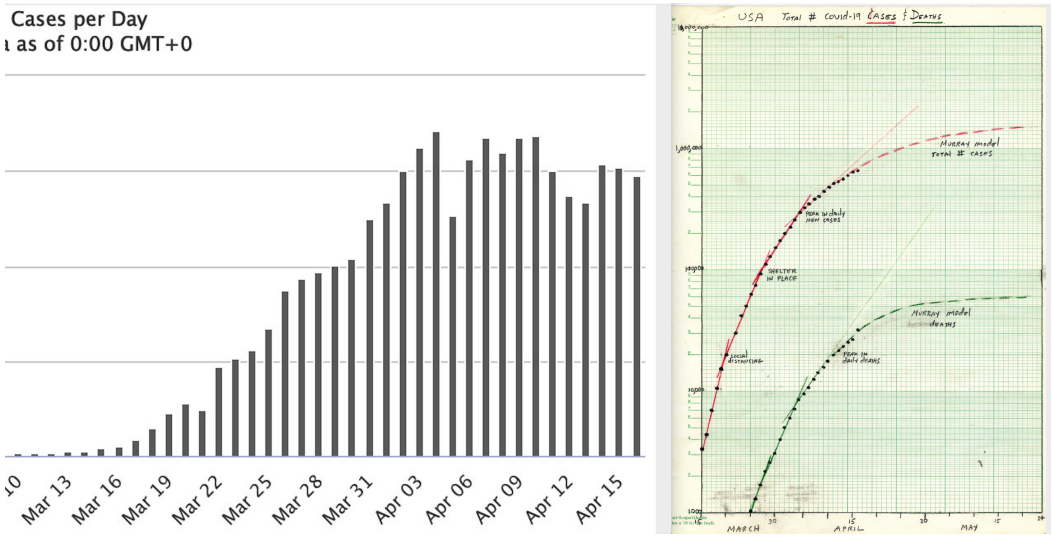
For my daughters: April 17, 2020

The Coronavirus Pandemic

New Guidelines

Our family's journey through the COVID-19 pandemic continues much as it has for the last several weeks, with social distancing and staying-at-home self-quarantining continuing to reduce the nation's COVID-19 r-naught number from 2.2 to below 1.0 (e.g. one infected person now tends to infect fewer than one other person). In NYC the r_0 is about 0.8, Gov. Como reports today. As a direct consequence of this reduced r_0, new cases in the United States have stopped rising. Today we are looking at some 680,000 infections and 35,000 dead, right where the Murray model projects the United States population would be with an r_0 value below 1.0:



This afternoon our federal government announced a new set of guidelines intended to help states open up their economies. While help is desperately needed, is this too soon? To help you digest what is being proposed, I thought it might be useful for the three of you to learn a bit more about the virus we are fighting to avoid. As a biology professor, I'll be your teacher for just a bit.

Why Can't You Just Kill the Damn Things?

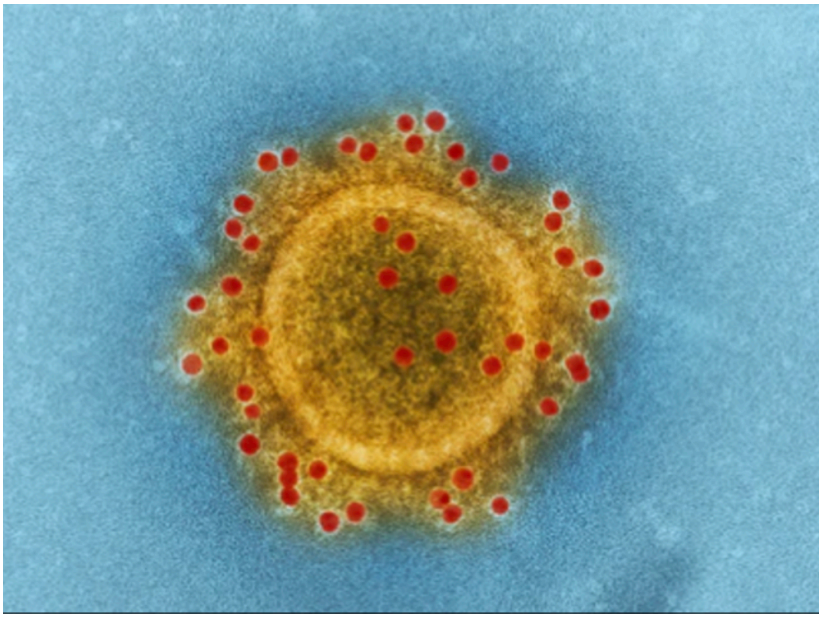
Scientists have always known viruses were a bit strange. You can remove bacteria from water by dripping the water through a fine filter, just like straining tea -- but not viruses, which pass right through a filter. When the first virus was purified by Stanley in 1933 at the Rockefeller Institute, he was amazed that the purified virus crystalized – it was a chemical, not an organism! A bit of RNA wrapped in protein, that was all . Stanley could separate the RNA and the protein of his virus, and each were harmless chemicals in a bottle; recombine them, and they were infectious viruses again. I tell you this story so that you see clearly that a virus is not a tiny organism – it is simply a detached fragment of some creature's DNA that happens to contains a gene for replicating and a gene encoding a protein. It uses its protein(s) to get inside a living cell, and uses its replication gene to direct the host's cell machinery to make copies of the virus chemical parts. Then the parts self-assemble into new viruses. The reason you cannot kill a virus is that it is not alive.

