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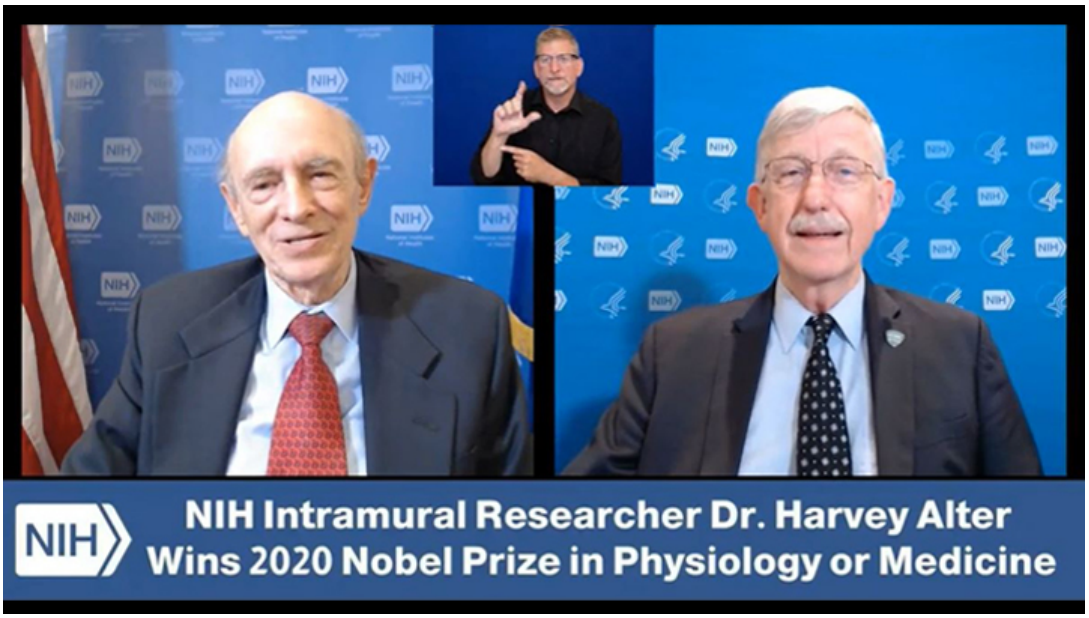
Discussing the Long Arc of Discovery with NIH's Newest Nobelist

Posted on October 8th, 2020 by Dr. Francis Collins



It's been a tough year for our whole world because of everything that's happening as a result of the coronavirus disease 2019 (COVID-19) pandemic. Yet there are bright spots that still shine through, and this week brought some fantastic news about NIH-supported researchers being named 2020 Nobel Prize Laureates for their pioneering work in two important fields: Chemistry and Physiology or Medicine.

In the wee hours of Wednesday morning, NIH grantee Jennifer A. Doudna, a biochemist at the University of California, Berkeley, got word that she and Emmanuelle Charpentier, a microbiologist at the Max Planck Institute for Infection Biology, Berlin, Germany, had won the 2020 Nobel Prize in Chemistry for developing the CRISPR/cas approach to genome editing. Doudna has received continuous NIH funding since 1997, mainly from the National Institute of General Medical Sciences and National Human Genome Research Institute.

The CRISPR/cas system, which consists of a short segment of RNA attached to the cas enzyme, provides the ability to make very precise changes in the sequence, or spelling, of the genetic instruction books of humans and other species. If used to make non-heritable edits in relevant tissues, such technology holds enormous potential to treat or even cure a wide range of devastating diseases, including thousands of genetic disorders where the DNA misspelling is precisely known.

Just two days before Doudna learned of her big award, a scientist who's spent almost his entire career at the NIH campus in Bethesda, MD, received news that he too was getting a Nobel—the 2020 Nobel Prize in Physiology or Medicine. Harvey Alter, a senior scholar in the NIH Clinical Center's Transfusion Medicine Department, was recognized for his contributions in identifying the potentially deadly hepatitis C virus. He shares this year's prize with Michael Houghton, now with University of Alberta, Edmonton, and Charles M. Rice, The Rockefeller University, New York, who's received continuous NIH funding since 1987, mainly from the National Institute of Allergy and Infectious Diseases.

In a long arc of discovery rooted in basic, translational, and clinical research that spanned several decades, Alter and his colleagues doggedly pursued biological clues that at first led to tests, then life-saving treatments, and, today, the very real hope of eradicating the global health threat posed by hepatitis C infections.

We at NIH are particularly proud of the fact that Alter is the sixth Nobel Prize winner—and the first in 26 years—to have done the entirety of his award-winning research in our Intramural Research Program. So, I jumped at the opportunity to talk with Harvey on NIH's Facebook Live and Twitter chats just hours after he got the good news on Monday. Here's a condensed version of our conversation, which took place on the NIH campus, but at a safe physical distance to minimize the risk of COVID-19 spread.

Collins: Harvey, let me start off by asking, how did you find out you'd won the Nobel Prize?

