This Week in Virology

With Vincent Racaniello, PhD

Episode 219: Fauci Pharmacy

Recorded 8 February 2013
Released 10 February 2013

http://www.microbe.tv/twiv/twiv-219-fauci-pharmacy/

Hosts: Vincent Racaniello, Rick Condit, Dr. Anthony Fauci

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Introduction

Vincent Racaniello: We have a special guest today.

Rich Condit: I'll say.

Vincent: Really special. It happens to be the Director of the National Institute of Allergy and Infectious Diseases of NIH, Dr. Anthony Fauci. Thank you for joining us today.

Anthony: It's good to be here, Vince.

Vincent: We feel like we've been working for you all our lives. [Laughter]

Anthony: Mutually, we've been working for each other.

Vincent: Rich and I are here on Study Section to try and give away your money and we thought—it was actually Rich's idea to come by and talk with you. Because we have a lot of listeners who love virology and they're not just virologists. They're different kinds of scientists but about 60% of our listeners are non-scientists.

Anthony: Really?

Vincent: Yes. We think that's cool that we can do a pretty advanced show like this and have so many people listening.

Anthony: Very good.

Vincent: So we thought we talk to you about science.

Anthony: Okay.

Vincent: I want to start in Brooklyn though. Because I understand that's where you born and raised?

Anthony: I was born in Brooklyn.

Vincent: So I have a friend who you may know. He's the Provost of Brooklyn College. And you got some honorary degree…

Anthony: Yes, I did. Two years ago.

Vincent: He asked me to ask you—so, first of all, he said he used to go to the pharmacy across the street from St. Bernadette's.

Anthony: Right.

Vincent: Your father owned that?

Anthony: My father owns Fauci Pharmacy on 83rd St. and 13th Avenue in Brooklyn.

Vincent: Wow. Fauci Pharmacy, it's probably not there anymore.

Anthony: No, it's not. It's not.

Vincent: Because if it were, they'd be giving flu vaccines for $10.00, right?

Anthony: Exactly. No, it's not there.

Vincent: He said he used to go there. That's amazing. He also asks me to ask you—do you remember Sirocco's Restaurant?

Anthony: It was a restaurant on 81st St. and 13th Ave. two blocks from my house. That, even now, after decades, it's probably the best pizza I've ever had.

Vincent: It's still there?

Anthony: It's still there but it's less of a restaurant than a big catering corporation now.

Vincent: Okay. It's changed. The neighborhood's clearly changed. So you grew up and you stayed in Brooklyn. Did you go to high school in Brooklyn?

Anthony: I went to high school in Manhattan. I was born and raised in Brooklyn. Born in the Bensonhurst section of Brooklyn and then moved up to Dyker Heights and went to elementary school at a Catholic school in the neighbourhood, in Bensonhurst, and then I went to Regis High School in Manhattan at 85th St. between Park and Madison. Then I went to college in Massachusetts, Holy Cross, and then I went to Cornell Medical School.

Vincent: Oh, back in the city.

Rich: In New York?

Anthony: Yes, Cornell Medical School is right on the east side, right on 69th/68th and York Ave.

Rich: And so you are an MD, right?

Anthony: I am.

Rich: And so did you then do a residency?

Anthony: I did. I finished medical school and I did internship and two years of residency in Internal Medicine at the New York Hospital Cornell Medical Center and then I came down to the NIH for a three-year fellowship combined Infectious Diseases/Immunology.

Rich: And never left?

Anthony: No. I went back to New York for one year as chief resident in Medicine to completely round out my clinical training and then I came back after that and came back to the same organization here at NIAID that I was a fellow in and have been here ever since.

Vincent: When you returned, that was in the '60s?

Anthony: When I returned it was 1972.

Vincent: Okay. So it was before AIDS was recognized?

[0:04:13.3]

A Career Change

Anthony: Yes. Actually, that was a very interesting change in my career. I came down in the combined Immunology/Infectious Diseases and my main bench research was trying to dissect out the regulatory mechanisms of the human immune system and the interface between host defence mechanisms, the immunological aspects as opposed to the non-specific and either infections or hyperactivity such as the autoimmune diseases. So I did a lot of studies on the vasculitides—Wegener's granulomatosis and polyarteritis nodosa—I developed some therapies for that. I did that for about nine years from '72 to '81 and then when the first cases of HIV—not known as "HIV" at the time—but the first cases of AIDS were

reported from Los Angeles in the summer of 1981. Immediately, after the first MMWR, about 26 additional cases. Again, this time from New York, San Francisco and LA, I made the decision then I was going to completely turn around my career and then become an immunologist interested in a virological disease. So I kind of trained myself as a virologist ten years into my career as being fundamentally an immunologist and now the borders between immunology and virology are blurred, at least, in my own career.

Rich: So at the time you returned to NIH, were you still practicing medicine or you morphed into entirely on research?

Anthony: I have never given up seeing patients. Even during my fellowship, even though I did very fundamental basic bench research, I also had clinical protocols that I directed as a fellow with the help of my mentor at the time. When I came back after my chief residency in 1972, I did the same thing. It was sort of a dichotomous career where you were doing very fundamental work at the bench at the same time you were seeing patients.

When I got involved with HIV, it really coalesced together because the bench work that I was doing was on HIV-infected individuals asking about delineating the immune defect, the role of the reservoir, cytokines and immune activation and things like that. So my clinical responsibilities have actually at a certain percentage of the week, of the day, was actually taking care of HIV-infected individuals at the same time as I was doing rather fundamental research on the virus and on the immune system/viral interface.

Rich: So that's really the classic model for a physician/scientist. That's the real deal.

Rich: Yes, absolutely. Probably it helped that it was a virus that infects the immune system too.