Viruses are found in every organism that has been investigated, and many have the ability to infect organisms other than those in which they arose. Influenza is a bird virus, Ebola is a virus of fruit bats, and the HIV that causes AIDS is a chimpanzee virus -- but all three of these viruses have passed from animal of origin to humans in recent years.

Respiratory Viruses Kill

Viruses from other animals, once they get into a human, can be very good at passing from one human to another. This is particularly true of so-called respiratory viruses, which pass from person to person via tiny airborne water droplets. When we breath the droplets in, the viruses infect the lungs. Because passage thru the air like this is very efficient, these viruses often have very large r_0 numbers: mumps 12, measles 10, chickenpox 10. Perhaps the greatest killer of humans has been the respiratory virus influenza. The 1918 pandemic strain had an r_0 number of about 2.8 and killed millions of people in just two years. Strains of flu continue to arise in Asia that infect lots of Americans today, usually with an r_0 number of about 1.3. You probably don't realize how many of us Americans die each year of these flu infections: some 20,000 or more!

Among the respiratory viruses is a distinctive group called the corona viruses, named for their crown (corona) of surface proteins which you can see in the photo below. The virus uses these surface proteins to attach to and penetrate their host cells. Some 20% - 30% of common colds are caused by corona viruses, but until recently corona viruses have not caused serious illnesses in people, and so nobody has paid much attention to them.



That all changed with the appearance in 2002 of a deadly corona virus in China. Called **S**evere **A**cute **R**espiratory **S**yndrome - **Co**rona **Vi**rus **D**isease, or SARS-COVID, the SARS virus infected 8,098 people in the 2003 outbreak, almost all in Asia, killing just under 10% of those it infected. That's a lot more deadly than today's strains of flu, which takes out about 0.1% of those infected. Chinese scientists were able to trace the origin of the SARS virus to cave-dwelling horseshoe bats in Yunnan province, passed to humans via civets, a kind of wild cat eaten as a delicacy in China. No known transmission of SARS has occurred since 2004.

Having made this abrupt appearance on the human stage, the corona viruses hasn't stayed away. Eight years ago in Saudi Arabia, another deadly respiratory corona virus appeared, called **M**iddle **E**ast **R**espiratory **S**yndrome-**Co**rona **Vi**rus **D**isease, or MERS-COVID. MERS is another bat corona virus, in this case apparently spread to humans by camels (God alone knows how the bat-to-camel transfer happened!). Over 2,000 cases of MERS were reported over two years before the outbreak subsided. Fully 36% of those diagnosed with the disease died of it!