Alter: At 4:15 this morning. I was asleep and heard the telephone ringing. I ignored it. Five minutes later, I got another call. Now, I'm getting kind of perturbed. But I ignored it, thinking the call must be some kind of solicitation. Then, the phone rang a third time. I answered it, prepared to tell the person on the other end not to call me anymore. I heard a man's voice say, "I'm the Secretary General of the Nobel Prize, calling you from Stockholm." At that point, I just froze.

Collins: Did you think it might be a hoax?

Alter: No, I didn't think it was a hoax. But I wasn't expecting to win the prize. I knew about three years ago that I'd been on a Nobel list. But it didn't happen, and I just forgot about it. Truthfully, I didn't know that today was the day that the announcement was being made. The news came as a complete shock.

Collins: Please say a few words about viral hepatitis. What is it?

Alter: Sure. Viral hepatitis is an infection of the liver that causes inflammation and can lead to scarring, or cirrhosis. Early in my career, two viruses were known to cause the disease. One was the hepatitis A virus. You got it from consuming contaminated water or food. The second was the hepatitis B virus, which has a blood-borne transmission, typically from blood transfusions. In the 1970s, we realized that some other agent was causing most of the hepatitis from blood transfusions. Since it wasn't A and it wasn't B, we cleverly decided to call it: non-A, non-B. We did that because we hadn't yet proven that the causative agent was a virus.

Collins: So, even though you screened donor units for the hepatitis B virus to eliminate tainted blood, people were still getting hepatitis from blood transfusions. How did you go about trying to solve this mystery?

Alter: The main thing was to follow patients prospectively, meaning forward in time. We drew a blood sample before they were transfused, and then serially afterwards. We saved those samples and also the donor samples to compare them. Using a liver function test, we found that 30 percent of patients who had open heart surgery at NIH prior to 1970 developed liver abnormalities indicative of hepatitis. That's 1 in 3 people.

We then looked for the reasons. We found the main one was our source of blood. We were buying blood, which was then in short supply, from commercial laboratories. It turned out that their paid donors were engaging in high-risk behaviors [Note: like IV drug users sharing hypodermic needles]. We immediately stopped using these laboratories, and, through various other measures, we got the rate down to around 4 percent in 1987.

That's when Michael Houghton, then at Chiron Corp. and a co-recipient of this year's prize, cloned the virus. Think about it, he and his colleagues looked at 6 million clones and found just one that reacted with the convalescent serum of a patient with non-A, non-B. In other words, having contracted the virus, the patient already made antibodies against it that were present in the serum. If that one clone came from the virus, the antibodies in the serum would recognize it. They did, and Chiron then developed an assay to detect antibodies to the virus.

Collins: And that's when they contacted you.

Alter: Yes, they wanted to use our panel of patient blood samples that had fooled a lot of people who claimed to have developed a non-A, non-B assay. Nobody else had "broken" this panel, but the Chiron Corp. did. We found that every case of non-A, non-B was really hepatitis C, the agent that they had cloned. Hepatitis C was the missing piece. As far as we could tell, there were no other agents beside hepatitis B and C that would result in transfusion transmission of the disease.

Collins: This story is clearly one of persistence. So, say something about persistence as an important characteristic of a scientist. You're a great example of someone who was always looking out for opportunities that might not have seemed so promising at first.

Alter: I first learned persistence from Dr. Baruch Blumberg, my first NIH mentor who discovered the hepatitis B virus in 1967. [Note: Other NIH researchers identified the hepatitis A virus in 1977] The discovery started when we found this "Australian antigen," a molecular structure that the immune system recognizes as foreign and attacks. It was a serendipitous finding that could have been easily just dropped. But he just kept at it, kept at it, kept at it. He had this famous wall where he diagrammed his hypotheses with all the contingencies if one worked or failed. Then, all of a sudden, the antigen was associated with hepatitis B. It became the basis of the hepatitis B vaccine, which is highly effective and used throughout the world. Dr. Blumberg won the Nobel Prize for his work on the hepatitis B virus in 1976.

Collins: Sometimes people look at NIH and ask why we don't focus all of our efforts on curing a particular disease. I keep answering, 'Wait a moment, we don't know enough to know how to do that.' What's the balance that we ought to be seeking between basic research and clinical applications?

Alter: There is this tendency now to pursue highly directed research to solve a problem. That's certainly how biopharma works. They want a payoff. The NIH is different. It's a place where you can pursue your scientific interests, wherever they lead. The NIH leadership understands that the details of a problem often aren't obvious at first. Researchers need to be allowed to observe things and then to pursue their leads as far as possible, with the understanding that not everything will work out. I think it's very

important to keep this basic research component in parallel with the more clinical applications. In the case of hepatitis C, it started as a clinical problem that led to a basic research investigation, which led back to a clinical problem. It was bedside-to-bench-to-bedside.

Collins: Are people still getting infected with hepatitis C?

Alter: Yes, hepatitis C remains a global problem. Seventy million people have contracted the virus, though the majority are generally asymptomatic, meaning they don't get sick from it. Instead, they carry around the virus for decades without knowing it. That's because the hepatitis C virus likes to persist, and our immune system doesn't seem to be able to get rid of it easily.

