For my daughters: August 1, 2020

The Coronavirus Pandemic

Looking For Safety

It has not been a happy week. Coronavirus deaths climbed past 150,000, a toll not dreamed of when we set out on this pandemic journey in March. "Dog day news," says Paddington:

My last letter was received with a gasp: "*Is Dad really going to jump on an airplane? Didn't Fauci say not to?*" Sorry to scare you. Of course I am not. I'll explain why in this letter, then take a look at what's being done to treat those who do get the virus.

The problem with my account last week was that in comparing the relative difficulties of safe travel by car, train or plane, I stopped my analysis too soon. The risk of my contracting COVID-19 is only part of the equation. What happens to me next is every bit as important. Every decision we make these days about our behavior relative to COVID-19 is basically solving a probability equation with two independent risk factors:

Risk of serious illness = risk of contracting virus X risk of becoming ill

We do this same analysis every day, in every move we make:

Air Travel. As I pointed out in my previous letter, the risks of air travel come mostly from unavoidable close contact with others when you board and leave the airplane. Overall, I assess the *risk of contracting virus* while travelling via commercial air as not nothing, but relatively low. The risk of my becoming ill is quite another point. This risk varies a lot from one person to the next, but not randomly. Two *risk-of-illness* factors stand out:

1. AGE. Old people get a lot sicker than young ones -- patients in their 80s are more than 20 times as likely to die of COVID-19 as those in their 50s.
2. UNDERLYING CONDITIONS. The CDC says that 76% of COVID-19 fatalities have at least one underlying condition. Massachusetts for example reports 4,071 deaths of patients with at least one underlying condition, and only 73 without. What underlying conditions? The big ones are uncontrolled diabetes (1.95 times more likely to die), liver disease (1.75), respiratory disease (1.63), moderate obesity (1.40) and chronic heart disease/high blood pressure (1.17).

So when I make the decision about air travel, I assess the risk of contracting the virus as low, but the risk of death if I do so as high (I am 78 years old and have 3 of the 5 underlying conditions listed above). Multiplying a modest number by a very large number, I get an unacceptably large risk of serious illness: too great to warrant taking the risk. And there is also the risk of my transmitting COVID-19 to granddaughter Jed. Not going to allow that to happen.

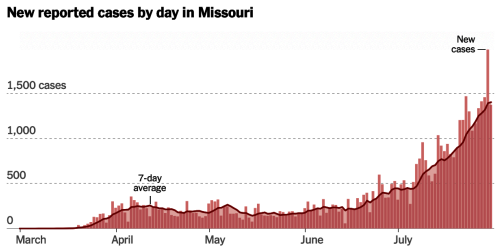
Sending the Kids to School. The very same analysis applies to a question much in the news these days: should parents send their kids back to school?

What is the *risk of contracting virus*? Depends on where the school is. The recently-softened CDC guidelines strongly urging a return to school give us a yardstick, actually similar to the WHO recommendation: don't open schools in "hot spots." The CDC defines *hot spots* as places where greater than 5% of the population of the school's community is testing positive for the virus. Well, 33 states are testing above 5%! Across the country, 77 counties are red-hot, testing more than 10% positive for COVID-19 and adding more than 100 new cases per 100,000 people each week. So to assess the risk of transmission in your school, first ask if the school is in a county testing greater than 5%.

But what if we can distance the kids in the classroom, monitor CO_2 levels to assure adequate ventilation, and insist that the children wear face masks? The risk of contracting the virus will still be high, in my estimation, if the kids are coming from a community where the virus is common. Teachers may space the desks apart, but kids will be kids. Children in school are going to come into contact with lots of other children – isn't that the whole point of GOING to school? And, just like crowding into an airplane, all the close contact will spread the virus.

The *risk of becoming ill*, however, is said to be far less for kids than for adults. Actually, there aren't a lot of studies. The largest clinical study conducted so far has been in England: U.K. researchers studied 582 children (from the ages of 3 days old to 18 years old) with confirmed COVID-19 cases, and found that most experienced a mild disease. Fewer than 1% of the infected children died, and most of these had underlying conditions like pulmonary disease. A few developed multisystem inflammatory syndrome. Overall, the risk of becoming seriously ill was far lower than is seen in adults.

So, to make the decision about sending the kids to school, a parent must weigh the great risk of the child contracting the virus with the low risk of it making the child sick. If not living in one of the 77 "red hot" counties, the risk to your child's heath may be judged acceptable. But in a "hot" county with a positive testing rate over 5%, every school child would become a potential carrier of the disease, and the risk to the parents' health would rise exponentially. The pandemic is intensifying in Missouri:



and in Saint Louis -- our home -- the number of people currently testing positive is 8.7% and rising. I am very glad you girls are past the age your mother and I would have to face this choice.

