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THE THIRD CULTURE

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We should be and we can be doing a much better job to predict and prevent pandemics. But the really bold idea is that we could reach a point—and this is a distant point in the future—where we become so good at this that we really reach a point where we have the "final plague," and where we are really capable of catching so many of these things that new pandemics become an oddity. I think that is something that we should certainly have as an ideal.

WAITING FOR "THE FINAL PLAGUE" [1.30.09]

A Talk with Nathan Wolfe



INTRODUCTION

Nathan Wolfe trained at Harvard under [Marc Hauser](#) (where he was Hauser's first doctoral student) and [Richard Wrangham](#). "I started working with Richard and thinking about self-medicating behavior of chimpanzees," he says. "Richard encouraged me to understand what the chimps may be treating, and so I starting thinking about what are the viruses, what are the microorganisms of chimps that they may be consuming plants in order to treat. Then I never really came back from that."

Subsequently he lived in Malaysia for three years and then in Africa for close to seven years. He describes himself as "a nice Jewish boy from suburban Detroit", which opens up an interesting line of research for *Edge* scientists, given that our other pandemics expert, Larry Brilliant, Executive Director of Google.org. and the man credited with eliminating smallpox, is also "a nice Jewish boy from suburban Detroit".

"I'm sure it was some kind of rebellion," Wolfe said, "but I'm not sure what it was. My grandmother, for years, even when I became an assistant professor at Hopkins, said, "Will this let you go back and get an MD now, Nathan?" Something like that. I do come from that sort of family background, but they just figure it is working out okay. They certainly wish

I would make a lot more money. But I told them you were going to help me with that. "

—John Brockman

NATHAN WOLFE is the Lorry Lokey Visiting Professor of Human Biology at Stanford University and directs the Global Viral Forecasting Initiative (www.gvfi.org). His research combines methods from molecular virology, ecology, evolutionary biology, and anthropology to study the biology of viral emergence.

Nathan Wolfe's *Edge* Bio Page.

WAITING FOR "THE FINAL PLAGUE"

In a general sense what I'm interested in is very much a biological universe parallel to our own, which is the universe comprised of microorganisms. Of particular interest to me are viruses, but also bacteria—fascinating organisms—and a range of parasites.

These exist in the same moment in history that we exist, in the same space that we occupy, but inhabit a very different world. Yet, they respond to many of the exact same pressures we do, but in a much shorter time span. Of course, they are subject to natural selection. They are incredibly important to our planet, to us as a species, and the reality is that we understand very little about them. We are actually in a very interesting space with respect to the technologies that we have now, and these are some of the things that have come about through molecular biology.

For example, we have metagenomic techniques, where we can take a drop of water or a drop of plasma and understand the incredible diversity of nucleic acids and different organisms that exist in those fluids, or in solids, in soil or in feces, or in saliva, whatever it is that you want to do.

For a biologist it is a fascinating point in time because we're not required to culture every one of these organisms. We can understand the genetic nature of them much more simply, so we have the luxury of going back and being natural historians in trying to explore the diversity of these microorganisms that we really understand very little of. Our knowledge of viral diversity on the planet is trivial. We don't even know the size of the iceberg. We know that most viral diversity is completely undiscovered and unknown. We don't know exactly what percentage of it is under water but it is probably a very high percentage.

That is my interest, and I am really just a biologist and a natural historian who happens to be interested primarily in microorganisms, but in the context of human evolution and in the context of mammalian diversity and biogeography. But I think it is a wonderful time when we really can go back and have the luxury of basic discovery. We discover novel viruses all the

time. You can't discover new primates all the time. We have discovered most of them, but that is not the case with viruses.

Obviously, there is a tremendous interest in viruses that are deleterious. One of the things I would point out, first of all, is that there is so much diversity of viruses: most of them are probably neutral, many of them are ecologically important, some of them are actually mutualistic with their hosts. Having said that, there is a huge fascination with negative viruses, and negative microorganisms, that can spread like the 1918 influenza and HIV—SARS had the potential to do this. These are all agents, which have the potential to relatively quickly have a devastating impact on human populations.

Generally, if you look at global disease control, which is done mostly not by biologists and not in the realm of science, but instead is very much applied science and medical science, public-health science, effectively it is disease control. It is waiting for pandemics to occur, and it is doing the best that we can to try and control them once they have already happened.

But one of the things that we have found in analyzing the diversity of important infectious diseases is that most of them have animal origins. The way that almost all of these important diseases started is as diseases of animals that bubble up into humans who for whatever reason are exposed, through contact with water, mosquitoes, blood, by hunters, which is a lot of the work we do. They are exposed to these agents, these agents are constantly bubbling up, and you have this constant chatter, this viral chatter, individuals who are exposed to these agents.

Most of those things will go nowhere. They will almost instantaneously go extinct in either those individuals or, if they spread from person to person, which is really when these things start to have the potential to be very important and potentially dangerous, even those will mostly go extinct, burning out within local populations. You have to have the conditions be just right really to effectively jump through. At that point these agents are not perfectly adapted to humans. That is where most of the action occurs in these pandemics.

