For my daughters: February 9, 2021

The Coronavirus Pandemic

A Virus Named E484K

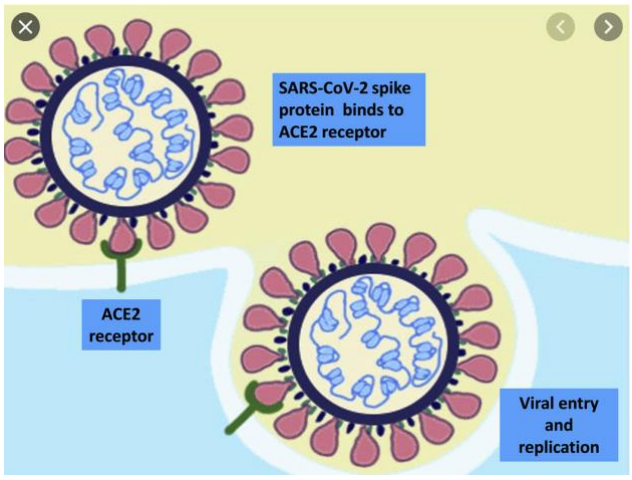
You girls will be happy to learn that your father got his initial COVID vaccination last week (Pfizer), with no ill effects other than a sore arm for a few days. My second shot is scheduled for three weeks from now, and I am delighted to be getting it. I hope very much that you three will be soon able to follow me to this safer place. However, I don't want for a minute to suggest that when our family has all gotten our shots, we will then be out of the woods. Far from it.

It is my belief that Americans are still in the early stages of what will prove to be a long battle. No doubt you've heard about COVID-19 variants and are wondering about the impact they will have. The short answer is "a big one." To help you see why I am going to step back and tell you a story – the story of a little virus that is having a big impact on our world. I will present its story as a play in four acts. To see where we are going in this pandemic, we must first see where we – and the virus -- have come from.

Act One: INFECTION

We first meet our protagonist, a busy little bat virus, in December 2019 in a large city in central China. Of course bats don't live on the streets of this city, Wuhan. The bat virus – a kind called a coronavirus -- has learned to live in other mammals, and one of these alternative animal hosts (a civet cat, perhaps?) is being sold in an open-air food market. Growing happily within this animal's cells, the virus has no impact on the humans handling the animal – it has no way of entering human cells, and so cannot infect a person.

How do coronaviruses get into bat or civet cells to reproduce? They hijack a chemical communication system animal cells use to talk to each other: One animal cell emits a hormone or other chemical signal into the animal's bloodstream, and that chemical keeps travelling through its body until the signal reaches a cell with a surface "receptor" – a protein that recognizes the chemical. When signal and receptor come into contact, the cell reacts by engulfing the signal chemical, a process called *endocytosis* ("to drink in"). That is how a coronavirus gains entry to an animal cell -- by triggering a chemical-signaling receptor:



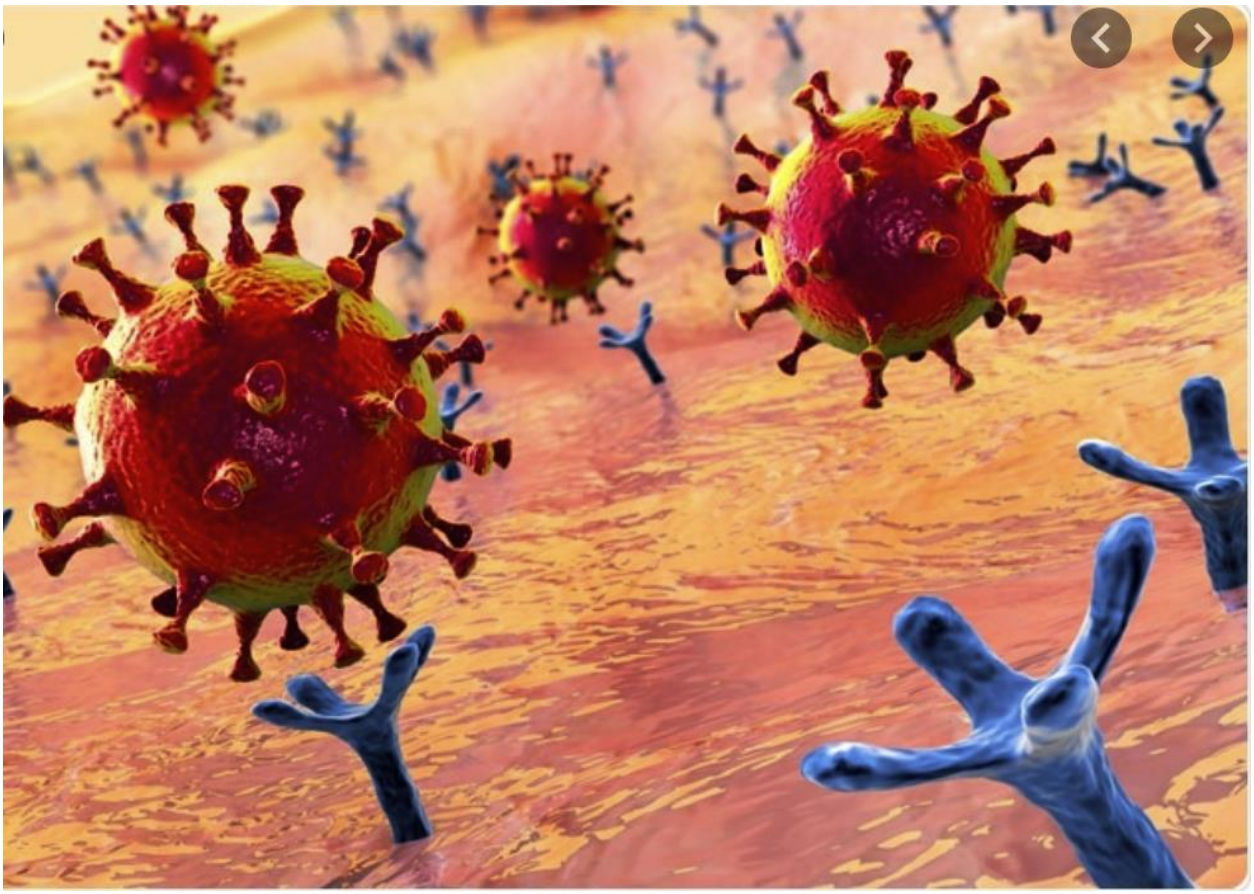
How does a coronavirus virus trigger the receptor on a bat or civet cell? The spikes that protrude out from its surface act like keys to fit into and unlock the animal cell's chemical receptor. Like sticking your finger into a cocked mouse trap, the spike protein sticks into a cleft in the receptor protein where the chemical signal would usually fit. The tickled receptor snaps shut, engulfing the virus particle. Now inside the bat or civet cell, the virus can disassemble and reproduce.

Then in late November of 2019 something happens in the Wuhan food market that will change human history. A coronavirus learned how to enter a human cell.

What happened was a mistake: A virus was made with a defect. One of the 30,000 letters of the RNA instructions that determine what the virus will be like was copied incorrectly, the wrong letter inserted into the message. Like copying "message" as "massage," this sort of mistake, called a *mutation*, can totally change the meaning. And this little change had a BIG consequence.

The mutation was in the gene called "s." This gene encodes the protein spike that triggers receptor-mediated endocytosis. The mutation caused the tip of the coronavirus spike to fit into a new receptor it had never been able to "see" before. Called ACE2 receptors, humans use these receptors to lower blood pressure. ACE2 receptors (blue below) are common in nasal passages and lungs -- the parts of a human that our virus (red below) would encounter if a person were to breath the virus in.

Armed with a spike now able to interact with a human receptor, for the first time, in Wuhan, China in December 2019, the virus could enter a human cell.



And it did. Soon, people in Wuhan started to get sick. Travelling around the world from this large city (many times the size of NYC), the virus was soon infecting people throughout Europe and the Americas. Within ten weeks, on March 11, the World Health Organization declared the coronavirus outbreak a worldwide pandemic.

Act Two: *D614G* - TRANSMISSION

The Wuhan coronavirus spread very well among humans because a lot of the people who contracted it didn't get sick – over 30% show no symptoms at all, and still broadcast the virus with each breath. Quarantining those with symptoms misses these infected and infectious individuals, who continue to spread the disease. About 2% of those they infect die.