Anthony: Well, yes. That's the reason why when I was sitting in my office and I remember—because I told the story frequently. Because people want to know because now it's been 30 years since that happened. I was sitting in my office and saying to myself, "I really am excited about what I'm doing. I was quite successful and enjoying it."

Then, all of a sudden, this new disease comes along. Even before it was proven to be HIV, everybody knew who was in the field that it had to be a virus. It had to be, up to this point, undescribed virus. So I said to myself, "Here it is, a virus, still to be determined, that's affecting profoundly and destroying the human immune system. Here I am, having trained ten years ago as an immunologist and an infectious disease person." It was almost as if all of my training up to that point was for me to get into the field of HIV. That's why I got in to it, literally, within weeks of the first description of the cases.

Rich: I talked to other physicians who were involved in the AIDS epidemic and they described almost—it was really startling or I don't know if it's scary or whatever—but this was something really big that came on all of a sudden. How did you feel about it?

Anthony: Well, I wrote a paper. It's very interesting historically that when I made that decision to essentially shift everything—both my lab and my clinical work—to this new disease that was affecting exclusively gay men at the time, a couple of injection drug users but mostly gay men, we're talking about the very beginning of the recognition of the epidemic. My colleagues and my mentors told me I was nuts. "Why are you giving up a really successful career that's on a real steep trajectory upward to study this crazy disease that's affecting a very small fraction of a disenfranchised population?"

I wrote a commentary in the Annals of Internal Medicine in the winter of 1981 which was published in the spring of 1982 that said, "Anybody who thinks that this unusual disease is going to stay confined to a small population of individuals is making that assumption based on no science at all." Because the way it's looking, it's sexually-transmitted; we don't know what it is yet; we know that it's a virus and it's acting like a sexually-transmitted disease. And, guess what, unique among sexually-transmitted diseases, it's killing everybody. So that was the real unique aspect of it.

So I sensed, I never imagined it would be as enormous as it turned out to be with over 60 million people infected and already over 30 million dead and 34 million people living with HIV. I never imagine it would get that big but I was absolutely convinced that it would be much bigger than what people were assuming it would be.

From my own personal thing about taking care of patients, what was very unusual about it is that I had been used to for previous years when I was at the NIH at a very, very early part of my career developing therapies that were curing people. I was in the mode of taking care of patients, making them better and feeling really good about it. I went through several years, in those early years, that every one of my patients died. So that is very, very—I wouldn't say "shocking" but it's numbing for a physician who is trained to heal who's not healing anybody and everybody's dying. So we went through several years of that. That was the dark years of my medical career—exciting years of my scientific career but dark years of my medical career.

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Vincent: So there's a lot of scientific progress in these years but taking care of patients lagged behind, right?

Anthony: Yes. It was very important. It kept you grounded as to the importance of what you were doing.

Vincent: So at this time when AIDS broke, were you the director of NIAID yet?

Anthony: No, I was not. I was not. I became director in 1984 and I started working on HIV in the fall of 1981. So it took three years. That was actually one of the motivations that got me to take on administrative job. The conditions that I laid down for accepting the job would that I would have to continue to do my own research and continue to see patients. And the director of NIH at the time, Jim Weingarten and the Secretary of HHS at the time had no problem with that. They said, "Fine. Go ahead and do your thing so long as you put a considerable amount, if not, the bulk of your effort in running the institute," which I've done. So it was three years of working on AIDS before I became director. One of the motivating forces was that I really felt that the National Institute of Allergy and Infectious Diseases, which was sort of a very small institute at the time, the budget was about $320 million, now it is $4.6 billion. We really needed to reach out and start expanding in the sense of global health, infectious disease, viral diseases, bacterial diseases. So we had an explosion of activity and that's what I felt was one of the missions that I wanted to do was to bring infectious diseases up in to the spotlight of biomedical research. So we are now the second largest institute just below cancer.

Vincent: Remember in the '60s when someone, I think it might have been the surgeon general who said, "Infections are over."

Anthony: Oh, yes.

Vincent: "We got them licked."

Anthony: Right. "The era of infectious diseases is over. We now should concentrate our efforts on chronic diseases." Well, he's correct that we should be concentrating efforts on chronic diseases but he was absolutely incorrect that the era of infectious disease was over.

[0:12:44.3]

The Fauci Lab and Vaccines

Vincent: So to this day, you still have a lab and still see patients?

Anthony: I do. I still see patients and I still have a lab.

Vincent: What do you do in your lab?

Anthony: Well, our lab is focused fundamentally on the pathogenic mechanisms of HIV. And we started off by describing the early years, the immune defect.

Now, we're very focused on number of things. One is the reservoir of HIV, how it's formed, are there going to be creative ways now that we have good therapy, to essentially either totally suppress or eliminate that reservoir? That's not going to be an easy task but it's something that I think is doable. The work is going very well.

We're also looking at the role of immune activation on driving of HIV replication. And we discovered over a period of years a new receptor for HIV on CD4-positive T-cells. That is not absolutely essential for the cell to be infected but makes a cell in transmission much more permissive to initial infections. So it's very prone to bind to the founder or transmitting viruses and then we're delineating more the nature of the immune defect in HIV.

Much underappreciated was the fact that HIV has a profound effect on every aspect of the immune system including the B-cell line. One of the real questions is why does the body not make an adequate immune response against HIV? It's the only viral infection that we really know of, of this magnitude, where the body makes a completely inadequate response: neutralizing antibodies occur rarely, they occur late and they're ineffective. So how do you get them to be induced early enough to be protective? In order to do that, you need to understand the interface between the HIV, particularly, its envelope, and the B-cell repertoire. Are we programmed to make a good response early enough? And if so, how do you do that? How do you induce that with the vaccine? So it's a combination of pathogenesis in describing the fundamental pathogenic defects in HIV infection and to use that understanding of pathogenesis to get insight into both therapies, as well as, vaccine development.

