As of March 20, more than 8,700 people worldwide had died of COVID-19, the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Caltech trustee David Ho (BS '74) of the Aaron Diamond AIDS Research Center, Columbia University, says that this is just the tip of the iceberg. Ho, an expert on viral epidemics, has spent decades researching HIV/AIDS, having begun his career in Los Angeles, "ground zero" of the first outbreak, in the early 1980s. On March 18, Ho sat down with members of the Caltech community to discuss the novel coronavirus and the future of our society in the light of this global pandemic.

Walk us through the spread of the virus in the United States. What does the country look like right now?

Let me just give you a picture of what I see here in New York. About two weeks ago, we had our initial case, and now in New York City newly diagnosed confirmed cases are tripling every two days. In our New York Presbyterian Hospital, approximately 25 percent of the swab samples that are submitted for testing are positive. In the suburban communities outside of New York, approximately 10 percent of the swabs submitted are positive. So, the virus is everywhere. And in New York, we know that we are in the exponential growth phase of the epidemic.

Looking back at what has transpired throughout the world, we saw the first wave hit China; the second wave hit South Korea, Italy, and Iran; and then, trailed by only about a week or so, France, Germany, Spain, and the U.S. We all know that China went through a period of great devastation. It has over 80,000 cases. Italy is rapidly catching up, with over 31,000 cases. We suspect that in the U.S. this will rapidly sweep from the coastal regions and it will hit middle America. It is already there, but we will see exponential growth very, very soon. Then of course we are all worried about what would happen when this epidemic strikes places like Africa and India where the health care system is less developed.

Can you tell us about the pathology of the disease?

COVID-19 typically causes fever and a dry cough. One may have aches in the body—the muscles—and if it's severe enough, there would be shortness of breath due to pneumonia.

Gastrointestinal symptoms can occur and are an indication of more severe disease. It's not very common to have a runny nose or the sniffles, and a sore throat is not common either.

The incubation period from exposure to onset of symptoms is between four and six days; and if you want to cover 95–98 percent of the cases it is between three and 10 days. It's pretty rare to have an incubation period outside of that range.

What in particular makes this virus so dangerous?

What is disturbing is that virus shedding, as detected in the mouth or nose, is very, very common and could be there prior to onset of symptoms. That's why transmission could occur from asymptomatic individuals. And virus shedding could continue for days up to three weeks after a person recovers. That is extremely worrisome for the spread of this virus. Furthermore, the stability of this virus is

worrisome as well. If you put it in aerosol form and keep it in the air, the half-life is several hours; if you drop it on surfaces of copper or cardboard, it could survive about a day. But if it's on steel or plastic surfaces, you could still detect infectious virus after 72 hours, although the infectivity decreases with time.

What do we know about the biology of the virus?

The virus is highly related to another coronavirus called SARS coronavirus. That was another outbreak that occurred worldwide 17-18 years ago, and largely in China and Asia.

The two viruses are about 80 percent identical. We know the origin of SARS was from a bat through an intermediary animal called the civet cat.

Another virus called Middle Eastern Respiratory Virus, MERS, also originated in bats and infected camels, and camels passed it to humans. For COVID-19, we believe the original host must be a bat species, because that animal carries a virus that's 97 percent identical to what we're seeing now.

Because of the SARS outbreak and the MERS outbreak, and research done on those two pathogens, we actually know quite a bit about coronaviruses.

The outbreak began in China; how have they been dealing with the virus?

This epidemic was first identified in a few cases with pneumonia in December 2019. In retrospect, there were scattered cases in November according to Chinese officials. I would say that initially there were missteps and lack of transparency that contributed to the explosive outbreak in the city of Wuhan in the central province of Hubei. That epidemic in central China accounts for 85 percent of the confirmed cases in China. It led Beijing officials to quarantine the entire province of 50 million people. The epidemic peaked in early February with 4,000 newly diagnosed cases each day. But since the lockdown and the various draconian measures applied, the number of new cases each day has been declining by half every week, and remarkably it's now down to about 20 per day. The rest of China's other provinces also applied very harsh measures and they indeed successfully flattened the curve outside of Hubei province.