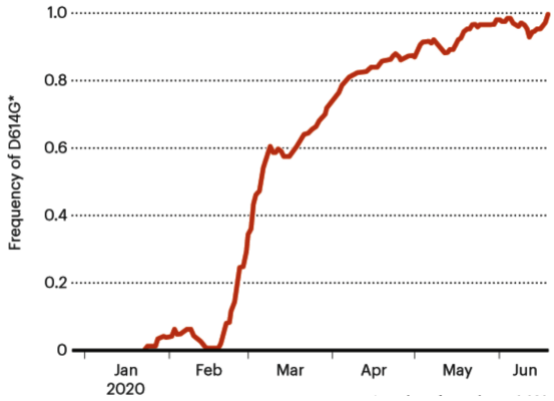
At first our virus protagonist wasn't very good at leaping from person to person. Its spike protein fits only loosely into a human ACE2 receptor -- imagine a toothbrush sitting in a glass. The fit was good enough to trigger endocytosis sometimes, but as a consequence of this very loose fit, the virus wasn't that easy to transmit from one infected person to another. A lot of people did become infected, all over the world. But while large swaths of the United States had cases, most occurred in highly crowded cities like New York.

In mid-November in Germany a mutation occurred in our virus that changed that. At position 614 of the spike protein (the protein is a chain of 1200 amino acids; this was the **614**th) there is usually the acidic (negatively charged) amino acid aspartate (symbolized **D**). In the new mid-November mutant the amino acid at position 614 became the non-charged amino acid glycine (symbolized **G**).

The new mutation, called "D614G", seems to affect how the protein twists its shape after interaction with ACE2. In essence, the fit between spike and receptor became better, and as a consequence each virus-receptor encounter had a greater chance of triggering endocytosis.

Bottom line? Our virus protagonist has become more transmissible!

Very quickly, viruses carrying the D614G mutation became the most frequently reported form, all over the world:

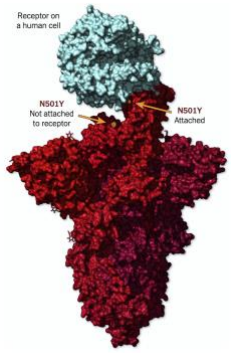


D614G didn't make you any sicker. It just increased transmission, making a bad problem worse.

Most of the vaccines being developed to combat COVID-19, including the Pfzer vaccine I took last week and the Moderna vaccine, were targeted at this D614G mutant form. All of the variant mutant forms that we will encounter later in this letter arose from this form and contain the D614G mutation.

Act Three: *N501Y* - ACCELERATION

Now things begin to get interesting. Our virus protagonist is changing. The tip of its spike protein consists of six amino acids that interact directly with the ACE2 receptor site. Well, sometime in August 2020 in Northern Italy one of the six, the tip amino acid at position 501, mutated from asparagine (symbolized N) to tyrosine (symbolized Y).



This new mutation spread very rapidly. Called N501Y because it was a change from N to Y at position 501, it was first reported in Kent, South East England on September 20, and was soon found throughout the UK. It is now commonly called "the UK variant." This same N501Y mutation arose quite independently in December in South Africa, spreading rapidly there as well.

With coronaviruses, binding better to ACE2 translates as transmitting better between people – so, as you might expect, the N501Y mutation increases infectivity by 30% - 50%.

With N501Y, our virus protagonist has reached adulthood, and is probably about as infective as its going to get. And it's really getting around: In the last few months N501Y has reached 70 countries and many places in the United States (610 cases in 33 states!) It is expected to be the dominant form of COVID-19 in the United States by summer.

Act Four: *E484K* - EVASION

The final act in our little drama takes place simultaneously in South Africa and in Brazil (many Americans don't know that Brazil has the world's most COVID-19 infections after the United States). Imagine for a moment you are a newly-minted COVID-19 virus particle in one of the counties of South Africa or Brazil where the pandemic has raged. There is a very good chance that the person who inhales you is going to have had the disease and be loaded with anti-COVID-19 antibodies. The only viruses with a decent shot at prospering would be ones ignored by these antibodies. As you can see, there would be strong natural selection favoring any COVID-19 mutant that was able to evade antibodies!

And that is just what has happened. In October in Brazil and even earlier in South Africa a mutation near the tip of the spike at position 484 changed the amino acid glutamic acid (E) to lysine (K). Note that glutamic acid is an acid and so carries a negative charge, while lysine is a base and carries a positive charge. Opposites attract. This is important, because the 484 position is part of where the antibody grasps the spike protein. The negatively-charged glutamic acid of the spike would foster close attraction to a positively-charged portion of the antibody protein. Changing negative to positive would change attraction to repulsion, preventing the antibody from attaching itself to the spike.

Does E484K escape antibody neutralization? In a word, yes. In South Africa, Dr Fauci says, there is "*a very high rate of reinfection to the point where previous infection does not seem to protect you*."

And the vaccines? Do they protect against E484K?