Vincent: So that's a problem for vaccine development, right?

Anthony: Absolutely.

Vincent: So we have to be better than the body is.

[0:15:12.6]

Anthony: No doubt. We have to induce what I refer to frequently as "unnatural immunity." Because natural immunity doesn't work. The bottom line of the strategy of vaccines that we've made successfully over the years is do exactly what natural infection does but do it before the person gets infected. So if you look at all the great killers: smallpox, measles, mumps, rubella, polio. All of those, the immune system and the body itself has already given us a proof-of-concept. That if you recover from the disease, and you don't die, the immune system rids the body of the virus and it gives you lifelong protection after infection. So the model of what you want to strive for in a vaccine, nature has already given you the proof-of-concept. Unfortunately, with HIV, nature has told us, "Guess what? I don't make a good immune response against this virus. So if you are going to want a vaccine, you're going to have to do better than natural infection does." And that's a real challenge. It's exciting but it's really challenging.

Vincent: Is it possible? Can we do that?

Anthony: I think it is. It's not going to be easy. There are so many disadvantages with HIV which is—if you want to metaphorically give it a life, it's one of the most cunning viruses we've ever dealt with. Because when you have an influenza vaccine, a polio vaccine or smallpox vaccine, when the virus enters the body, it can start to replicate, infect cells and kill cells and you could still suppress disease by a vaccine because by the time the virus replication gets to the point to give you clinically-apparent disease—be it smallpox, influenza or measles—the immune system has come in as a result of the vaccine and has suppressed it. So you have the grace period of having multiple rounds of virus replication and still having protection from disease. With HIV, once it starts replicates, integrates and forms a reservoir, the ballgame's over. Because that's it, you're infected. And then when the immune system gets destroyed, then that's it.

Vincent: You have to stop it really early.

Anthony: You have to stop it really, really early.

Rich: Are there any vaccines that prevent infection?

Anthony: You know, there are probably are but most of the ones that we deal with allow a certain degree of replication. It stays below the radar of clinical disease.

[0:17:47.7]

<u>Viral reservoir cure</u>

Rich: I've heard a lot of different ideas about curing a reservoir. Okay. Do you think this is possible?

Anthony: I think it's going to be one of the most difficult task. I call it "aspirational." I think it's going to be very, very difficult.

There are two types of cures with regards to the reservoir. One is to completely eradicate the virus. Now you got a real problem because you have integrated pro-virus in a cell that's resting and otherwise not doing anything. So how do you get the virus out of that and get the cell to die? We tried years ago of artificially activating the immune system in vivo, getting the virus to spit out while you're giving them antiretrovirals thinking that you would prevent the other cells from getting infected from the virus that was released by your antiviral therapy and the cell that was spitting out the virus would die. Unfortunately, the cells that was spitting out the virus didn't die. They just spit out the virus and we

prevented other cells from getting infected. So it didn't work but there are more clever, sophisticated ways of doing that. That's called "eradication cure."

The other cure is what we refer to as a "functional cure." I coined that term a few years ago saying, "You don't cure in the sense of no-virus-around but you make the immune system strong enough that when the reservoir is small enough that when you stop therapy you have enough immune function to keep the virus suppressed."

And then there's more draconian ways like gene therapy which people have—but may not turn out to be practical from the tens of millions of people who are infected. But it's the way of rendering the body essentially refractory to getting infected. I mean, changing the CCR5 by gene therapy so that you don't bind the virus. That's tough to do that. People are trying it. We hope that it will work but that's tough.

Vincent: You're talking about giving people bone marrow transplants with CCR5-negative…?

Anthony: Well, that's totally impractical. That's done in the few people who have lymphomas who need a stem cell transplant to begin with but you're not going to trade a pill a day that can suppress virus in someone because they don't want to be on medicine. You're going to give them a stem cell transplant that's allogeneic that would require immunosuppressive drugs for the rest of their lives. So what are you trading? The fire for the fire.

Rich: That's the difference between a physician and [appendicitis].

Vincent: Absolutely. That's right. So could you—does it make sense to treat pre-emptively with antiretrovirals, to reduce the burden of virus globally?

Anthony: Absolutely. In fact, one of the real breakthroughs as simple as this sounds, it's not in the rocket science category, is that we showed with an NIH-funded study a couple of years ago that if you treat people who are infected and bring the level of virus to below detectable level, you decrease by 96% the chance of their transmitting the virus to their uninfected sexual partner. So years ago, there was this tension and debate: should we put resources into prevention or should we put it into treatment? And there were a non-necessary debate that was now essentially obviated by the fact that treatment is part of prevention. So if you could seek out voluntary tests linked to care and treat the infected individuals you would dramatically diminish the likelihood that they're going to infect somebody else. At the same time, as you're doing more classic non-therapy-related prevention modalities: condom use; circumcision, particularly in the developing world; mother-to-child transmission prevention; even pre-exposure prophylaxis.

Vincent: So is this being done anywhere?

Anthony: Oh, yes. It's been implemented worldwide and that's the reason why we had a very transforming International AIDS Conference in Washington, D.C. in July of 2012 where the theme was "Turning the Tide Together." And for the first time with the PEPFAR which is the "President's Emergency Plan for AIDS Relief," the global fund, the implementation of already-existing treatment and prevention modalities is starting to show a diminution in the curve of the trajectory of the pandemic. And if we actually accelerate that greatly, we could decrease even more the inflection of that curve to the point where we could actually be thinking about what Secretary Clinton has been referring to as an "AIDS-free generation."

[0:22:16.8]

History of AIDS and AIDS Research

Vincent: That'll be something. I've been reading a book called "The Origin of AIDS" by Pepin?

Anthony: Yes.