It is yet a third appearance of a bat corona virus that we are dealing with today, a virus closely related to SARS that appeared on our radar screens for the first time in Wuhan, the 9th largest city in China (while you probably have never heard of it, its population of 11 million far exceeds New York City's population of 8 million). The first case of this new virus was reported to a field office of the World Health Organization (WHO) in China on December 31, 2019, adhering to the WHO's routine protocol for disease surveillance. German scientists, working at WHO's direction, quickly developed a test for the newly-discovered virus, again a standard WHO precaution. When in a few weeks reports emerged from China of large numbers of people sick from this virus, the WHO on January 23 declared a Public Health Emergency of International Concern, assigning the virus the formal name SARS-COVID2 (that is, **SARS Co**rona **Vi**rus **D**isease, version **2**) because it is so like the SARS virus - the name is usually shortened to COVID-19, with the 19 referring to the year when the disease first appeared, 2019. In February the WHO supplied countries all over the world with its COVID-19 test, and published the recipe on the internet so anyone could have access.

Scientists have concluded that 86% of all the people infected with COVID-19 in China before January 23 were not detected by the WHO and Chinese health people at the time, and that these non-symptomatic people went on to infect ¾ of all those who eventually came to be infected – in other words, the bulk of transmission of the virus in China was spread by people not sick enough to get the attention of doctors. This was a warning call for the need of near-universal testing, but it is a call that has not yet been heeded. `

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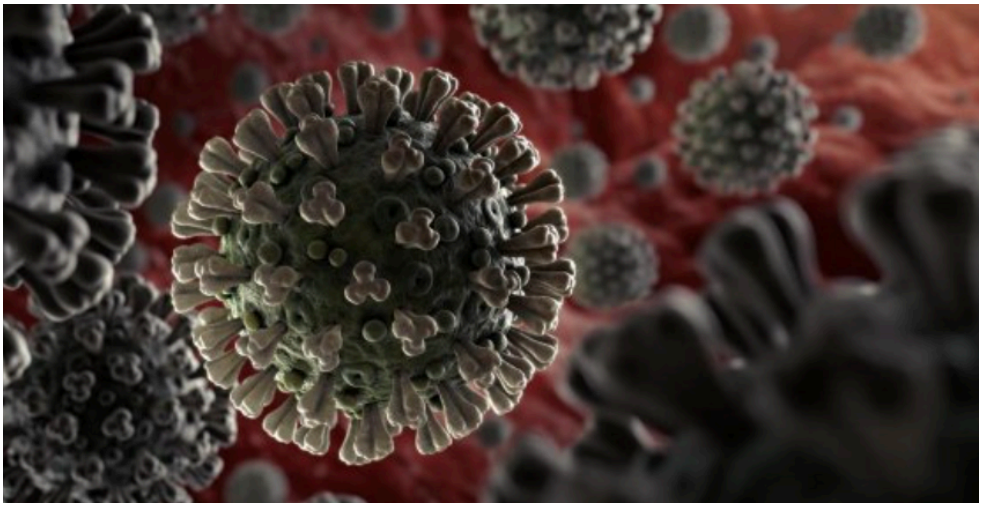
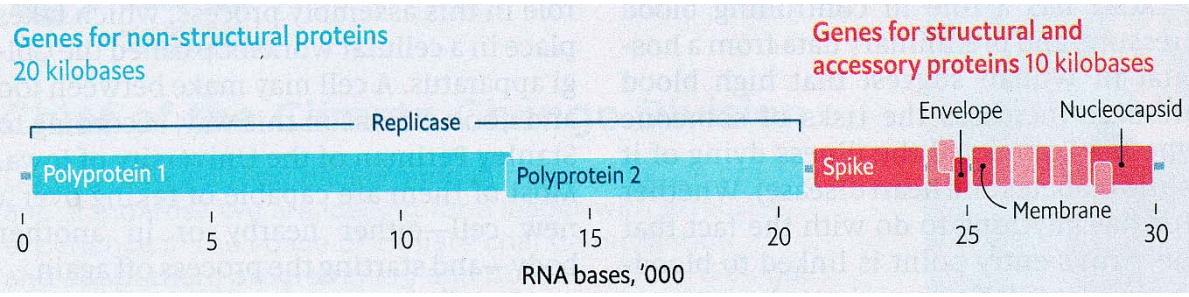
Structure of Covid-19