We know what they've done is not sustainable and the question is: What is China going to do now if it relaxes the infection control measures? Some of the recovered patients are still shedding virus and now China is surrounded by sick neighbors. Surely if they open up their borders, infection will come in the same way it came into the U.S. The world is waiting to see what China is going to do.

Now in terms of the U.S., we obviously are undergoing exponential growth. The 10,400 confirmed cases is a gross underestimate. The lack of testing is embarrassing. It's an outright failure in leadership.

What are the tests we need to detect coronavirus infection?

Everybody's talking about testing and that's actually referring to PCR [polymerase chain reaction] testing, looking for viral RNA to determine whether a person is

infected. But there's still no talk of antibody testing to determine which people have had it and are immune, and that is another crucial tool we need to combat this epidemic. Many research labs throughout the country—I'm sure at Caltech too—could be running antibody tests right now to survey the population and tell us what the real penetrance of this pathogen is in our communities. We are, on a research basis, embarking on that to understand the degree of infection in New York City and outside of New York City.

How long before the U.S. sees test availability similar to what South Korea has implemented?

The PCR testing, which is the one that's approved, is now ramping up very, very rapidly in state and local labs as well as in academic medical centers and in the commercial sector. Their production will grow tremendously. Roche has a machine that will run 1,000 samples at a time. If you go to a commercial lab, they take a swab, they package it, they quite often send it to another facility somewhere else. The turnaround time is typically 72 hours. In that period, it's very, very hard to manage patients and their contacts. It's a nightmare for the healthcare worker.

We need point-of-care tests. Those kinds of tests are available for HIV and for many other diseases; you use a finger stick, drop the blood on a small device, and have a readout in 15 minutes. These tests measure antibody response to the virus and are extremely useful. Yet we don't have a single test licensed in the U.S. In China, in South Korea, and in Europe, those tests are used. The manufacturer for this rapid test is producing a million a day. It's there. But in the name of protecting the public, the FDA has moved very, very slowly. That delay, in my view, has caused more harm than good.

Can you elaborate on point-of-care testing?

It's almost like a home pregnancy test or home HIV test. These tests have been around for a long time. The test that I'm specifically referring to, coming out of China, South Korea, and approved in Europe, is an antibody test. You put a drop of blood on a plastic slide, add another drop of the buffer that comes with the test, and you let it sit for 15 minutes. Then, you look at the bands. You're negative if you have just one band, or you're positive if you have more than one band. The test also tells you type of antibody. There's a type of antibody called IgG [immunoglobulin G] and another type called IgM [immunoglobulin M]. Typically, when a person is infected, the IgM response is earlier and the IgG response is later. The two bands indicate the course of the infection.

This kind of test is available all over the world for HIV. The technology is there, the tests are there. But they're not FDA approved. While I think they are fairly close to being approved, we have let several weeks go by and to me that's tragic.

Will this coronavirus be seasonal?

Everyone is asking whether this virus is here to stay. Initially, just based on what China did with SARS long ago, there was hope that warmer weather and more sunlight would help kill the virus in our environment and therefore lower the probability of transmission.

But now this virus has gained such a strong foothold in the human population. It's already 25 times larger than SARS and it's already embedded in the Southern hemisphere. If you look at Australia, South Africa, Argentina, Brazil, there are cases there already, and community transmission is occurring. As the weather changes, perhaps the Northern hemisphere will gain an advantage. But the epidemic in the Southern hemisphere is going to accelerate.

The long-term outcome may resemble influenza so that we have seasonal bouts, with the virus bouncing back and forth between the Northern and Southern hemispheres. This is of course just speculation, but that's what we see with influenza.

Why does COVID-19 have less impact on children and more impact on the elderly?

Well, the latter part is easy. Older people generally do less well with all sorts of respiratory infections, including influenza and SARS. So that's just the typical scenario we see. The children, however, are a mystery. As you know, children typically get flu or other respiratory viruses very quickly and bring them home to infect the parents. But in this particular case, the number of children infected in China, after extensive studies, don't seem to indicate that this is the case for this coronavirus.