Vincent: And I am amazed that something starting in the early parts of the 1900s going from a chimp to maybe one or a few humans could end up infecting 60 million people.

Anthony: Right. A virologic phenomenon collides with the sociological environment when you had the disillusion of colonialism. You had breakdown of family units. Moving of men to cities and mines while families stay in the village. So you probably had little blips of people getting infected from a chimp. The person stays in their village. They infect their wife. They both die. Nobody notices because people die of malaria, tuberculosis and all those other diseases nobody noticed it. And then when you get to that critical, that point where all of a sudden it becomes an explosive pandemic.

Vincent: The insidious nature is scary. The fact that it was around since then we had no clue until 1981. And it could be that hep C had similar origins.

Anthony: Yes. It's possible. The tragedy of history of it is that the reason it exploded in the gay population in the United States was that it started to percolate up to be a low-level epidemic at a time when the gay sexual revolution occurred—the 1960s, Stonewall Riots, the open bath house culture where you'd have many, many, many concomitant sexual partners at the same time. So people wondered, why gay men? It just happened to coincide with almost the revolution in sexual behavior among gay men who had been suppressed for so long by society and now said, "I'm going to express myself as whoever I want." The worst thing you can do is that it's at a time that an unknown virus gets inserted into the population. That's the reason why it happened. And now as it's been shown globally, it's a heterosexual pandemic. But it started off and still is in certain segments. Even in this country, it's still predominantly men who have sex with men.

Rich: So do you see an end to this?

Anthony: I do. I really do. I've been working on it for 30 years now or more, 31 years, but what I'm seeing when we've taken and I—and that was the theme of what I was speaking about at the keynote lecture in Washington at the International AIDS Society—it's really a beautiful example of how you took basic and clinical research in its very earliest simple form when we discover the virus and then we work with the virus and identified targets for any viral therapy, delineated the nature of the immune response and the pathogenesis, develop therapies, develop treatments. So it went from basic science to development of interventions, fundamentally in the form of treatment and prevention. And then to take those interventions and implement them on a global scale that I am actually cautiously optimistic that we are going to end this. It's not going to be next year or the year after but I think it's going to happen.

Rich: It sounds to me as if, in the end, that's going to be as much therapy and prevention as vaccine. Maybe there won't even be a vaccine.

Anthony: That's a very good point. And I believe there will be. That will be the final nail in the coffin for the HIV pandemic but I believe we can get to the point substantially diminishing the trajectory to the

point you could almost say we're approaching an AIDS-free generation before we get a vaccine because we have the tools. We have the treatment tools. We have the prevention tools. If we had a vaccine, that would be it. That would be the ball game. But we can start to get there even before a vaccine is available.

Rich: I love it when humans actually cooperate on a global scale to do something good.

Vincent: Sometimes we do that. Yes.

Rich: Sometimes we do that. Yes.

[0:26:31.1]

NIAID and Infectious Diseases

Vincent: But AIDS is eradicable, right? Because there's no—I mean, there's a reservoir, SIV, but it would to have to jump over and all these things that conspire…

Anthony: Exactly. But the only difficulty—the answer is theoretically it is eradicable, particularly. The only thing it's going to be butting against is that the infrastructure of healthcare globally is so uneven that you're not going to be able to get everybody down—it could be eradicable if we get a vaccine. I think it's suppressible and highly controllable without a vaccine. If you're going to think about eradication, then you really going to have to have a highly effective vaccine.

Vincent: Okay. We're almost there with polio, right?

Anthony: We did it with smallpox and we're just on the threshold with polio.

Vincent: The unevenness of the healthcare around the world, was that less of an issue for smallpox and polio as it is for AIDS?

Anthony: Yes, because we had the vaccine. We had the vaccine and we needed to implement the vaccine. If you're going to do a non-vaccine-related suppression and ultimately eradication it's tough to do in the absence of a vaccine when you have such uneven access to healthcare. Whereas, when you did the smallpox eradication, you would just go into the villages and—boom—you would do it. Whether they had access to healthcare or not, you just send in your army there of health providers and community people and they would be doing the vaccines.

Rich: It was hit-and-run. Okay. But this is maintenance.

Anthony: Exactly. Yes. That's a very good way to describe it.

Vincent: So you think polio will be eradicated?

Anthony: I do. We had that unfortunate situation in Nigeria where there was a semi-political, ideological backlash against it and then that's spread now. So we still have pockets in Pakistan and Afghanistan, India and other places. But I think we're going to get there. I think we're going to get there.

Vincent: So AIDS I'm sure you would consider the biggest infectious disease problem we have right now, right?

Anthony: Yes. It is. But let's not forget malaria and tuberculosis. Because that's right there also with but if you were to pick out one, you would say it was HIV.

Vincent: And after HIV, you would say malaria, tuber...?

Anthony: Malaria, tuberculosis, neglected tropical diseases. We're just starting—it's very interesting how things evolved and how the world becomes aware of and pays attention to things. When HIV/AIDS was first recognized in the United States, even though it started someplace else, when we know it became a global issue, we focused a lot on the developing world, particularly in sub-Saharan Africa. We went there. We set up networks of trials, collaborations. And then when you get them, you realized, "Oh, my goodness, AIDS is devastating," but malaria is really bad, as is TB, as is neglected tropical diseases. So in some uncanny way, AIDS has put the spotlight on global diseases of high significance that we did not appreciate before because it was them not us. Now that we're living in a global society, it's everything that we're aware of.

Vincent: Yes.

Rich: And your vision must be of NIAID as a global organization?

Anthony: It is. I made that decision a very long time ago. Infectious diseases is a global problem. And it's more than just—it could possibly come here. So we in a live in a global society and every year that goes by, we're more interconnected with the rest of the world. So it's impossible for us to just neglect the fact that malaria, every 30 seconds, kills a baby in Africa. That there are 675,000 deaths a year. TB is 1.4 million deaths per year. You can't ignore that anymore. Even though it isn't here, in Bethesda, Maryland, where there's not a lot of TB-infected people, TB is a big deal in the world.

