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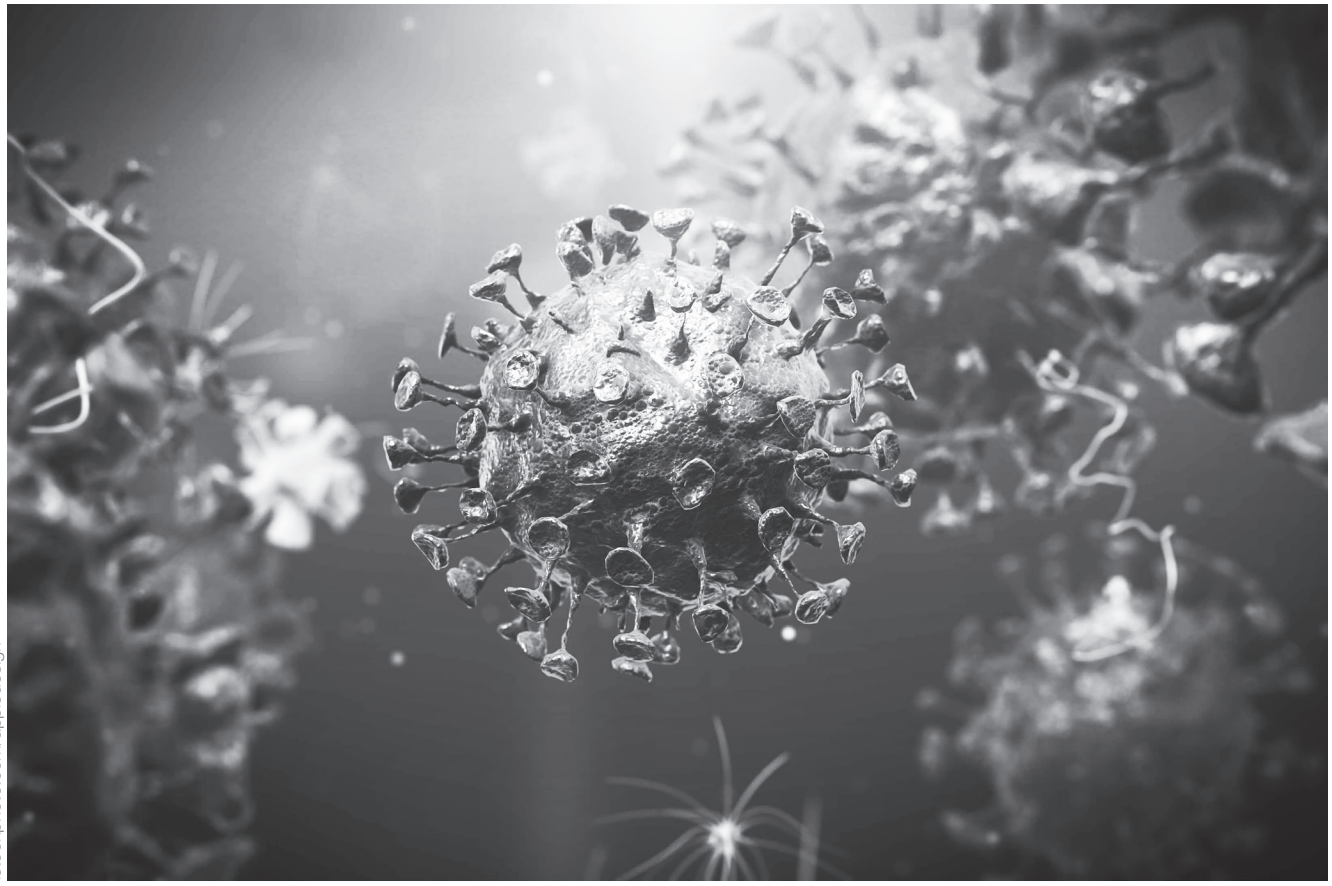

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A 3D rendering of coronavirus outbreak and influenza disease virus

INVESTIGATING COVID-19

BY FRITZ GUY AND BRIAN BULL

Editor's Note: Fritz Guy and Brian Bull have written three books together. In the early days of the pandemic, at Spectrum*'s request, Guy questioned Bull about his research on COVID-19 at Bull's Pathology Laboratory in Loma Linda, California. In July, they added an update to their conversation. It is included at the end of the article.*

Fritz Guy: From a medical science perspective, what is COVID-19, what's special about it and, in particular, how is it similar to and different from the flu—with which it is often compared nowadays?

