



A Conversation with Anthony Fauci, M.D. Director, National Institute of Allergy and Infectious Diseases

For more than six decades, the National Institute of Allergy and Infectious Diseases (NIAID) has been at the forefront of research in infectious and immune mediated diseases, microbiology, immunology, and related disciplines. It conducts and supports basic and applied research to better understand, diagnose, prevent, and treat infectious diseases including HIV/AIDS, tuberculosis, and malaria, as well as immune mediated disorders such as lupus and asthma. This work has led to new vaccines, therapeutics, diagnostics, and other technologies that have improved health and saved millions of lives in the United States and around the world.

What are the strategic priorities of NIAID? How is NIAID accelerating findings from basic research into health care practice? What have we learned from the study of emerging and reemerging infectious diseases? What's on the horizon for NIAID? Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases, joined me on The Business of Government Hour to explore these questions and more. The following provides an edited excerpt from our interview. – Michael J. Keegan



On the Strategic Priorities for NIAID

The four major areas of emphasis are:

- HIV/AIDS
- Infectious diseases other than HIV/AIDS, which include the standard established infections, emerging and reemerging infections, and even bio-defense such as having defense against anthrax or other attacks
- Basic and clinical research into the immune system— understanding how it works, diseases of aberrant function of the immune system, or deficiency of the immune system
- Global health, focusing on a vision of where we want to go

Regarding HIV/AIDS, three-plus decades since the [recorded manifestation] of this devastating pandemic, we have the scientific basis for development of prevention modalities and

treatment that's highly effective. We are also on a quest for a vaccine. We feel we can turn around the trajectory of the pandemic, and within a reasonable period of time, we'll see an AIDS-free generation, where the number of new infections is less than the number of people who are put on therapy.

The strategic vision for tackling emerging and reemerging infectious diseases involves developing platforms of vaccines and drugs that would have universal applicability, rather than trying to chase everything that might emerge. With regard to immunology, it's just fundamentally good, sound basic research to understand the mechanisms of immune function to properly understand how we might suppress aberrant mechanisms and enhance deficient mechanisms.

It's becoming quite evident that we live in a "global community" [with] certain consequences. The idea that we worry about certain diseases and there are diseases other people worry about is antiquated.

On Challenges Facing NIAID

We live in an era of constrained resources [and unprecedented] scientific opportunities. This is a real challenge: how do you get the best bang for the buck? How do we pursue groundbreaking research that will ultimately benefit public health under tight budgets? We meet this challenge by prioritization, which is essential because there are a lot of good ideas, but in an era of fiscal constraint you can't pursue them all.

The next significant challenge we face is particular to NIAID's unique mission—anticipating the unexpected! Most institutes at NIH, including NIAID, are responsible for the basic and clinical research in a particular area, whether it's focusing on heart, lung, blood, kidney, etc. For us, it's infectious diseases and immunology. In addition to that predictable translation from a basic concept to an applied clinical concept, NIAID must also always be ready for the unexpected. At a moment's notice we may need to respond to a completely new infection.

This is exactly what we faced in the summer of 1981. At that time, the CDC's Morbidity and Mortality Weekly Report reported the first five cases of pneumocystis pneumonia in gay men from Los Angeles. One month later, an additional 26 young gay men from New York, San Francisco, and LA presented with this strange disease. Immediately, it was our task to figure what it was and what can be done. This need to deal with the unexpected and unpredictable presents a unique challenge for NIAID. It isn't every week that a new cancer is discovered or a new form of heart disease, but at any given time we could face a brand new infectious disease.

On the Characteristics of Infectious Diseases

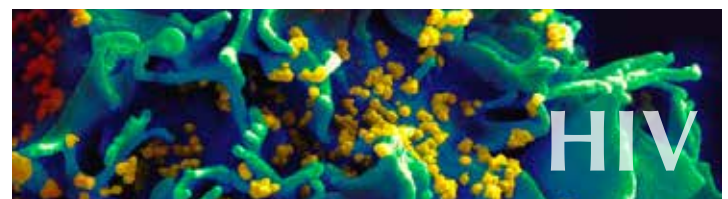
Infectious diseases have a number of unique characteristics. Microbes have the capability, through mutations, of changing characteristics in minutes to days because of their replication capability. Microbes like HIV replicate thousands of times per day. When you're talking about infectious diseases, it's a constant evolution. You have a disease. It spreads. You develop a drug. You treat a person, and then all of a sudden after a period of years, the virus or the bacteria develops resistance and you have to come in with another drug. It's a constant, dynamic, emerging world of microbes that we'll never completely wipe out; microbes constantly adapt for



their own survival. We need to stay a step ahead of it all with our intervention, therapies, vaccines, or diagnostics.