Nope.

The Novavax vaccine tested 96% effective against the original D614G strains, and 89% effective against the UK N501Y strains -- but only 49% effective against the South African E484K strains.

The same pattern is seen with the other two vaccines tested in South Africa against E484: The Johnson & Johnson vaccine tested 72% effective against D614G strains, but only 57% against E484K. In its recently-reported South Africa test, the Oxford/AstraZeneca vaccine provided no significant E484K protection either -- there were 19 cases of COVID-19 caused by E484K among people who received the Oxford vaccine and 20 cases among people who got a placebo. That's an effectiveness of merely 10%.

So our COVID-19 protagonist has learned to breach the human immune defenses, evading the diverse repertoire of antibodies generated in response to previous infection or vaccines.

Indeed, this seems to have happened at least twice independently in South Africa and Brazil. This same evolutionary process has been reproduced in the lab as well: researchers grew COVID-19 in low levels of serum collected from a recovered coronavirus patient, and within 90 days the virus had picked up three new mutations, one of them the very same E484K.

And our protagonist is still busy. In early February the E484K mutation was found in eleven samples collected in the UK. It is too soon to know if the vaccine-evading mutation evolved there in the UK, or was brought in from South Africa or Brazil. Only a handful of cases of E484K have been reported in the United States yet, but efforts to look for variants through genetic sequencing have lagged far behind in our country. The fact we haven't seen E484K yet may be largely for lack of looking.

What Comes Next

Obviously, it will be important to get on top of this quickly. We have vaccinated 10% of Americans, and are rushing to "give the shot" to more.

While we wait, are those 27 million Americans who have already had the disease out of the woods? No. "*The level of immunity that you get from natural infection is obviously not enough to protect against infection with the mutant*," Dr Fauci says.

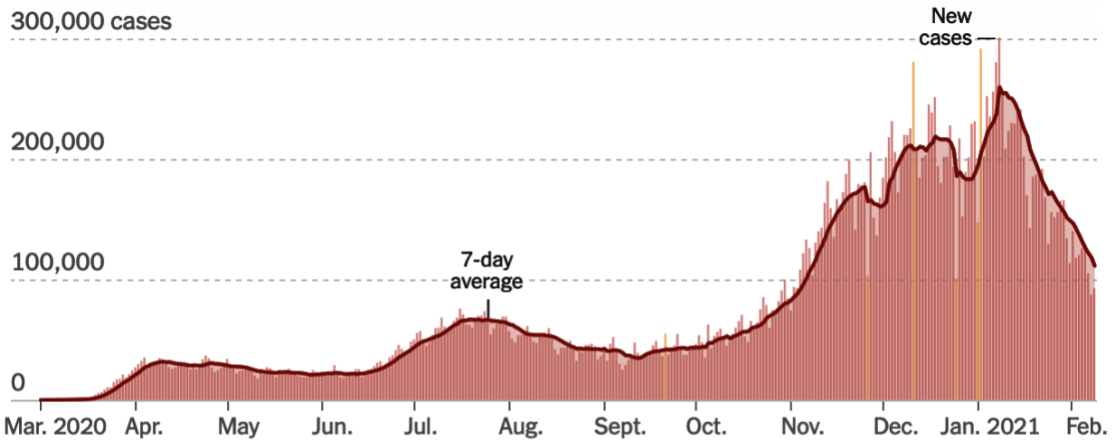
Vaccine developers are rushing to modify their vaccines to address the E484K variant. This should be very straightforward to do. We can only hope that the extra testing that the FDA will require for modification of approved vaccines can be done quickly. The much-touted goal of having vaccine in everyone who wants to be vaccinated by summer must be stretched to include the goal of everyone also receiving a E484K booster by fall.

There's one thing we can do right now that will make a huge difference: screen for variants among COVID-19 patients. Most countries have been doing this for months. It's not hard: you collect serum from recovering COVID-19 patients and sequence the coronavirus RNA. This week the CDC director announced a ten-fold increase in our sequencing efforts. We are going to need to be able to detect not only E484K, but also any new mutants that might arise. Our protagonist, when confronted with vaccines that target E484K, will almost surely respond with other mutations that evade antibody binding in other ways. Natural selection is a powerful thing, and not to be ignored.

We can outsmart new mutants – but only if we know they are there.