Yet global disease control only focuses on the very few that get to the top of the pyramid but have spread globally. If you think of HIV as an example, go back to 1981, right here down the street at UCLA where the first cases of AIDS were really sort of identified as a syndrome. But in 1981 it is estimated that there were at least 100,000 global infections with HIV, probably many more.

So you have missed a critical period where you could have really addressed this pandemic. By then it is too late. Obviously, this is an African disease, an African virus that has made its way to individuals at UCLA Medical Center. At that point it took three years to even identify the agent HIV that causes AIDS. It took seven years for the President of the United States to be able even to use the word 'AIDS'.

Now I would like to spin a slightly different scenario. Let's say we had been studying more comprehensively this interface between humans and animals and trying proactively to predict these pandemic. We would have known about a neglected virus that existed in Central Africa. We would have known that it was transmitted through many, many different routes in Africa, most commonly through heterosexual forms of transmission. We would have potentially had diagnostics. It would have been a neglected tropical disease. But then when cases started really hitting, for example here in the United States, we would have had a tremendous head start.

If you think of this as the benefits of compounding interest, every month, every year of early warning that we get for these pandemics has huge gain in terms of the ultimate outcome. Now we are 30 years into this pandemic—we are really many more years, if you count when the thing really crossed over to humans, which is probably sometime in the early 20th century. In 50 or 100 years when people look back on this period of history, they will see that what we are doing is in some ways how we were treating heart disease in the '50s and '60s. We weren't preventing it. It wasn't about measuring cholesterol levels. It wasn't about measuring blood pressure and trying to change smoking activity. It was effectively waiting for a heart attack. When it comes to pandemics, we wait for the heart attacks.

The bold idea is that we should be and we can be doing a much better job to predict and prevent pandemics. But the really bold idea is that we could reach a point—and this is a distant point in the future—where we become so good at this that we have the "final plague," and where we are really capable of catching so many of these things that new pandemics become an oddity. That is something that we should certainly have as an ideal. And if you ask most people doing public health, they won't even have thought about whether we could have prevented HIV, let alone whether can we reach a point at which there won't any more plagues, which we don't have to think about going back and trying to eradicate.

Eradication right now in public health is the ideal. And obviously there is vaccination. I can't sit here as someone in this field and dent on eradication or vaccines. But on the other hand these are very reactive responses. They are certainly more cost effective than treatment but they are certainly a lot less cost effective than preventing the plague in the first place.

I'm in the process of looking for large amounts of resources to set up listening points around the world to actually monitor individuals who are highly exposed to wild animals, to catch this viral chatter, this movement of these agents from animals into humans and use this to get a sense, first of all, of what is out there.

What is the diversity of agents that are circulating? You can kind of think of this as the virome, or the microbiome. What is the diversity of microorganisms that are present in humans and the animals that we have contact with?

First of all, just to have a list so that in the future when we see things, we will be able to know what it is. And, second of all, to be able to catch things as they try to move into the space where we can have a preventative system for doing this. This is a particularly costly endeavor, but no matter how much we spend on it, all we have to do is catch one and we have instantly paid for this entire system. For SARS, which really at the end of the day affected only about 1,500 - 2,000 individuals, the estimates are billions of dollars of economic impact from even that, which was an aborted pandemic. It was a very short and aborted pandemic. Really what my work is about is trying to aim at this objective of achieving the final plague.

The way that I go about it is I study how pandemics are born, how they die and how we can move towards forecasting; prediction and prevention of these pandemics.

On one level, the final plague is an ideal. If you take a look at the 20th century, there is constant chatter and there will always be constant chatter. Every time you walk down the beach in Venice and you see somebody licking their dog. I'm not saying that is a dangerous activity but you're seeing an exchange of microorganisms. It's happening constantly. There is constant movement of microorganisms from individual to individual, within a species and between species.

As I said, most of those are unimportant. But still, if you look within the 20th century, there are a number of agents, many of which were never even caught, which had this movement from animal to human, and spread globally. Some of them may not have caused tremendous disease. Some of them may have been confused with other things that we knew were diseases and we thought it was probably just that. There is entirely new malaria, which is now spreading in Southwest Asia, which is a malaria of macaques, an Asian monkey, called *Plasmodium knowlesi*.

When people in public health actually diagnose malaria, they look under a microscope and they are forced to call a parasite as one of four human parasites, so all these things were misdiagnosed. You couldn't know it unless you went back and you studied the thing. Lo and behold, *Plasmodium knowlesi* was spreading and it was just identified as another kind of parasite. It is a deadly malarial parasite of animals.

During the 20th century I can't even tell you how many pandemics there were, but there were many pandemics. The point is, if we get good at these sorts of things, and probably we will never be focused on the things that don't cause disease. For example, one out of every three to five individuals is infected with a virus called GBV virus. It is a virus that is very transmissible. It doesn't cause much in the way of disease. Maybe the prevalence is slightly lower. But whatever it is, it's a pandemic virus. Who cares?