However, some of those infected will have bad outcomes, such as cirrhosis or cancer of the liver. But there's no way of knowing who will and who won't get sick over time. The trick now is to identify people when they're asymptomatic and without obvious disease.

That involves testing. We're in a unique position with hepatitis C, where we have great tests that are highly sensitive and very specific to the virus. We also have great treatments. We can cure everybody who is tested and found to be positive.

Collins: People may be surprised to hear that. Here is a chronic viral illness, for which we actually have a cure. That's come along fairly recently. Say a bit more about that—it's such a great story of success.

Alter: For many years, the only treatment for hepatitis C was interferon, a very difficult treatment that initially had only about a 6 percent cure rate. With further progress, it got up to around 50 percent. But the big breakthrough came in the late 1990s when Gilead Corp., having the sequenced genome of the hepatitis C virus, deduced what it needs to replicate. If we know what it needs and we interfere with that, we can stop the replication. Gilead came out with a blockbuster drug that, now in combination with another drug, aims at two different sites on the virus and cures at least 98 percent of people. It's an oral therapy taken for only 12 weeks, sometimes as little as 8 weeks, and with virtually no side-effects. It's like a miracle drug.

Collins: What would you say to somebody who is thinking about becoming a scientist? How do you pick an area of research that will be right for you?

Alter: It's a tough question. Medical research is very difficult, but there's nothing more rewarding than doing something for patients and to see a good outcome like we had with hepatitis C.

The best path forward is to work for somebody who's already an established investigator and a good teacher. Work in his or her lab for a few years and get involved in a project. I've learned not get into a lot of projects. Get into something where you can become the expert and pursue it.
The other thing is to collaborate. There's no way that one person can do everything these days. You need too much technology and lots of different areas of expertise.

Collins: You took on a high-risk project in which you didn't know that you'd find the answer. What's the right balance between a project that you know will be productive, and something that might be risky, but, boy, if it works, could be transformative? How did you decide which of those paths to go?

Alter: I don't think I decided. I just went! But there were interim rewards. Finding that the paid donors were bad was a reward and it had a big impact. And the different donor testing, decreasing the amount of blood [transfused], there were all kinds of steps along the way that gave you a reward. Now, did I think that there would be a treatment, an eradication of post-transfusion hepatitis at the end of my line? No, I didn't.

And it wouldn't have happened if it was only me. I just got the ball rolling. But it needed Houghton's group. It needed the technology of Charlie Rice, a co-recipient of this year's Nobel Prize. It needed joint company involvement. So, it required massive cooperation, and I have to say that here at NIH, Bob Purcell did most of the really basic work in his lab. Patrizia Farci, my closest collaborator, does things that I can't do. You just need people who have a different expertise.

Collins: Harvey, it's been maybe six hours since you found out that you won the Nobel Prize. How are you going to spend the rest of your day?

Alter: Well, I have to tell you a story that just happened. We had a press conference earlier today at NIH. Afterwards, I wanted to return to my NIH office and the easiest route was through the parking garage across the street from where we held the press conference. When I entered the garage, a security guard said, "You can't come in, you haven't been screened for COVID." I assured him that I had been screened when I drove onto the NIH campus. He repeated that I had to go around to the front of the building to get screened.

Finally, I said to him, "Would it make any difference if I told you that I won the Nobel Prize today?" He replied, 'That's nice, but you must go around to the front of the building.'" So, winning the Nobel doesn't give you immediate rewards!

Collins: Let me find that security guard and give him a bonus for doing a good job. Well, Harvey, will there be that trip to Stockholm coming up in December?

Alter: Not this year. I've heard that they will invite us to Stockholm next year to receive the award. But there's going to be something in the US. I don't know what it will be. I'll invite you.

Collins: I will be glad to take part in the celebration. Well, Harvey, I really want to thank you for taking some time on this special day to reflect on your career and how the Nobel Committee came calling at 4:30 this morning. We're really proud of you!

Alter: Thank you.

Links:

Hepatitis C (National Institute of Diabetes and Digestive and Kidney Diseases/NIH)

"The Nobel Assembly at Karolinska Institutet has today decided to award the 2020 Nobel Prize in Physiology or Medicine jointly to Harvey J. Alter, Michael Houghton and Charles M. Rice for the discovery of Hepatitis C virus," Nobel Prize announcement, October 5,2020.

Harvey Alter (Clinical Center/NIH)

"The Road Not Taken, or How I Learned to Love the Liver: A Personal Perspective on Hepatitis History" Alter HJ, Hepatology. 2014 Jan;59(1):4-12.

"Reflections on the History of HCV: A Posthumous Examination." Alter HJ, Farci P, Bukh J, Purcell RH. Clinical Liver Disease, 15:1, Feb 2020.

"Is Elimination of Hepatitis B and C a Pipe Dream or Reality?" Alter HJ, Chisari FV. Gastroenterology. 2019 Jan;156(2):294-296.

Michael Houghton (University of Alberta, Edmonton)

Charles Rice (The Rockefeller University, New York)

What is genome editing? (National Human Genome Research Institute/NIH)

Jennifer Doudna (University of California, Berkeley)

Emmanuelle Charpentier (Max Planck Institute for Infection Biology, Berlin, Germany)

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