Brian Bull: It is appropriate to compare COVID-19 to the flu because both are respiratory diseases. That is, both viruses multiply in the cells that line the air passages of the lungs—the bronchi and bronchioles—and in the lining cells of the tiny little air sacs called alveoli at the end of the smallest air passages, where the blood picks up oxygen. In the lining cells of the air passages, both viruses co-opt the machinery in the cell cytoplasm—the machinery for making things. They hijack the cell to produce more copies of themselves. These newly formed viruses then spread out and infect other cells lining the respiratory tract.

What you have been saying is true of the flu as well as of COVID-19?

Correct. They don't belong to the same family of viruses though. However, there are viruses that you may have heard about that are much more like COVID-19 than influenza. The SARS virus was quite similar and so was MERS, the Middle East Respiratory Syndrome virus. All three are coronaviruses and so, under an electron microscope, they would look very much like each other and not at all like the influenza virus.

Now, can you unpack the term "corona," which sounds very much like a crown or at least a circle?

The virologist who first named it thought it looked like a crown! It is a spherical virus with knobs scattered over its surface. To me it doesn't look much like a crown but the name sticks once the viruses of a particular group have been named. When more viruses are discovered in the same group, not surprisingly they are given the same name—in this case corona.

Let's get back to the flu. How is COVID-19 disease similar to and how is it different from the "good old flu" that most of us grew up with?

Well, as I mentioned, it's similar in that it lives in the respiratory tract. Both viruses are alike in that both produce pneumonia—fluid filling portions of the lung and making that part of the lung useless for getting oxygen into the blood. However, the similarity ends there, for the pneumonia that is produced by COVID-19 and the pneumonia that is produced by the flu virus are quite different. The flu virus produces a pneumonia that has bacteria multiplying in a fluid-filled portion of the lung, making it impossible for oxygen-containing air to get into the little air sacs—the alveoli—because the air sacs are full of fluid.

Bacteria are not directly involved in the pneumonia caused by the coronavirus. Rather, it looks as though clots in the tiny blood vessels in the air sac walls are preventing the blood from getting to the oxygen. Either way, because of fluid filling the air sac or because of blood vessels around the air sac being plugged, the blood and the oxygen don't meet. Patients with either type of pneumonia may be put onto ventilators to get the blood and the oxygen interacting again.

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The COVID-19 pneumonia has other features that are very strange. Its onset is sudden, very sudden. A patient might be sit-

ting up in bed chatting to the nurse or doctor—or maybe checking a cellphone—and 45 minutes later is struggling for air and getting rapidly exhausted. Given how suddenly patients can start fighting for air, we are reasonably sure that it is not bacteria that have suddenly infiltrated their lungs. Our best guess is that it is a shower of tiny clots that are plugging up small blood vessels.

Now, given those clots, does that make COVID-19 more deadly; is the mortality rate from COVID-19 higher than it is from similar diseases?

Yes, it is higher, but just how much higher we're not sure. We know that it is more deadly; it may be a great deal more deadly. We know that influenza kills about 0.1% of those it infects. That would be one in every thousand. Early on in the pandemic, COVID-19 seemed to be a great deal more deadly, causing death in 2–3% of patients; that would be twenty to thirty deaths for every thousand people infected. We now know that a lot of people infected with COVID-19 are never identified as being "sick." Thus, the mortality is a lot lower because the number infected for every person who dies is a lot larger than we thought at the beginning. At present, our best guess is that COVID-19 causes death in about two to three patients per 1,000. That would make it about two to three times as lethal as the flu not twenty to thirty times as it seemed early on.

So then, I could very well be infected, not have any symptoms, and not realize I have had it until I get tested?