It's a constant state of surprise given the extraordinary capability of microbes, viruses, bacteria, and parasites to evolve, emerge newly, or reemerge in a different setting and under different circumstances. I gave the example of HIV/AIDS emerging in 1981 as a truly new infection. In addition, we also face reemerging infections; these are infections that have historically existed that may be dominant, but reemerge either in a different form or a different location. For example, we have drug-resistant malaria. For years, we were able to treat malaria easily, and then drug-resistant forms emerged. We have diseases that have been around a long time, but not in our backyard. A classic example of that is West Nile Virus, which was in the Middle East and in Africa for centuries, but only within the last couple of decades has come to the U.S. It's not so much a state of surprise, but [a] constant state of the unexpected.

On the Pursuit of Progress: HIV/AIDS



In the mid-80s and early 90s, the median survival of my patients with HIV/AIDS was six to eight months, meaning

that 50 percent of the patients would be dead in six to eight months, which is horrible. By applying fundamental basic research that involves understanding the replication cycle, targeting the vulnerable components of that replication cycle, and designing a drug therapy ... fast-forward 30 years [to] today, we now have more than 30 FDA-approved anti-retroviral drugs. When we use these drugs in combination, a recently infected person could [possibly] live an additional 50 years. That's a dramatic turnaround over a 30-year period. Along with these anti-retroviral drugs, we have effective low-tech forms of prevention.

In addition, we're actively pursuing the development of an HIV vaccine. The question is, can we cure people? Can we get to the point where you suppress the virus enough that you could stop the drug and the virus won't rebound? I don't know ... but it's certainly ... worth trying Over the last three years, the advance ... toward a vaccine is much more than what we had seen in the previous 15 to 20 years.

On Bringing Tuberculosis (TB) Research into the 21st Century



Tuberculosis is one of these enduring global health issues. It has been neglected because of a good dose of complacency—that it's somebody else's problem, not a problem for the developed world. One-third of the world's population is infected with latent tuberculosis. That's over two billion people. Though they're not sick, they have latent TB, with about eight million new cases a year and about 1.3 million deaths per year.

Our goal is to bring the science of tuberculosis into the 21st century. Until recently, we haven't had a new drug for tuberculosis in over 40 years. Just this past year, we had the first drug that was specifically approved only for TB.

We have a very ineffective tuberculosis vaccine. We have diagnostics that are antiquated. We don't have enough drugs and the drugs we do have require six months to a year to suppress the disease. We need to play serious catch-up. We're doing that by aggressively applying modern techniques such as the ability to rapidly sequence strains of TB, identify vulnerable parts of the microbacteria susceptible to drugs, and code for antigens that might be used for a vaccine. We

have ways of not only diagnosing TB, but also determining at the point of care whether we're dealing with a resistant tuberculosis.

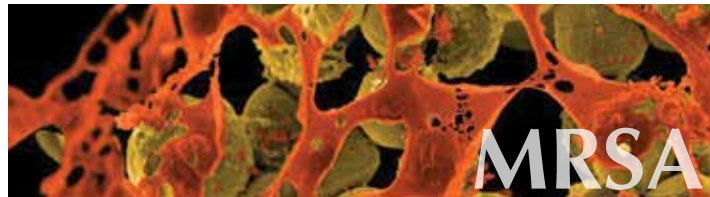
About 10 percent of the two billion-plus who are latently infected with TB will, during their lifetime, manifest active TB. We don't understand this mechanism. We don't understand the fundamental pathogenesis of tuberculosis or the systems biology of the immune system. Why doesn't the immune system completely eradicate tuberculosis? Why do you always have a little bit that remains and is latent? What is the proper immune response to protect you? We are applying microbial genomic sequencing technologies, investing in the basic science underlying point-of-care diagnostics, supporting research to develop vaccine candidates, and engaging in public-private partnerships for drug development.