Vincent: I get the sense that malaria and TB are very difficult to crack and part of it is that this country doesn't put a lot of effort in. There are some I know and the Gates is helping a lot but—because it's not here.

Anthony: Yes. But that's changing. If you look at what we've done with our tuberculosis portfolio and our malaria portfolio, at a time when the NIH budget has stayed flat. We had the doubling from 1998 to 2003 and then from 2003 to now, the budget has been essentially flat. During that flat period, we have selectively with resources continue to grow the malaria portfolio, the TB portfolio. Trying to get a universal flu vaccine, things like that. Those are the things that we're focusing.

Vincent: So how does flu fit into the picture? It's not as serious as AIDS, right, but it can kill people.

Anthony: It does fit in to the picture. Again, if you look at those areas of the portfolio that have actually grown disproportionately to the mean of what growth of the institution as a whole, certainly, influenza has. We have a long way to go with influenza. We have been relatively complacent about the fact that we have a vaccine. It's not something that you think of as the big killer, the equal opportunity killer. It kills old people. It kills very, very young people. It's very dangerous to pregnant women. But the normal young healthy person thinks upon the flu as, "Oh, it's the flu." It doesn't mean—but it can be a serious disease. It recurs every year on a seasonal basis. And every once in a while you get a pandemic. When that happens, it could be a public health and global health catastrophe. But the thing about influenza is that the scientific opportunities to do better are really substantial. We have settled for I would think is a less-than-optimal scientific endpoint for influenza. We have to do with better vaccines. We have drugs that are okay but they're not showstoppers. Even the best of the drugs, you don't come in and take it all

of a sudden you feel better. No, you don't. You could shave off a day or so of your illness. Vaccines, the percentage of vaccines is among the lowest of effective vaccines. It's not the 98%, 95%, 90% that we have with other vaccines. At best, it's 60% mean, 65%, and elderly people it's below 50%. We have a long way to go. Even though the perception is that it's not an overwhelmingly serious disease—(a) that's wrong. It is. But even if you don't know that, the fact is the scientific opportunities are really there particularly in the arena of universal flu vaccine. It has always bothered me before I became a flu person, why is it that people get infected every year with flu, they get vaccinated every once in a while and you still get susceptible when there's a new flu strain? Because it's one of the few viruses that really does change in the area—that's the protective area, the hemagglutinin, it changes. Now we know as you all know that the head of the hemagglutinin changes a bit but the stem stays pretty constant. And that's going to be the target of a universal flu vaccine.

Vincent: I'm amazed that we use basically Jonas Salk's vaccine from the '40s still. Why hasn't there been a desire to do better? I know people now are working on universal vaccines but…

Anthony: Yes. You know it's a very interesting complicated issue, guys, that I don't think there's a single answer. It's probably multifaceted. One of the issues is that vaccines are taken for granted because they're given to well-people. It isn't like somebody's dying with the disease and you have to get a therapy for it, number one. Number two, it has evolved over the years as almost an entitlement in the sense of companies come in and they—people charge $40.00 for a pill with the bad disease and influenza vaccine, the profit margin is very, very small. So there really isn't an incentive. Companies say, "Well, we have a vaccine, it's been tried and true. It's either whole-killed or it's attenuated and it doesn't work as well as we wanted to but then again we've done it this way. We've grown it in chickens and now we've made this incredibly transforming move to growing it in cells." But it's still the same concept. You still have to grow the virus. Only recently are we now saying, "Hey, wait a minute. We have virus-like particles. We got recombinant DNAs. We have a lot of ways to do it and maybe we can actually induce a better response." So the last several years, we're starting to see that but for decades it was an acceptance of something that was not optimal and that's, I think, the reason why we are where we are.

Vincent: Yes, I do see a lot more activity on universal vaccines, other approaches. So maybe that'll keep going—maybe it's been influenced by people, as you say, working on AIDS vaccines. It spills over into other areas.

Anthony: Yes. The realization that the scientific opportunities are better than they've ever been before.

[0:35:51.5]

<u>Hepatitis C</u>

Vincent: But hep C though, now we are just starting the new antiviral area, right?

Anthony: Yes. Hep C's exciting because we're going to be able to cure hepatitis C. What the non-interferon-based therapy with ribavirin worked in a certain percentage of people. If you happen to be black or co-infected with HIV or genotype 1, not so good, but still not bad. Now that they've added to the regimens the direct-acting agents: polymerase inhibitors, protease inhibitors, et cetera, the results are striking. The next step is to get rid of the interferon-based and just have direct-acting agents. And the results of those are striking. I think within our scientific lifetime, we're going to see a cure for hepatitis C.

Vincent: That is eradicable because, again, no known animal reservoir.

Anthony: Absolutely. I think we're going to see a cure of hepatitis C.

Rich: And so can we cure that one without a vaccine?

Anthony: Yes. I think you could cure it. I think that you can eliminate it. Because, remember, many people who are hepatitis C-infected don't know it. And those are the ones that can transmit it. So if you look at the risk groups, you had the vaccine, you'd go a long way together with treatment to getting to an eradication.

Rich: So you can cure the disease but to eradicate it, we're going to need a vaccine?

Anthony: Yes. Right. Exactly.

Vincent: You can talk with anything with them. Isn't it amazing?

Rich: Oh, yes.

Vincent: It's great.

[0:37:21.5]

Drug Resistance

Rich: So we've talked about—I'm wondering what the other bugs on your radar are. Okay. We've talked about HIV, malaria, TB, flu…

Anthony: Neglected tropical diseases.

