaria in pregnant women,
 <time begin="01:07:07.44"/><clear/>we should continue to develop

the drug and
hopefully try to develop some kind of technologies
 <time begin="01:07:14.03"/><clear/>where we can forecast the

types of conditions
that are going to lead to malaria outbreak.
 <time begin="01:07:19.33"/><clear/>And these are some big

picture challenges
that I think, how do I say this?
 <time begin="01:07:28.83"/><clear/>You don't want to leave

things
for the next generation
 <time begin="01:07:31.24"/><clear/>because that means you

haven't
done your job right.
 <time begin="01:07:33.58"/><clear/>Does that make sense?
 <time begin="01:07:35.58"/><clear/>However should we not be

successful, there
are some things that are probably likely
 <time begin="01:07:42.12"/><clear/>to be available to those of

you who
are considering getting into the field.
 <time begin="01:07:45.68"/><clear/>And as that, I think we

should
consider development of a live vaccine.
 <time begin="01:07:49.34"/><clear/>So any of you who are

interested in this
kind of stuff, we can talk about that.
 <time begin="01:07:52.95"/><clear/>Because live vaccines tend to

work very well.
 <time begin="01:07:55.44"/><clear/>Alright? As you can imagine,

I work with
genetically engineered organisms and the talk
 <time begin="01:08:03.12"/><clear/>about and thoughts of release

of genetically
modified organisms into the field is enough

<time begin="01:08:08.03"/><clear/>to stimulate very lively

discussion.
<time begin="01:08:10.60"/><clear/>So I have a tremendous

attack, attack
is not the word I wanted to use.
<time begin="01:08:17.02"/><clear/>Yeah, we're attacked all the

time,
but we have a tremendous obligation
<time begin="01:08:23.20"/><clear/>to educate people what we're

about, what
we're talking about when we're talking
<time begin="01:08:26.70"/><clear/>about genetically modified

organisms and
so we can bring the public up to speed
<time begin="01:08:30.91"/><clear/>on why we don't, as

scientists
don't think they're a threat.
<time begin="01:08:33.84"/><clear/>But why we're also in a

position, why
we can't forcefully advocate their use,
<time begin="01:08:38.10"/><clear/>that this is work that has to

be
left with public health officials.
<time begin="01:08:42.34"/><clear/>I've had this discussion
with a number of people.
<time begin="01:08:45.62"/><clear/>We talked about the

development
of various avenues, vaccines,
<time begin="01:08:50.32"/><clear/>drug development, etcetera,

to control malaria.
<time begin="01:08:54.01"/><clear/>And bed nets are also a good

example.
<time begin="01:08:56.31"/><clear/>And right now we have

successes in
those areas, but they're not complete.
<time begin="01:09:00.55"/><clear/>We get thirty percent

efficacy here,
we get a fifty percent efficacy here,
<time begin="01:09:04.75"/><clear/>but none of them are complete

to the point
where we're seeing elimination of malaria.
<time begin="01:09:09.47"/><clear/>And this is the consequence

of the fact that
people who work in bed nets, work in drugs
<time begin="01:09:13.18"/><clear/>and work in vaccines

don't
often talk amongst one another.

<time begin="01:09:16.47"/><clear/>So the one thing that would

unite them
is some concept that they're trying
<time begin="01:09:19.96"/><clear/>to approach eradication of

malaria as a goal.
<time begin="01:09:22.96"/><clear/>Now most people will tell

you, that
this is highly unlikely to be achieved.
<time begin="01:09:28.07"/><clear/>However I think the idea

conceptualizing
it is something that will bring groups
<time begin="01:09:31.93"/><clear/>of people together who

normally
don't talk with one another
<time begin="01:09:34.41"/><clear/>and perhaps we can get an

additive effect
out of all these different approaches.
<time begin="01:09:39.26"/><clear/>And this was written on the

slide before we got
our Gates funding, but basically the funding
<time begin="01:09:47.79"/><clear/>that is available for

malaria
research now is still insufficient.
<time begin="01:09:54.59"/><clear/>People have made the comment

that,
well you can't just throw money
<time begin="01:09:58.10"/><clear/>at a problem and expect a

solution to occur.
<time begin="01:10:01.01"/><clear/>But I would like to point out

that that's
not necessarily true and this visualization
<time begin="01:10:07.49"/><clear/>of throwing money at a

problem
is incorrect, alright.
<time begin="01:10:11.83"/><clear/>H, and I use HIV as an

example of this, alright?
<time begin="01:10:15.12"/><clear/>When HIV was first started to

be
researched in the mid eighties,
<time begin="01:10:20.14"/><clear/>it was recognized that it was

going to be a
serious challenge to people and it was going
<time begin="01:10:24.51"/><clear/>to be a serious public health