Fomites. I love that word. A fomite is an inanimate surface or object. It is the Latin plural of "*fomes*" which means tinder – just as tinder is a catalyst of fire, a fomite can kindle disease, if a virus or bacterium is present on its surface when you touch it. We touch lots of things each day that might have been handled or breathed on by others: mail, groceries, furniture in other places than your house, the seat of a taxi… How much risk of serious illness is involved in these hundreds of everyday contacts with fomites?

The idea that COVID-19 can be transmitted via fomites has its basis in studies done on SARS, a close relative of COVID-19. In these studies, very large numbers of virus particles were used (up to 10^7 per square inch) and survival of the virus on the fomites was observed for 2 to 6 days. However, the huge virus numbers employed in these studies are nothing like a real-life situation. Actual measurements of the number of flu virus particles in an aerosol droplet yield numbers from 10 to 100 virus particles, some fraction of which survive from 1 to 3 hours on a variety of hard surfaces. In repeated studies mimicking actual conditions in which a surface might be contaminated by a patient, no viable COVID-19 virus particles at all could be detected on surfaces.

I conclude from all this that while the *risk of becoming ill* if infected by handling fomites is the same as the risk when infected by any other means, the *risk of contracting virus* from fomites is very small. In non-hospital settings, the only danger would come if an infected person coughed or sneezed on a surface that you then touched within an hour. Hospital workers face an entirely different situation, of course, as they handle patients and objects repeatedly. On balance, it does no harm wiping down packages and other things coming into your house, but don't worry overmuch -- you don't need to leave the mail on the floor to "toast" for two days.

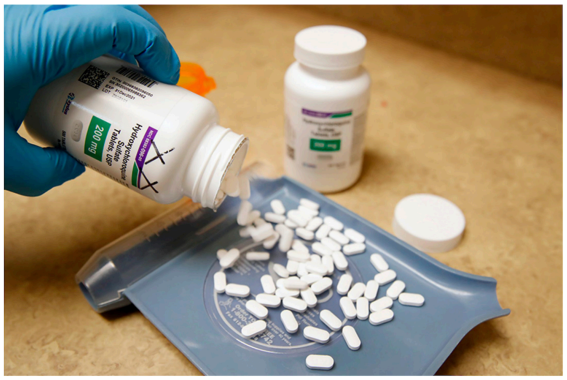
Searching For a Cure

It seems pretty clear to me that we are looking at six-nine months of tight living while we await a vaccine in the spring. In that interval a lot of people are going to become infected with COVID-19. What is being done to find a treatment for all the ill individuals? Quite a lot, actually.

Re-purposed Drugs

The initial focus has been on re-purposed drugs. Because these drugs have already passed FDA safety screening, a drug previously approved for another clinical use could be re-purposed to treat COVID-19 patients right now. But are any existing drugs useful in treating COVID-19 infection? Two have been seriously promoted as miracle cures:

***Hydroxychloroquine*.** Hydroxychloroquine is an antimalarial drug. Since March, President Trump has been promoting it as a treatment for COVID-19. No one knows quite where he got that idea, although it seems to have originated from anecdotal reports on the internet. However, as I wrote you on April 6, there is no evidence to support this claim. Bending to political pressure, the FDA gave emergency authorization in March for hydroxychloroquine as a treatment for COVID-19, an approval which it withdrew last month after evidence accumulated that the drug did no good and caused potential cardiac problems. The FDA withdrawing approval did not stop the federal government from stockpiling 60 million doses in the Strategic National Stockpile, against the day the FDA re-approves the drug.



The White House, citing a recent Henry Ford study, this week urged the FDA to issue a second emergency order "within days, not weeks or months." This Ford study, which involved over 2,400 patients hospitalized for COVID-19 between March and May, found death rates were 50% lower for patients treated with hydroxychloroquine soon after they were hospitalized. However, the study is sharply criticized by health scientists, who point out it was an observational study ("*Look what happened*"), considered much less rigorous than a randomized clinical trial in which patients are randomly assigned to receive a treatment or not. And its results are directly contradicted by three major randomized trails that have found that hydroxychloroquine is not effective in treating or preventing COVID-19.

Remdesivir. Remdesivir is an anti-viral drug originally developed to combat hepatitis C and later the Ebola virus. Remdesivir is thought to interfere with the mechanisms these viruses use to make copies of themselves. Because these same mechanism are used by coronaviruses, remdesivir was tested with dramatic impact late last year in human lung cell cultures against an array of coronaviruses, including both SARS and MERS. There was as yet no COVID-19, and there were no longer any SARS or MERS patients, so the drug sat on the shelf. When COVID-19 appeared in China, the manufacturer sent remdesivir there for emergency compassionate use.