The Good News

After such a gloomy prognostication, I am glad to be able to end with good news. The pandemic has definitely crested in the United States. The daily load of new cases continues to fall steeply:

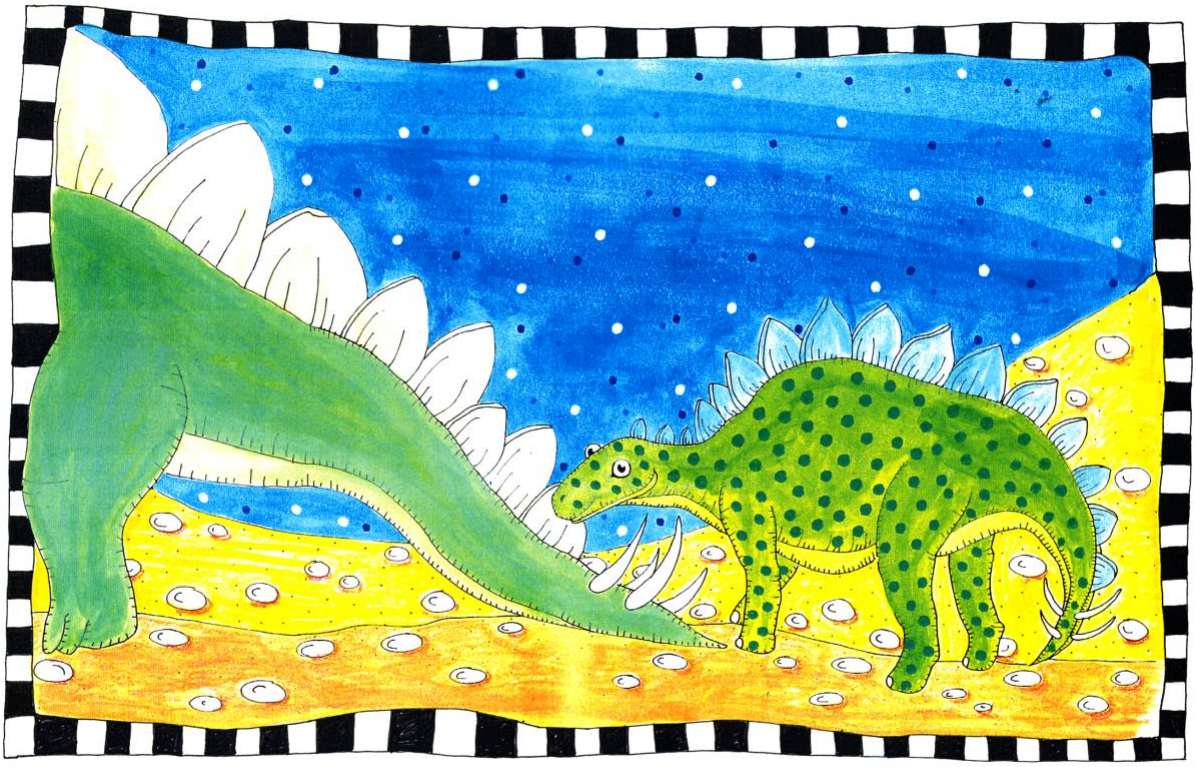


	TOTAL REPORTED	ON FEB. 8	14-DAY CHANGE
Cases	27.1 million+	92,603	-36% ↘
Deaths	464,921	1,547	-12% →

Federal health officials are optimistic variants won't change this, telling us that if we can get people vaccinated quickly enough, the virus will not be multiplying enough to generate many variants. "…*the combination of vaccination and public health measures will bring the level of virus down so low you won't give it a chance to mutate*," Dr Fauci told MSNBC four days ago.

I'm not quite that optimistic. I judge this to be a worldwide battle not to be won in the United States, or in any one country. The coronavirus's evolution of E484K in South Africa and independently in Brazil is a glimpse of the future. It looks to me like our virus is going to become endemic – something that confronts us every year with new variants, just as the flu does. We will just have to keep adjusting our coronavirus vaccine in response, with annual covid shots to match our annual flu shots. Not pretty, but a resounding victory nonetheless.

In the meantime, hunker down and await your vaccination shots. As for me, I have spent time this last week on my web site (www.biologywriter.com) reviewing columns I wrote when you girls were young, That's not to say you are old now, but rather that I used to read you stories at night. Remember the holiday column I wrote about when we set out to test the theory of Santa Clause? And I used to make up stories on the spot too -- of Steggie the dinosaur, featuring Splaticus, a warrior mouse who fights with farts! As a dad and grandpa I miss those golden times.



Stay safe. Your mother and I love you lots and lots.

Dad