problem.
<time begin="01:10:26.78"/><clear/>The National Institutes of

Health also

recognized that and invested a tremendous amount
 <time begin="01:10:31.29"/><clear/>of money in trying to

develop
approaches to dealing with HIV.
 <time begin="01:10:37.66"/><clear/>Now it is true that in the

first
series of grants and the first rounds
 <time begin="01:10:41.52"/><clear/>of grants there was a lot of

bad science.
 <time begin="01:10:44.14"/><clear/>Alright? There's no question

about it.
 <time begin="01:10:46.27"/><clear/>However those grants don't

get
renewed, so there's a five year period
 <time begin="01:10:49.46"/><clear/>where some bad stuff was

done,
bad meaning that, it was just,
 <time begin="01:10:53.28"/><clear/>you know not bad that people

were hurt, but it
was just bad science, bad ideas kind of stuff.
 <time begin="01:10:58.61"/><clear/>You know, really things that

just
weren't going to get worked out.
 <time begin="01:11:02.43"/><clear/>But those don't survive the

first round.
 <time begin="01:11:04.38"/><clear/>I mean, well they survived

the first
round but they don't get refunded.
 <time begin="01:11:07.20"/><clear/>So you have a bad idea, you

know, and
it's something that's really important,
 <time begin="01:11:10.28"/><clear/>there's a lot of money

there,
you'll get that first grant,
 <time begin="01:11:12.28"/><clear/>but when it comes time

to
renew it, it won't happen.
 <time begin="01:11:15.03"/><clear/>So very quickly this idea

that you're throwing
money out there and you're getting bad sciences
 <time begin="01:11:22.04"/><clear/>as a consequence of that,

just throwing it out
there, there's a mechanism for regulating that
 <time begin="01:11:26.50"/><clear/>and that's the renewal

period, alright?
 <time begin="01:11:28.69"/><clear/>So considerable money was put

in it.
 <time begin="01:11:31.41"/><clear/>And what did we get?
 <time begin="01:11:32.62"/><clear/>So this is actually something

which I think is
really important and that is that you know, HIV,
 <time begin="01:11:38.13"/><clear/>I'm no way encouraging

anybody to
experiment with it in any fashion.
 <time begin="01:11:41.90"/><clear/>Stay as far away from it as

you can.
 <time begin="01:11:44.05"/><clear/>But I will say it's no longer

the death
sentence that it was fifteen years ago.
 <time begin="01:11:49.04"/><clear/>Alright? For those of you old

enough to remember
what the environment was like fifteen years ago,
 <time begin="01:11:54.51"/><clear/>twenty years ago at this

point
now, diagnostic or diagnosis
 <time begin="01:11:58.79"/><clear/>of HIV was essentially

that,
it was a death sentence.
 <time begin="01:12:03.33"/><clear/>Alright? And it's no longer

that way.
 <time begin="01:12:05.39"/><clear/>As a consequence of the fact

that we have drug
regimens now that can control the disease.
 <time begin="01:12:10.58"/><clear/>So this idea that you can't

put money
into a problem and expect that alone
 <time begin="01:12:13.99"/><clear/>to solve it, it's not

necessarily true.
 <time begin="01:12:16.33"/><clear/>If you put the money into a

problem,
you recruit good scientists to that
 <time begin="01:12:19.91"/><clear/>and you'll get something good

out of it.
 <time begin="01:12:21.27"/><clear/>And I would like to argue

that
the same kind of investment
 <time begin="01:12:24.39"/><clear/>in malaria will give us

the
same kind of results.
 <time begin="01:12:27.10"/><clear/>And Jeffery Sacks someone I

mentioned
earlier, has estimated the debt somewhere
 <time begin="01:12:30.22"/><clear/>between 1.3 and

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3 billion dollars a year.<br/>
 <time begin="01:12:33.71"/><clear/>Which sounds like a lot of

money and if it<br/>
was just coming to my lab it would be a lot<br/>
 <time begin="01:12:37.13"/><clear/>of money, but it's

actually<br/>
an overall scale of things.<br/>
 <time begin="01:12:41.09"/><clear/>It's not that much money at

all.<br/>
 <time begin="01:12:43.09"/><clear/>For that meager amount of

investment we could<br/>
expect, I think, probably significant results.<br/>
 <time begin="01:12:49.08"/><clear/>So this little line here

still counts.<br/>
 <time begin="01:12:51.75"/><clear/>And I think that's it.<br/>
 <time begin="01:12:53.57"/><clear/>Thank you.<br/>
 <time begin="01:12:55.51"/><clear/>[ applause ]<br/>
 <time begin="01:13:07.62"/><clear/>[ music ]<br/>
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