That is correct. However, the chances of you having been infected without showing any symptoms are significantly less than the chances of somebody else who is significantly younger than you are.

Which is most of the population!

I would agree; that would, indeed, be most of the population! The mortality in COVID-19 pneumonia primarily affects people over the age of 65. The very depressing lethality statistic for those like you and me, who are older, is that the mortality is ten times higher for those above 65 than those below the age of 55!

Can you explain why that is so?

No I can't. We don't know what it is about age that makes you and I so much more likely to die. That is one of the reasons we are having so much difficulty deciding how patients with COVID-19 are best treated because we don't understand why getting older makes a person so much more likely to die.

I find your confession of "professional ignorance" just astounding! One would suppose that as long as medical science has been interested in aging and mortality somebody would have figured out some connections between the way one "is" at 55, and how one is different at 65! What do you have to say, as a medical scientist about a topic that is practically universal (we all get older) and about which you are so ignorant?

We've been getting older for a very long time and medical science knows a lot about aging in general, but how COVID-19 infection interacts with aging is another matter entirely. The virus has been available for study for maybe three months, even less time than that in North America. During the several weeks that patients have been coming down with COVID-19 in North America—and some have been dying—we haven't yet figured out why this virus is so much more likely to kill people than the flu virus, and we haven't yet figured out why it's more likely to kill old people! But while we are on the topic, there are a whole series of even more curious coincidences. COVID-19 kills disproportionately, not just older people, but also people who have high blood pressure. It kills diabetics, and it particularly targets people who are significantly overweight. Our ignorance is extensive indeed!

Is gender a factor at all?

Gender does appear to be a factor, and you would be troubled to hear that males die more frequently than

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females. The difference is not great but it is statistically significant—in the data from New York, one of the hardest hit places in the US, mortality has been about 60/40 in favor of males. So elderly males are definitely a vulnerable population!

Now this gives me a good excuse to go back to a question I asked you a few days ago, "Is there any statistical information about COVID-19 and Adventists?" The Adventist lifestyle is purported to contribute to longevity—it certainly appears to have done so in my case. You, I know, are well acquainted with the Adventist Health Study. Are there any implications here? I don't know of any Adventists who have died of COVID-19; are there any numbers on this at all?

No, and for the very reason you just commented on. All of those who join the Adventist Health Study make their contribution to the statistics on longevity only on the occasion of their death!

Oh, okay.

And since neither you nor I are aware, at present, of any Adventists who have died, we cannot begin to study the matter until some COVID-19 deaths are entered into the database of the Adventist Health Study.

Doesn't that leave us in an awkward emotional position? We can hardly wish that some Adventists would die of COVID-19 in order to give us some information. On the other hand, I am intrigued by the question, "Does the Adventist lifestyle, whether it has to do with diet or something else, have any impact on the mortality rate or even the morbidity of COVID-19?"

Well, we could study the morbidity of COVID-19, all right; but the Adventist Health Study is a study of longevity among Adventists. To study longevity it is necessary to know when your study subjects died. The Adventist Health Study, of course, also records what they died from.

We hope that data on Adventist deaths from COVID-19 will be a long way off! Changing the subject a bit, are there any additional preventive measures besides what I call the "big three": staying at home away from crowds; covering your face; and maintaining physical distance? By the way, I find the term "social distancing" odd because it isn't *social* distance that we seem to care about but it is the actual physical distance of people who are socially connected.

I assume you would approve of the terminology "physical distancing of people who are socially connected."

Yes, that may sound a little pedantic but it does the trick.

To a former editor such as yourself, that phraseology would warm the "cockles of the heart"?

Yes, yes. Are there any dietary implications here? I mean, you medical scientists ought to be useful at a time like this! Are there any foods that we ought to avoid?

There are some dietary implications, but not of the sort you are asking for. Obesity—that is, eating too much food over a long period of time—is a strong co-morbidity. More than half of the patients I have had the opportunity to study have been obese. It has been the most common finding in that particular group of COVID-19 patients.