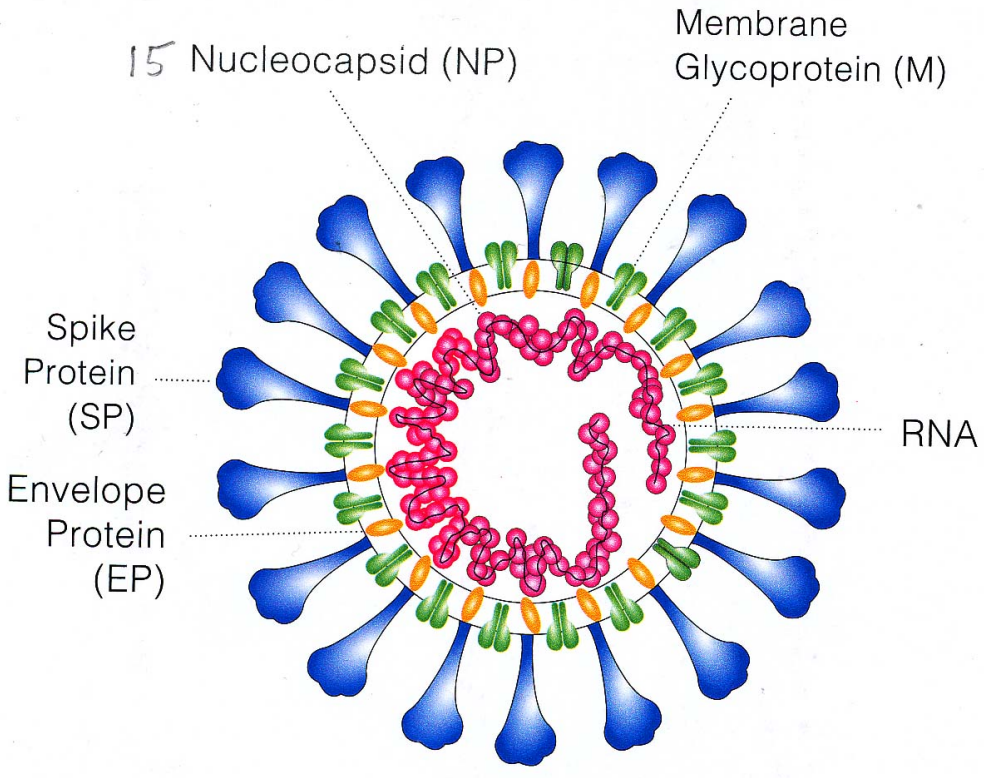
So what do we know about the COVID-19 virus? Quite a lot. It was first isolated and grown in a laboratory by Chinese and WHO scientists in mid-January, and soon after by Australian scientists, who isolated COVID-19 from a Wuhan patient sample provided by the WHO.



The genome of the cultured virus was first sequenced by Dr. Wang Jianwei of China's National Academy of Medical Science five weeks later, in late February. The sequence was immediately put on the web by the WHO so that scientists throughout the world could have access to it. The COVID-19 sequence proved to be 79% similar to SARS, confirming that the two viruses are closely related. More interesting, the sequence of the COVID-19 genome was 87% similar to that of coronavirus genomes of Chinese horseshoe bats! This solidly confirms that COIVID-19 is yet another one of those Chinese bat virus.



The COVID-19 genome is fairly large for a virus, with 30,000 RNA letters encoding 29 different proteins. Only four of them (spike, E,M and N) are structural proteins. They make up the protein coat of the virus. Another nine accessory proteins are involved in stabilizing the long RNA chain when it is packed tightly within its protein coat. Two huge genes (blue above) encode so-called "polyproteins" that after being made are cut into 16 pieces, each bit with a function in replicating the virus. So, a complicated little puppy:



How Do You Test For It?

The full genome sequence of COVID-19 was published on January 10 of this year by Chinese scientists working with WHO, just weeks after the disease was first identified by WHO surveillance teams in Wuhan, China. The WHO forwarded samples of the new virus to German scientists, who a week later released the first diagnostic test for COVID-19 infection. The test looks at two virus genes, asking the question "*Do the genes in the sample being tested resemble known COVID-19 genes*?" The two genes they selected for their test were E, which codes for the envelope that surrounds the viral shell, and RdRP, which codes for the RNA polymerase that replicates the virus RNA genome. These genes were picked because their sequences in COVID-19 are a bit different from the same genes in other corona viruses.