Rich: Flu.

Vincent: HCV, anything else?

Anthony: Yes. There's something that's very important that people don't fully appreciate it is this whole issue of drug resistance, multiple-drug resistant bacteria and to some extent, drug-resistant viruses. But a real problem, it used to be confined to hospitalizations where people would get infected with drug-resistant bacteria: staphylococcus, enterococcus, Klebsiella, et cetera, et cetera. Now, it's starting in some respects even to be community-acquired. That's really bad. The reason it's bad, of course, it's the constellation of things that are coming together. It's bad enough that when you have a serious microbe—in this case, usually a bacteria—that develops multiple drug resistance, what could have been easy to cure last month, when it's resistant, becomes like the pre-antibiotic era. Or you have to use so many toxic antibiotics that the treatment itself creates significant toxicities. That's the reality of the science. Then it's getting the pharmaceutical companies incentivize to get a robust pipeline of new antibiotics. And it's the same philosophy almost with the vaccine because drug companies, in general—not all, some walk-the-walk—drug companies are saying, "Why should I put an investment?" Because to get a new product, it's usually anywhere between a $500 million to $1 billion for an investment. So if you make an investment for a drug that a very small percentage of the population is going to use for 7 to 10 days a year versus the investment of a drug that many people are going to use every day—a new Viagra, a new lipid-lowering agent, a new antihypertensive—so the investments on the part of the company is going to that. So that's kind of a long-winded way of saying that there's double-barrelled problem here with drug-

resistant microbes: (1) They exist and it's very dangerous when they occur; and (2) there's very little incentive to make invested money to be able to get a new pipeline.

Rich: Now I'm blanking on the name, but isn't there a new, say, initiative in the NIH to try and help out with that sort of thing?

Anthony: There is.

Rich: And what's that?

Anthony: Yes. There is a leadership network for antimicrobial resistance. So we developed several years ago a network of clinical trial capabilities that was originally directed at HIV/AIDS. It was a treatment group, the HIV treatment group. There was the HIV Prevention Trials Network. We have the HIV Vaccine Trial Network. We have the Pediatric Network. So it's worked so well that we now created a leadership group that's going to get funded in 2014 that's going to be specifically directed at studying antimicrobial resistance.

[0:40:44.5]

NIH and Drug Development

Rich: How about a role of NIH in helping support drug development?

Anthony: We do. What we do—if you look at it sort of schematically as a spectrum, let's say, if you're looking from left to right. Left is concept. Right is product. So the classic way the NIH works is they do the fundamental basic research. They develop a concept and then they put it into early phase, pre-clinical and maybe phase one. The company is the one that takes that and then they really know how to make a product and that's how they make a product. So if the company has a really big incentive to do it, they will push that envelope all the way from the right to the left and they'll take extra risks with even doing their own basic research, even doing their own pre-clinical studies, et cetera. When companies don't have the incentive to get involved, that's when the government, i.e. the NIH, has to push their part a little bit more from the left to the right where you go beyond just concept, beyond just pre-clinical and actually start "de-risking" it, we call it, from the companies. Take away some of the risk so that they'll get involved in the ballgame.

Vincent: Is this the initiative that Dr. Collins has started to begin to do some—take some of that work away from the company?

Anthony: Yes. What I'm talking about has been going for a long time, particularly, in the big institutes like my institute, Infectious Diseases, Cancer, Heart and the Blood. What Francis Collins is doing, what the National Center for the Advancement of Translational Science, is to actually promote the science of translational research, to make the process of translational research more founded in the best science. So it's sort of one of those things where it lifts all the boats. It's not just becoming a drug company to make something. It's—"How do we get translational science to function at its optimal?" And that's really the purpose of NCATS which is the "National Center for the Advancement of Translational Science."

Vincent: Does it make any sense to move some of that drug development that goes on at a company to government-supported institute, say, throughout the country have institutes all over that can do this?

Anthony: You know, the answer is that has been tried with the military and there's nobody, no group, like a really good pharmaceutical company to make your product. You just got to get them involved. You got to get them collaborating. You got to get them incentivized. I would be reluctant to say the government is going to take over the drug manufacturing business even in a small way. I would rather create an atmosphere and an environment to get the drug companies to want to be involved in making the products.

Vincent: Because many people complain that profit-driven drug development is partly flawed because some of the needs are not highly profitable.

Anthony: Right. So when you take the risk away, you make it more profitable for them.

Vincent: Sure. That's the way to do it. Yes. Now you mentioned—let's move in to another area that we wanted to talk about. You mentioned two things that were leads for us. One is this—you mentioned the flat budget of the whole NIH, I guess, not just your institute.

Anthony: Definitely.

Vincent: So we've just come from Study Section and I have been, for 13 years, on the Study Sections and—it's been the worst ever in the past few years. And both young investigators and older ones don't see a future because the budget levels are flat and research is being squeezed. So what kind of message can we send to everyone? Is it ever going to get better? Is it going to remain flat for another 50 years?

Anthony: Well, I can't predict the future but I tell you what I tell everyone…

Vincent: You're not Yogi Berra either.

[0:44:40.6]

Anthony: I'm not Yogi Berra. But I tell you what I tell my own fellows as well as my colleagues like yourselves is that we are in a serious budget crunch. This year's a bad year. 2014 will unlikely be any better at all. But what I see is a future, I think we're caught right now in this crunch of ideological differences about how you handle budget problems—taxes, entitlements, et cetera, et cetera. That's going to get fixed. I don't know when it's going to get fixed. But when that gets fixed, I am cautiously optimistic that good people and calm intelligent minds will prevail that the scientific enterprise, particularly in biomedical research, is not a discretionary part of the government. To me, it should be a mandatory highly supported part of what the federal government does.