Maybe the connection of obesity to COVID-19 morbidity will give us another "scare tactic" to get people to avoid becoming obese?

Yes, but for those who are now obese it is very difficult to rectify the situation in the time period which appears to be available. That would be on the order of twelve to eighteen months before a vaccine becomes available. Then, of course, the "fear factor" would become a great deal less intense. Once vaccinated, it is likely that a person would be immune for at least a year or two.

We don't know for certain if that is true, but we assume it is so because that has been true for other viruses, including other coronaviruses.

I would like to shift the subject a bit. Why does it take so long to develop a vaccine? I mean, we're supposed to be the most scientifically advanced country in the world and yet the time frame I hear is twelve to eighteen months to develop an effective vaccine against COVID-19. Why does it take so long? Why aren't you guys smarter than that?

It is easy enough to take a portion of the COVID-19 virus and multiply it, and then expose volunteers to it (in an aerosol, perhaps). Then, a couple of weeks later, determine if they have produced antibodies. That can

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be checked in a laboratory by using cultures of the virus and plasma from those volunteers who have been exposed. Does their plasma inactivate the virus?

This, however, is only the first step. It is now necessary to determine first that the vaccine is safe, and next, to determine if it is effective. Further, to the question of safety, suppose that two or three months (or two or three years) in the future, some of these vaccine recipients develop some new or hitherto poorly described medical condition (or even a medical condition that is well understood, such as heart disease or liver disease) in significantly increased numbers—what then? But even more difficult—and this is why we don't have a vaccine for other corona viruses that have recently afflicted populations around the world—when the vaccine has shown itself to be safe, there must still be people getting sick. In order to determine if this new vaccine is protective, members of a population must still be getting sick. So, if COVID-19 disappears before that twelve to eighteen months is up (which is devoutly to be hoped!), vaccine development grinds to a halt. The only other way we could proceed to see if the vaccine worked would be to give it to some people randomly selected in a population, withhold it from others (also randomly selected), and then arrange to have both groups exposed to the virus. Given that 0.1–0.3% of the exposed but unvaccinated group would likely die, that could obviously not be done for ethical reasons.

Yes, and I think we can understand why volunteers might be reluctant to participate in such an experiment! I regard myself as a generous and ethically caring soul but if you were to ask me to be infected with the virus and also to take a vaccine to see if the vaccine was effective—I would be very hesitant to participate in such a project!

Could you break down that "very hesitant" into a crisper category?

Well, I think I would say "no way!"

There you go! And, that is one of the reasons it takes a long time to develop a vaccine. But, of course, we don't actually ever do that in developing a vaccine. What we actually do is vaccinate members of a population and then look to see if they are protected against the natural infection—infections that people are going to get regardless. But, in order to do that, the disease must still be progressing through the population.

Yes, so the participants in the vaccine trial must at least have an average chance, a reasonable statistical probability of encountering the virus and becoming infected. Now that leads me to my last set of questions. What is your best guess about the future of COVID-19? Is it here to stay? Is it likely to be a recurring outbreak and is it going to become increasingly severe? Or is it going to kind of fade away as the human population gets more experienced with it? What happens to this kind of virus?

Well, everything that I might say on this topic is a guess—a moderately informed guess, but a guess, nonetheless. But in this case, because it is a virus that is still so poorly understood, everything that I might say about its future course is even more speculative

Excuse me, you say "poorly understood." Could

you give additional detail on that? I know what the words mean.

"Poorly understood," in this case, means that we do not yet understand the pathophysiology—the specific malfunctioning of body mechanisms—that make the disease so lethal. We do not yet understand how this virus kills, and until we understand how and why this virus kills people, we are not going to be able to devise an intelligent and coherent strategy. Of course, it is possible that we may hit upon an effective treatment by accident—it has happened before—but we are much more likely to overcome a disease that we thoroughly understand than one that remains stubbornly enigmatic.

In the meantime, we are treating the symptoms of the disease as they make their appearance. If patients have trouble breathing, we can put them on a respirator. That is not going to get us to an understanding of *why* they are having trouble breathing, but it may well save lives. So, until we understand the pathophysiology—the disordered functioning of various body organs and glands that the virus causes—until we understand that, it is a wildly speculative guess as to what its future course might be.