This test, adopted by the WHO and sent to over 40 laboratories around the world, takes advantage of a fancy laboratory procedure called reverse transcriptase polymerase chain reaction (RT-PCR) to amplify very small quantities of DNA. Here's how the test works:

1. You chemically extract the RNA from the patient's nasal swab.
2. You add this sample to a RT-PCR machine (photo above) , which converts the minute amount of RNA in the sample to the corresponding DNA sequence using an enzyme called reverse transcriptase (RT).
3. You add to the mix in the machine tiny molecular "probes," fragments of DNA with the COVID-19 sequence of the E or RdRP gene. These probes will only bind to snippets of DNA in your sample if your sample contains the E or RdRP genes.
4. If the probes find their target, the PCR machine proceeds to carry out a so-called "polymerase chain reaction (PCR)," making many copies of the bound DNA, each one of which then make many copies, each one of which make many more copies…in an endless chain reaction, until there are literally millions of copies. If the E or RdRP genes are not present in your sample, this molecular Xeroxing won't occur.
5. The RT-PCR machine adds to the mix some fluorescent dye that lights up when it binds to DNA. If one of the COVID-19 target genes is being PCR-amplified in the machine, the sample will begin to glow as more copies of DNA are produced. After a few dozen cycles of DNA PCR replication, the glow will become intense, indicating the patient is infected with COVID-19.

Typically the test is carried out on the E gene first. If positive, the test is repeated on the RdRP gene. Only if this is also positive is the result considered conclusive. This WHO test has been used successfully all over the world. There has been no suggestion of fake positives, as results have been confirmed with whole-genome sequencing and viral cultures in many countries. If the WHO test says you have it, you have it.

However, there have been suggestions that the WHO test generates false negatives, failing to properly identify cases of COVID-19 infection. Perhaps for this reason, the US Centers for Disease Control and Prevention (CDC) elected not to adopt the WHO's recommended test, choosing instead to develop its own. It also employs RT-PCR, but to increase sensitivity the CDC elected to ignore the E gene, instead targeting three sequences within the N gene; as with the WHO test, the second target was the RdRP gene. Like many complex procedures, the CDC test took months to prefect, and when first put to work in the field the CDC test did not work well – the damn thing was too sensitive! The same samples tested twice sometimes gave false positives. Back to the shop. The new version of the CDC test released in mid-March seems to work fine.

The key reason I have dragged you girls through this complicated explanation of COVID-19 testing is so that you can see clearly that RC-PCR tests are inevitably complex to administer. It's not like a peeing-on-a-stick pregnancy test, simple with an immediate result. With the technology used over the last two months, the sample being tested for COVID-19 must be shipped to a lab with both a RT-PCR machine for analysis and staff that can carry out the procedure. These tests typically take several days to perform and report back the test's result.

Why is this important? Because, as I keep telling you, the real problem we face with testing is that so far we have only had enough capacity to test those people with symptoms, while a potentially large fraction of the population (size unknown and unmeasured) is infected and infectious without exhibiting any symptoms. This was true in China, and there is no reason to believe we are any different.

Today's Announcement of New COVID-19 Guidelines

The announcement today of new guidelines for COVID-19 that will begin to open up the US economy is welcome news, because the proposals address the testing problem directly:

- We relax social constraints, but only in counties where the r_0 number is staying below 1.0. How is this measured? By applying the simple and yet powerful rule that the number of daily new cases must have fallen consistently for 14 days.
- We only continue to relax social constraints when sentinel surveillance does not reveal a significant number of non-symptomatic COVID-19 infections.

Beautiful! In my judgement, this ought to really work. Anywhere the infection is not a problem will be released from social restrictions, while releasing no city or county where the corona virus continues to be a problem. There are three stages to the suggested guidelines, things relaxing more and more as r_0 remains low. State governors will do what they want, of course – they don't need the President's permission - but this is a good plan.

The key element of this plan, as you will understand from your journey above through the confusing business of COVID-19 testing, is sentinel surveillance. In nursing homes and city centers, random individuals who are asymptomatic are tested for COVID-19. The contacts of anyone who tests positive are traced and also tested. If there is COVID-19 circulating within the community, this will detect it. Nor will we have to rely on those awful deep-up-the-nose swabs.

Washington University Medical School researchers have developed a saliva test that they say will be available in one to two weeks, greatly simplifying sample collection.