So there used to be that spirit of magnificent growth in biomedical research. The Halcyon days of the NIH back in the '60s and the '50s and the '70s and the '80s. I think that what we do and the product that we give, both from a health domestic and global as well as from an economic boost to the country, will be realized again because it's the truth. Right now, we're caught in a battle that's almost not our battle. It doesn't involve us. It's a battle of how you handle an economy that got out of control with debt and deficit, et cetera. I think that we're going to have to fix that for our survival. But once that gets fixed, what doesn't go away is the importance of biomedical research. So that's a constant. That's not going to change with the tides. And I think when we do get that other aspect of it fixed, there's going to be a return not only of enthusiasm but resources to support biomedical research. So I tell my fellows, "Hang in there. The scientific opportunities that we have right now never has it been more exciting to be involved in biomedical research than now. We can do things now that were unimaginable 10 or 20 years

ago. In our own field of infectious diseases, you see that. Our ability to in days sequence quasi-species of microbes that would take years to do to immediately nail down everything from understanding pathogenesis to drug resistance to vaccine development, everything."

Rich: You spend a lot of time in the public realm. What's your perspective on—does the public appreciate this? Does the public appreciate the impact of basic scientific research, biomedical research?

Anthony: To some extent but not to the extent that I think we could. So we, as scientists, really need to do better in explaining in a way that's understandable and meaningful to people, the importance of what we do without appearing to be self-serving and tooting our own horn but in a way that they can understand.

Rich: Yes. And warm and fuzzy instead of…

Anthony: One of the things that I always say when people ask me about how I get my messages across to the White House or to the Congress or to the public and the constituencies is you really need the end product of what you do should be that they understand what you said and they can appreciate why it's important for them. The goal is not to impress people how smart you are. The classic thing that I make fun of is somebody listening to somebody and somebody walks away and says, "Boy, that guy was brilliant. I didn't have any idea what he said but he's brilliant." That's not the end that you want to get. That's not the end game. The end game is to get people to really understand what we do and to realize why it's important to them, to their children, to their family.

[0:48:58.9]

The RO1 Model

Rich: So talking about money, again, basically, I grew up in the RO1 model of science. Okay. So Investigator-Initiator Research. I've always been motivated by raw curiosity and I've been fortunate to maintain funding from the NIH just to pursue my curiosity. And sometimes I feel, and I have colleagues who felt, that there's a lot of money that goes into things that are more targeted and maybe feel like maybe there's too much of a shift towards targeted research, how do you feel about the balance of Investigator-Initiated versus targeted stuff?

Anthony: Well, I don't think anybody can give a percentage number. But the one thing that I feel strongly about and many of my colleagues do that, above all, you have to preserve a robust RO1 pool. If you get to the point where the balance of what's being fed into the system by pure curiosity-driven innovative ideas and research at the RO1 level, if that gets so crunched, sooner or later, it may take 15, 20, 30 years, the applications that people like to do are going to sink. So this is sort of a sacrosanct thing that you have to preserve.

Given the nature of science, there are initiatives that the normal curiosity of an individual investigator would never get to because that's not what that investigator's initiated [unintelligible]. So the typical example is we do programmatic initiatives to get people involved in AIDS. We had to get programmatic initiatives to get people to develop drugs. And people said, "Well, why don't we just do innovative science at the RO1 level?" That's good because we wouldn't be able to do what we're doing if we didn't have that. But if you didn't have some degree of work that is programmatically-directed and initiated then a lot of important things wouldn't happen. We would not have the drugs that we have now for HIV because we developed a very strong funding and collaboration with industry of drug discovery. That's

the first thing. The second thing, we would not, for example, when you want to develop a universal flu vaccine. It's not like a person is in the lab saying, "I'm going to develop a vaccine." They're going to say, "I want to see exactly what the confirmation of that epitope is on that hemagglutinin and I want to publish it in *Nature*." That's great. And that's what you need to ultimately get a universal flu vaccine. But somebody somewhere has got to say, "We have now got to have a directed effort to do that." Now if the only thing you do is directed effort and you really let the RO1 pool languish, that's really, really bad. So if there's anything that always needs to be protected, it's the RO1 pool.

Rich: Well, that's good to hear.

Vincent: The key is, what is the right ratio? When you say, "We don't know." But I think what's happening now in science, a lot of people like Rich and even young people who have been educated by people like Rich, are used to a situation where you could do whatever you want and that's not going to happen anymore.

Anthony: No.

Vincent: So we have to recalibrate and we are just worried that the RO1 basic stuff is going to be very, very minimal. And as you say that's the foundation for all the translational work. But you're confident that it'll be done in the right way.

Anthony: Well, I'm trying to do. You can simply explain to people that there are two major components of the funding stream: one is Investigator-Initiator (RO1) and the other is programmatic initiatives. We see a point where you can't let the RO1 pool get below a certain level. What you have to do is just curtail your initiatives. And we do that. Something that we would want to do this year, we may have to wait till next year. Something that you wanted to do 100%, you may only be able to do 75%. But when you lose an investigator, you lose them. You can't come back next year and salvage them. That's the point.

Vincent: Yes. When good trained people drop out because they haven't been funded, that's a big loss.

Anthony: That is a big loss.

Vincent: It's the loss for the next 20 years. They're not going to train people as well. So as Director of NIAID, do you also have oversight over all these issues? The RO1 pool, for example, the translational pool or—is that not something that you would…?

Anthony: We have input but it isn't like one of these days I'm going to—like I wake up, I say, "Okay, we're going to do this." There's a certain amount of money that's fixed, goes into certain pools that—but you can talk it considerably. For example, my philosophy has always been, as I've mentioned several times now, to try and protect the RO1 pool as much as you wanted the same time as doing the necessary initiatives. There are certain things that I don't have that other institutes have like enormous big centers. We have a center program but not a big center the way the Cancer institute has. And I just feel for what we do, the kind of work that we do, the flexibility that we need with emerging and re-emerging infections. But that's not the best way to do it. So I can have some control over that. But it's tough because you have a lot of commitments already. Much of what we fund on any given year are ongoing commitments and only a certain percentage is new things.