What we already know is that people infected with COVID-19 can die from a wide variety of immediate causes. At least fifteen (or maybe twenty) causes-of-death have been identified. Death can come from several different heart malfunctions, from strokes of a variety of types, from kidneys that fail, and also from "multisystem organ failure." That, as you can probably guess, covers a very wide territory. One of the commonest causes-of-death is lung failure. Often the disease looks like a pneumonia, but it acts differently from the usual pneumonia of the elderly. It was this difference in the way the pneumonia presented that led to the first cases in Wuhan, China, being identified. Until we understand how all of these different fatal outcomes are produced by a single virus, we are like the proverbial group of blind men feeling and attempting to describe an elephant.

Yes, and I can't think of any ethically acceptable alternative to just waiting until enough people are infected (and eventually die) to enable scientists to crack the mysteries surrounding the disease.

No one now knows what that time frame looks like. If someone can put all these disparate observations together into a coherent explanation it could be quite short. In the meantime, our puzzlement about the pathophysiology is affecting our ability to determine whether a drug is beneficial or hurtful. Clearly, if a drug becomes available that inactivates the virus or slows it down, that is going to be helpful. But most deaths are occurring for reasons other than an overwhelming growth of the virus. Patients are not dying from a very large number of virus particles overwhelming the body and causing multi-system organ failure; they are dying from causes that we understand, like strokes and heart attacks and liver failure. Why this particular virus manages to produce this wide variety of causes-of-death is what is making it so difficult to understand as a coherent disease process. This is one of the reasons it is so scary.

Yes, this really is a nightmare scenario, isn't it? We have a mortal threat that we don't understand and so don't know how to counteract. And, I gather that there's no way to speed up our learning process?

There are people who are trying. I have heard that somewhere in the US there is a multimillionaire who has funded a group to do just that. It is composed of a number of experts. But just how do such experts get chosen? If we don't know how the virus kills, do we put a virologist in the group, a pulmonologist, and maybe even a pathologist such as myself? Since it is not clear where the answer will come from or would look like, how do we select precisely the right experts?

So where does that leave us?

It leaves us physically distancing ourselves in social situations until we learn a whole lot more about the virus.

But what I'm hearing you say is that there is no ethical way to speed up that learning! Do we just have to wait until more people get ill and subsequently die?

I notice that both times you have asked this question you have underscored the word "ethical" I'm not sure why. At this point in time I cannot think of any *unethical* way in which we could speed up the learning process! After all, the virus is spreading through the population, and in so doing is providing us with ever more information about itself.

Well, that's good, I suppose. You researchers won't be tempted! I guess a simple-minded, high-

We are now so convinced that clotting is involved that all COVID-19 patients who are sick enough to be treated in an intensive care unit are given blood thinners. This is probably one of the reasons that the virus is killing fewer infected patients now than when we first spoke.

school-level proposal would be to select a prison population, perhaps, and infect half of them with the virus and not the other half, and see what happens?

It's the "see what happens" that's the tricky bit! We know already that what will happen is that two or three or four out of every thousand will die and, in all likelihood, they'll die from a wide variety of different causes, with pneumonia being the most common.

But presumably the people who have been deliberately infected would have a higher mortality rate than the people who were not infected?

Absolutely! But if those that were infected are going to die from several different causes where do we go next? Suppose recipient one died from heart failure, recipient two died from liver failure, recipient three died from a stroke, recipients four, five, and six died from what looked like a viral pneumonia (because at autopsy there was no evidence of bacteria in the non-functioning lungs), and recipient seven dies from bacterial pneumonia. That is exactly the information we already have! That is the information that we don't yet know how to integrate into a coherent picture.

So, where does that leave us? I guess with a need for patience, and hope?

Well, definitely a need for hope! The one thing we cannot do is to give up.

You anticipate that it will pass? Or do you think that COVID-19 is here to stay?