On the Development of a Universal Influenza Vaccine



We have made significant progress toward the production of vaccines, but for me and my colleagues in the field, the real goal is to develop what we call a universal influenza vaccine. This would obviate the need for annual influenza vaccination and enhance our ability to respond to ... influenza pandemics. A universal flu vaccine induces a response against that component of the influenza virus that doesn't change or changes very little from season to season. We are getting closer to this goal, so the exciting thing in influenza research is to develop a truly effective influenza vaccine that you may need to give once or two or three times throughout the lifetime to protect you against all strains.

On Combating Drug Resistance



It is a fact of life that microbes, given their replicative and mutational capability, adapt to whatever you throw at them. When you treat a patient with an antibiotic or an antiviral,

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unless you completely eliminate that bacteria or that virus, it will naturally select for the mutation that is resistant to getting killed. When you are infected with a virus or bacteria it isn’t a single homogenous microbe. Mutations occur that can make a microbe resistant. If you inadequately treat the sensitive microbes, resistant ones might emerge and dominate.

Therefore ... if you use antibiotics when you don’t need them or use them at the incorrect dose, you will inadvertently select for resistant microbes. The overuse and inappropriate use of antibiotics is a surefire way to help the microbe select for resistance, leading to drug-resistant forms.

On Technological Advancement and the Use of Scientific Technology

From the standpoint of infectious diseases, there are a number of technologies, but let me pick out one that is really transformative. It is the ability to rapidly sequence the genome of the microbes. To give you a sense of the transformation, when the first microbe was sequenced decades ago it took about a year and about \$40 million. Today, we can do it in a few hours for a couple of dollars. It’s just breathtaking what you can do. We refer to it as next generation sequencing, NGS, or deep sequencing where you could take a quasi-species of viruses and sequence every single one of them and know the signatures of resistance, transmissibility, and pathogenesis. This is the application of genomics, proteomics, and informatics. These are technically the most transforming advances that we’ve been able to make.

From a basic research perspective, we are able to better understand how the microbe works—all the genetic determinants of its functions. You arrive at a genotype and a phenotype. Genotype is what the genes are and the phenotype is how the microbe acts, what it does. To be able to make that correlation between genotype and phenotype instantaneously, as opposed to waiting, is phenomenal. From an applied research standpoint, the progress is breathtaking.

In an outbreak of a disease, using sequencing and computational biology, we can very rapidly know whether we are dealing with a microbe, for example a virus. We can then identify the class of virus: checking databases, we assess whether there is a virus that absolutely matches it. If this virus doesn’t match anything we’ve seen before, then wow, we’re dealing with a brand-new virus. Once you identify it and sequence it, you can actually create it and then





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manipulate it. This enables you to target drugs against it. These are activities that can be done today almost instantaneously, which years ago took months, if not a year or longer.

On the Evolving Strategies in Biodefense

Our biodefense strategy has evolved since the mid-2000s, [when] we were developing vaccines and drugs for threats we knew. It became clear that it was futile to try and make an intervention against each and every single potential microbe. We started to focus on what we call broad multi-use platforms for vaccines, antibiotics, and antivirals. We could have an antiviral that would be effective against multiple different classes of viruses.

This shift in strategies has been transformative for the entire field of microbiology. It allows us to develop sustainable interventions against microbes that someone might deliberately release, namely bioterrorism. It also helps us prepare against the more likely scenario and that is nature itself. The evolutions of microbes that have devastated civilizations are naturally occurring events. In the quest to protect and develop interventions against deliberately released microbes, we've come a long way to enhance our capability of responding to naturally occurring events.

On the Future

We can expect extraordinary, breathtaking opportunities in science. From the standpoint of infectious diseases and immunology, it is being able to unlock the intricacies and the secrets of the immune system. How might we control it when it's aberrant and supplement it when it's deficient? With regard to microbes, we remain ever vigilant for any emerging infectious disease. We also seek, beyond just an aspiration, to send HIV/AIDS, malaria, and tuberculosis the way of smallpox. We pursue these goals, and our mission, in an era of constrained resources at a time when some view scientific research as a discretionary component of the federal budget. Personally, I don't think science should be a discretionary component. It should be a mandatory component of what we do. ■



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