Vincent: Right. That's a problem that's been explained to us many times. Every year, we have to fund the previous grantees that have been awarded in addition to getting new people in. This whole problem with

tight money which has gone on for quite a while has been cited as one of the reasons why science is in trouble. I don't know if you have seen the few articles written about science needing reforming. There's too much competition for money and that leads to fraud and retraction of papers. What's your overall view? Is science basically healthier or are there things that need to be fixed?

[0:55:26.5]

Fixing Science

Anthony: I think fundamentally science is healthy. One of the things I think needs to be fixed is an accommodation more to the fact that although the single person in their lab with their postdoc is still a very, very important component, a lot of the science that we do, although it's very creative and original, involves a lot of collaboration into digitations. I don't mean wasteful big science. I mean science that goes beyond the individual expertise of a single person. When I started off, it was me—when I came back, you know, we talked about my history—when I came back from my chief residency to start my lab as a young senior investigator. It was myself, a technician, and one post-doc in a module-and-a-half. It was great work. It was a lot of fun. Now what we do, it got its tentacles and collaboration and people with expertise that's well beyond your own expertise.

So the point I'm trying to make is that when we train people right now, the thing I find disturbing is that unless a person gets their own RO1 and is considered an independent PI, they're looked upon failures. And they should not be looked upon as failures. There's enough room in the way science has evolved right now where people are necessary, important and an integral part of what we do that should be treated at the level of reward, promotion and respect in much the same way as individual PIs are. So to me, that's one of the things about science that I really think needs to be looked at.

Vincent: I think what you're saying is that the universities have to help out.

Anthony: Oh, absolutely. They do. They really do.

Vincent: Because a lot of them have had a ride for a long time, right, and I have always thought that many universities don't pay our salaries. They let NIH pay them. And they really need to realize they have a resource and to support it.

[0:57:53.8]

A Typical Day

Rich: I'm wondering, what do you do during the day? Yes, what's your day like?

Anthony: Okay. So I'll give you a typical day. I come in the morning about a little before 7:00. And I do emails, do some reading. I meet with my office crew every day. I meet with at least one, sometimes two of my fellows here in my office to go over data.

I have multiple meetings that relate to administrative things that we do. For example, this morning, at 7:00 in the morning, 7:30, I met with the Executive Committee of the American Society of Microbiology who were in town for their council meeting, the policy people. I explained to them the nature of where we are with the budget from 7:30 to 8:30. I came back to the NIH just in time to have a meeting with Senator Cardin who's the Democratic senator from the state of Maryland to discuss with him together

myself, Harold Varmus, Francis Collins, and Gary Gibbons. So it was the director of NIH and the director of the three largest institutes to talk with him about the difficulties that sequestration is going to have on the biomedical research community.

So I finished with that, came back here, and worked on some manuscripts that we're working on. Then I went for a run, which I didn't go outside, I stayed inside today because it was so horrible out there. So I went to the fitness center. Then I met with a fellow who just got an acceptance from the *Journal of Virology*. We're going over how we were going to revise the paper. I finished that. Met with a couple of other people who were—administrative things about plans that we had to do. And then I just went over to Building 1 and met with Francis Collins to talk about the 2014 budget, how we were going to handle that. I was there with the rest of the institute directors. I came back. I met with the director of my intramural research program who was the person you saw me in the room with there and spoke about some of the issues that I need to take care there. Came back. Doing this with you.

And when you guys leave, I'm probably going to sit down, do a couple of hundred emails and try and do some reading. So that's my day.

Rich: I sense a real passion from you about what you…

Anthony: Yes. No, it's fantastic.

Rich: Yes, that's great. What keeps you awake at night?

[1:00:39.0]

"What keeps you awake at night?"

Anthony: Well, a couple of things. The state of the biomedical research enterprise that we've been worried about here. The other thing that keeps me awake—and I wouldn't say "it keeps me awake" but it's always there—is really the threat of emerging infectious diseases. Things like a pandemic flu or something like that. I wouldn't say "it keeps me awake" where I'm looking at the ceiling but that's always the nagging thing about—are we prepared enough. Can we put to bear the scientific tools that we have to prepare ourselves there?

Rich: Do you have a lot of interface with the CDC in this…?

Anthony: Oh, yes. A lot.

Vincent: We took a tour of this BSL-4 in Boston a couple of months ago.

Anthony: Yes, the BU one.

Vincent: Yes, we made a movie. It's going to come out this month. It's a tour. They brought us in. They let us suit up and we saw it.

Anthony: Really? Terrific. Great.

Vincent: I think it's partly your money, right?

Anthony: Yes. Partly.

Vincent: [Laughter] What do you think about this new coronavirus in the Middle East? Do you think that's worrisome?

Anthony: Yes. Well, it's puzzling, isn't it? How it came out, was extremely serious in the people who got it, and then kind of—boom—it disappeared. It was kind of a mini-SARS. It's there and it's gone.

Rich: I bet you there's stuff like that going on all the time.

Anthony: Oh, that stuff hits my desk all the time.

Rich: Boom—it's gone. Now we have the tools to see what it is.

Vincent: We look hard now and we find these things but probably they always happen. We just didn't know what they are.

Anthony: Exactly.

Vincent: Do you miss Brooklyn?

Anthony: I don't miss it but I have fond affection for it in my heart. I really like the Washington, D.C. area. I live in the city and I like it very much but Brooklyn's a great place.

- End –

Transcribed by: Dr. Raphael Fernandez