But the United States is a big country. It contains 3,143 counties. Can we do this many sentinel surveillance tests? Maybe. The newly-announced Abbott point-of-care *I.D.Now* portable testing machine runs a test in only 13 minutes, 5 if the result is positive -- but only one test at a time. Can we make 5-10 thousand Abbott testing machines, and the millions of chemical cartridges they will require? This is how we will know if our federal government is serious about the guidelines announced today. As I write this, there are only 15 of these Abbott toaster-sized machines allocated to each state, each machine with only 150 cartridges. We need to get busy.

Where Did COVID-19 Come From?

The last science questions that might be fun for you girls to explore concern the origin of COVID-19 and how it got to be such a problem in the United States. First, origins: The Chinese government initially pointed the finger at a fish market in Wuhan. When that proved unlikely, others suggested a variety of critters that might have initiated the transfer of the virus to humans, including, of all things, pangolins (see the cute fella in the photo below). When examined, pangolins did prove to possess a corona virus, but not COVID-19. Theirs was a pangolin-only form of corona virus, bat-related but found in no other critter. To date, no one has any idea how COVID-19 transferred from bat to human.

Of course, that doesn't stop wild speculation. In February the Chinese press promoted the wild idea that COVID-19 was a US bioweapon, introduced to Wuhan by US soldiers who had recently visited. A silly suggestion that no one took seriously, this pipe dream has recently resurfaced in mirror-image, with reports today that our federal government is looking into the possibility that COVID-19 was accidently released from the Wuhan Institute of Virology biolab. This is hard to give credence, as detailed sequencing of the COVID-19 virus has revealed no evidence of gene engineering or other tinkering with the virus genome. When asked today about this weird idea, Chief of Staff Milley admitted that "*the weight of evidence seems to indicate natural origin.*" But he then added "*—but we don't know for certain*." And in this way, by sly hint, this 'lab leak' theory will become a political football, advanced to deflect criticism of our country's handling of the pandemic. Don't buy into this conspiracy nonsense, girls. There is no

evidence whatsoever that COVID-19 has anything other than a natural origin, a bat virus transferred to humans by some infected animal, just like SARS and MERS.

So How Did COVID-19 Get Here?

The last question I want to draw your attention to today is the matter of how COVID-19 got to the United States. Didn't President Trump "close the door" on February 2, barring travel to and from China? The WHO opposed his doing so, claiming that it would do little to stop spread of the disease around the world while hindering the transfer of WHO medical staff to China where they were desperately needed. But the President did it anyway, claiming in subsequent months that "*We're the ones that kept China out of here*."

So who was right, our President or the WHO? Well, it is now clear that the COVID-19 virus was not "*kept out,"* with today's number of COVID-19 infections in the United States topping 680,000. How did the virus get from China to here? Well, for one thing the door wasn't exactly shut. Trump's China travel ban did not affect American citizens, nearly 40,000 of whom arrived in the United States on direct flights from China in the first two months after Trump imposed travel restrictions.

We can get a very good idea of where particular strains of COVID-19 originate by looking in detail at the nucleotide sequence of the virus in various infected individuals. The virus makes occasional mistakes as it copies itself (an average of one to two mutations a month), and these changes are seen in all descendants of each mutated virus particle. Did any COVID-19 escape China after Trump shut the door? Yes. The COVID-19 viruses isolated from patients in a retirement home in Washington are descendants of the COVID-19 of Wuhan. A teenager who caught the virus by visiting relatives in the retirement home had a COVID-19 sequence that was <u>exactly</u> the same as the sequence first published in February from Wuhan, China.

How about New York City, the focus of the United States outbreak? When COVID-19 was sequenced from NYC patients, they were found to have unique mutations not found in China – but were practically identical to ones found around Europe. So far, Mount Sanai Hospital researchers have found seven separate lineages, and all of them seems to have entered New York City from Europe -- five of them most likely from Italy. The problem with the President's closing the barn door, as the WHO had predicted, was that he left other barn doors wide open. COVID-19 has entered the United States primarily from Europe, not China.

Enough. Sorry for such a heavy handed missive this week, but probably best to get the science under our belt now, to help sort through the new guidelines for how cities and counties are to handle the COVID-pandemic.

Stay Safe.

Dad