I'm guessing that it is going to end up like the flu, because it is now so widespread that at all seasons of the year there will be a flare-up somewhere in the world. Because it is so highly infectious, I don't think it will be possible to stamp it out in the same way we were able to stamp out smallpox. So, yes, I think it is with us to stay. But it will not be so scary once we have a vaccine and drugs or other therapeutic agents that lower its lethality to that of influenza.

Can you give me a descriptive term? Are you "confident," "hopeful," or maybe "desperate"? How should we feel about COVID-19 and the future—the future that is beyond our own, the future of our children and grandchildren?

In time it will probably be like the flu. It may spread more rapidly in colder weather, when people are more likely to be in closer contact. However, it will not be nearly as frightening as it is now, because then there will be a vaccine. Between those who are immune because they have been vaccinated and those who are immune because they have had the disease, the majority of the population will not be susceptible to infection—and the infection will spread much more slowly. Having a bout of COVID-19 will, by then, probably be so non-scary that a lot of us will not even bother to get vaccinated, just as many now skip getting vaccinated for the flu. For those who do come down with COVID-19, there will be drugs and/or other therapeutic agents that will decrease the intensity of the infection to that of a bad case of the flu.

Maybe on that hopeful note, (I don't know that I would say "optimistic note"), we can proceed into the future with COVID-19 since it looks very much as though we will not be proceeding *without* COVID-19.

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So, Brian, six weeks have passed and more than 130,000 people have died in the US. Last I heard, over three million people have been found with the COVID-19 virus in their noses. The test that found them sounds complicated and seems to take a very long time—days in fact. Why don't you speed up testing and why don't you test everybody? Why are you scientists limiting the tests so much?

The test to which you refer is very sophisticated. It belongs to a category that until very recently could be found only in University teaching-hospital labs and at research centers like the Centers for Disease Control (CDC). Tests of this sort have never before been produced and used on such a massive scale. These tests (RT-PCR) identify the presence of the virus in nose swabs by using enzymes (reverse transcriptase) that can multiply virus particles if they are present in the nose swabs, and do it without even identifying the virus particles first. This multiplication process takes time, and that is why the most sensitive RT-PCR tests take a minimum of several hours to complete. The multiplication process will raise the levels of the virus (if any are present to start with) to levels that can be confidently detected.

Okay, so the tests for the virus are complicated and you scientists are doing the best that you can. So what's with Remdesivir, is it a cure? And, how about Dexamethasone?

Remdesivir is not a cure, but it sure can help. It was developed to fight the Ebola virus and it is ingenious indeed. To a virus it looks like something that the virus needs to make more viruses. However, when the COVID-19 virus tries to use it in this way, it messes up the process by which new viruses are created. In general, it slows down the rate at which the virus multiplies and this, in turn, means that the antiviral defenses of the body have an easier time fighting off the attack.

As for Dexamethasone, it appears to be acting by quieting the body's defenses in situations where there is an overly exuberant response from the body. It is only effective later in the course of the disease when the virus is in retreat. If given too early, it seems to speed up the multiplication of the virus.

And when the defenses of the body are finally overwhelmed . . . What can you tell me now about how the virus kills?

Some weeks ago, when first you asked me that question, I guessed that clotting was probably involved—that clotting might account for the dramatic way this coronavirus pneumonia, over twenty minutes or so, could take a patient from breathing normally—to gasping for air, with chest muscles failing from exhaustion. We are now so convinced that clotting is involved that all COVID-19 patients who are sick enough to be treated in an intensive care unit are given blood thinners. This is probably one of the reasons that the virus is killing fewer infected patients now than when we first spoke. It also seems likely that clotting is a major way in which the virus can cause damage in widely separated body organs—the virus appears to be doing so by causing clotting in the small blood vessels in the heart, liver, kidneys etc., and also in the brain. It is an odd sort of clotting that we have not previously seen with other respiratory viruses, such as those that cause influenza and the common cold. This widespread clotting doesn't produce the kinds of symptoms that are usually associated with large vessel clots. This is likely an important clue as to why, and how, the virus kills. We still, though, have much to learn.

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