It's interesting to know about and in the future it could be something of significance, but really at the end of the day we are interested in the ones that are causing disease. If we start on a course where we get better at

predicting and preventing these things and aren't just focused on controlling them, then over time the idea is that the century-by-century rate of novel pandemics will decrease. I'm not saying that we will be able to really nail it at a moment—"OK, this is the final plague"—but our objective should be not only eradicating existing diseases but really eradicating novel diseases. It is going to take a long time to get there, but we need to change our conception to the point where that is the objective. Eradication can no longer be the ultimate objective.

If you want to think about my work, one way to think of me is as a curator of microbial collections. I have these massive repositories. I have sites all around the world that are aimed at collecting interesting microorganisms, and then I enter into collaborations with different groups. Instead of coming to look at my beetle collections, I send them specimens that I think they are likely to find of interest, and they study them for novel agents. Really it's sort of a microbial museum. As a consequence, I have a very low footprint in the USA. I have an office not much bigger than your suite. It's not huge. Even though my enterprise is very costly to sustain, it is very easy for me to move around.

I don't actually do all of the lab work myself. What I do is find experts in the world who are either using techniques to do work to identify novel agents, like Forest Rohwer or Joe Derisi or Eric Delwart, or who study specific groups, like the best flavovirologists in the world or the best molecular parasitologists. In addition to the laboratories I have in field sites throughout the world, I have 12 different collaborating labs, each of which I send specimens to.

My work is a counterpoint to HIV vaccine development. When HIV was discovered, we were promised by the Secretary of Health and Human Services, that within one year there would be a vaccine against HIV. This is 30 years later. A range of organizations have spent billions of dollars on research to come up with a HIV vaccine. The benefits of this investment has been questionable.

To make a long story short, it is really hard to create vaccines. The easy vaccines are actually ones that aren't really created by humans. They are ones that are discovered. Vaccinia, smallpox vaccine: it's not like we did anything technical to it. All we did was we took a cowpox virus, and what we do today is really not much more complicated than what Pasteur did, scraping a little bit, scraping it into an arm and it's a closely related virus. The person has a viral infection, and it protects him against the next one.

I got started when I went to Harvard to work with Marc Hauser and Richard Wrangham. I was Marc Hauser's first doctoral student. I was interested in the evolution of consciousness. I was fascinated by evolution. I had read Dawkins's *The Selfish Gene* in high school and was captured by it, and honestly that was probably was one of the things that made me fascinated by biology. I came into it with interest in evolution and ecology more than mechanism. I'm not mechanistically focused. Sometimes I have to use those tools or think about mechanism.

I studied biological anthropology at Harvard. I started working with Richard and thinking about self-medicating behavior of chimpanzees. Richard encouraged me to understand what the chimps may be treating, and so I starting thinking about what are the viruses, what are the microorganisms of chimps that they may be consuming plants in order to treat. Then I never really came back from that.

At the time I was frustrated in my reading and thinking about the evolution of consciousness. I just felt like it was a moving target. As soon as people would try to say, "OK, we see evidence in this species" the bar would shift ... I have left this area. I was frustrated with the methods to really capture the questions that I was most interested in that area. And then viruses—they are fascinating stories, they evolve very rapidly.

I got to viruses because I was looking at self-medicating behavior and I started looking into the viruses of chimpanzees. The stories were so phenomenally interesting. The story of HIV origins—it's a fascinating story and it was just alive and vibrant at that moment. It hadn't quite been captured.

Everyone was close to discovery of the origins of HIV but they hadn't quite captured it. And even malaria parasites. That was when I became interested in the origins of malaria. How is it that with something that is so profoundly important to human populations, we can know such excruciating detail about the intricate processes of malaria as an individual organism yet we have little clue as to where it came from?

I believe that is partially just a function of the biases in laboratory science in organizations like NIH, which are much less interested in big questions. They're interested in small questions. Not to say that there is anything wrong with small questions, if you have good scientific policy.

What I would love to do with this work is to make the study of pandemics a subset of biology. Not that what I care about is disciplinary boundaries, but I think what it needs is biologists to tackle it. A physician is very biased. Physicians are going to be like the people on the street who think viruses are all negative. A good virologist 20 years from now, or 50 years from now, if the field goes in the proper direction, will be like a herpetologist, like somebody studying snakes, who acknowledges that maybe the public is most interested in the venomous snakes, but would never delude themselves into thinking the venomous snakes weren't more than just a small percentage of their species and that there is much more of importance in the taxa.

This whole other range: they are ecologically important, they are fascinating organisms. The reason we think of viruses as negative entities is that physicians are the drunks looking under the lamppost for their keys. If you're just looking for negative viruses, that is all you're going to find. I think physicians have a lot to offer, but generally in a specific context. We're looking at biological phenomena and so it should be biologists who study them.

I will be honest with you. I try to go where my mind takes me, and I try to focus on the things I find of interest. For whatever reason, I am more interested in stopping the next malaria and understanding where malaria is from. I'm not as focused on trying to stamp malaria out. There are a lot of people who do that, and you have to make it your expertise to be good at it, and I'm not that interested in it.

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