Some people seem to show mild symptoms while others have a more severe experience. Has the virus already mutated?

RNA viruses all replicate with low fidelity. Mutations occur at pretty similar rates and these viruses typically don't have proofreading functions. In contrast, we replicate our DNA with high fidelity and we have a proofreading function to fix the errors. So, every time they replicate, there's a fixed rate of mutation. This virus is mutating but it has mutated very little so far. There are differences but probably they are functionally not important, so that's not the explanation for why you see different disease courses among the infected.

For HIV it's the same thing: 10 people could be infected by the same strain but you have very different outcomes. With HIV, genetics and environmental factors play a role. Some of the genetics has been worked out; we know that there are certain tissue types that would protect and others that would harm. I suspect it's the same here.

Once you become infected with the virus, can you get it again?

There are a few anecdotes from China about re-infection but, if you look at those reports carefully, they're not well-documented. It could be that folks just continued to shed virus from the initial infection. Only one study was formally done and it is not a human study. It's a macaque study. They infected macaques with this virus, then waited until the monkeys recovered and tried to re-infect them. They could not. This just came out in the past few days. That bodes well for human immunity.

We have now looked at a lot of serum from convalescent individuals and those serum samples have antibodies against the so-called spike protein of the virus. That's the protein that sits on the surface of the virus particle. By tightly binding, the antibody could neutralize the virus. Once an infected person develops antibodies, there should

be protective immunity for quite some time. That's why we need to buy time for immunity to develop in the population.

After a person recovers from the virus, how long are they still contagious?

That's a very important question. We're not sure; one individual in China was shown to have persistent virus shedding for over a month. But typically, we're looking at a three-week period from onset of symptoms.

What should we be doing to limit the spread of this epidemic?

The social distancing and good hygiene strategies have been successfully applied, in South Korea for example, to bring their epidemic down. They're the only other country that has flattened the curve—slowed down the number of new infections to not overwhelm the healthcare system—and gradually brought this epidemic under control. There are many places that have done a pretty good job of not allowing the epidemic to explode, such as Taiwan and Hong Kong. These are places that had quite a bit of experience in fighting SARS, 17 years ago.

Are you optimistic that these measures combined with research will be enough to combat the coronavirus?

I personally believe we will blunt this epidemic, but I think we wasted a good four to six weeks largely because of lack of testing and lack of a certain preparedness. But I think we could still make a difference and bring it under control with very harsh measures.

But again, are these measures sustainable? We've got to expect that businesses must reopen and schools must teach again. Whether it's travel or sports or live entertainment, we're going to have to return to some semblance of normalcy. But what are the measures that are effective and sustainable? That's a question we as a society have to deal with. We need to buy time so that gradually the population will have a degree of immunity.

Most importantly, we need to buy time to allow science to deliver solutions. We're going to have to develop drugs, antibodies, and vaccines. I think the mobilization by the scientific community, from my perspective, is amazing. So many people have mobilized and jumped on this and are contributing, from discovering small-molecule drugs that could block various enzymes of this virus to coming up with antibodies that could neutralize the virus. Researchers have already come up with a few promising chemicals that could be a good start to drug development. There are already a few neutralizing antibodies isolated from infected individuals; my own group is in the midst of doing all that.

And, of course, people are working on vaccines. A lot of companies are working on vaccines and those vaccines are at various stages. A couple are within weeks of entering human testing and that's quite, quite remarkable. There is one thing about vaccines, though: Some of the experiments previously done on SARS suggested that when animals developed antibodies and then were given the virus, they had greater lung injury due to the presence of the antibodies. The scientific community would have to resolve that issue quickly and its resolution would either halt the current

approaches or unleash them to move full speed ahead. We certainly will take a part in doing that. I think we have the real possibility that COVID-19 may become a fact of life until science comes through as it has done for past epidemics.

This is going to take some time. But I'm very confident that the science will rise to the task and provide a solution. But it's not going to be a few months as our president suggests. It's going to be much longer than that. I would say 18 months, or 24 months. I think we are all facing tough challenges ahead.