The Chinese reported in Lancet only slightly quicker recoveries and no decreases in the COVID-19 death rate. Subsequent randomized clinical trials in this country published by the New England Journal of Medicine showed shortened average recovery time (from 15 to 11 days) but like the Chinese they found no reduction in death rate. Recent observational studies by the drug manufacturer lead the manufacturer to suggest there may still be "a relative reduction in risk."

Where does that lead us? Another drug with no solid evidence that it works to cure COVID-19. The federal government has acquired 500,000 doses.

Plasma

While we await an effective vaccine that will render us safe from infection by COVID-19, it is useful to keep in mind how this vaccine is going to protect us. We reviewed this in my last letter: a vaccine will present a COVID-19 antigen to your immune system. Your immune system responds by making neutralizing antibodies, activating T cells, and placing memory cells in reserve. While we await a vaccine to do this for us, there is one group of folks who have already had this experience: those who have recovered from COVID-19! Over 2 million Americans have. Each recovered individual has circulating in his or her bloodstreams a profusion of antibodies directed against COVID-19. If he or she donate blood, the donated plasma (that is, the blood without cells) will contain a rich supply of anti-COVID-19 antibodies. No T cells or memory cells, of course, but still a potentially potent weapon against a COVID-19 infection.

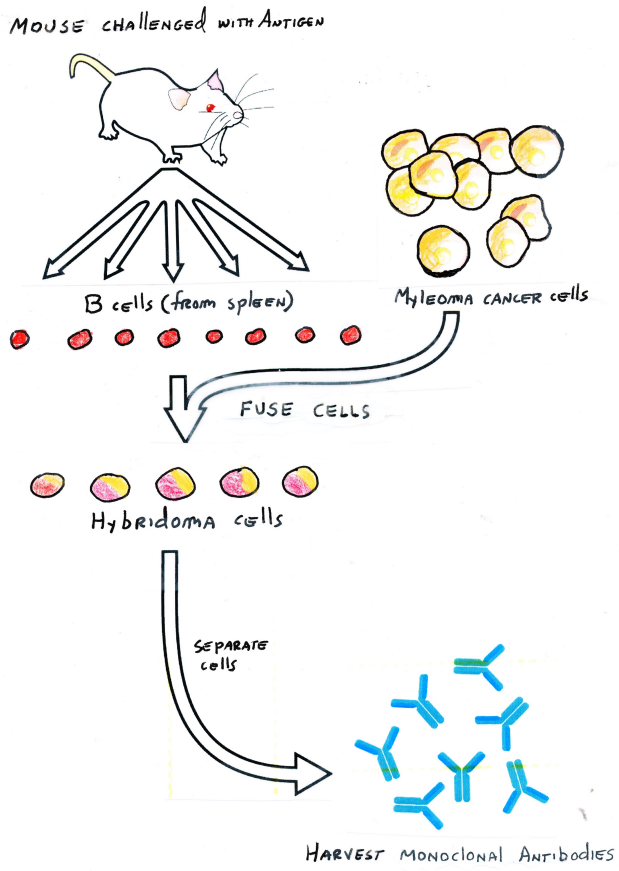
Does plasma from recovered COVID-19 patients work as a treatment for seriously ill COVID-19 patients? It does in some small controlled studies, although not all. There are no large studies reported yet, although the Mayo Clinic, citing "compassionate use," has overseen the giving of convalescent plasma to over 48,000 patients in hospitals around the country. How well is the plasma working? Reports I have been able to find are vague: the Mayo Clinic says convalescent plasma "appears to improve the survival of hospitalized patients." A controlled clinical study by several prominent medical schools (Pitt, Michigan, Stanford) has just received Federal funds to track 600 subjects. This study, focused on assessing the effectiveness of outpatient treatment with COVID-19 convalescent plasma, should settle the issue of plasma effectiveness once and for all.

Monoclonal Antibodies

Now comes the good news, a treatment that shows every sign of working very well. Imagine if you could teach a human cell culture to manufacture anti-COVID-19 antibodies, pounds and pounds of the stuff. It would be just like having all the plasma you could ever want! Anyone seriously ill could be injected with an antibody solution rather than placed on a ventilator, and have every prospect of a rapid recovery. That promise is what the coming monoclonal antibody drugs offer.

Like many major advances in medicine, the key discovery was made some time ago by researchers working on quite a different problem. In the 1970s they were studying a form of B cell cancer called multiple myeloma. Each myeloma cancer had its beginning as a DNA mutation in a single B cell. The researchers noted that, in each myeloma, all of the B cells produced the same type of antibody, as they all derived from the same original mutated cell. Now if only a B cell responsive to a particular antigen like COVID-19's spike protein could be made to grow like one of these cancer B cells…

In 1975 researchers found a way. They fused a B cell from the spleen of a mouse with a mouse myeloma (cancer) cell. The resulting clonal (e.g. of direct descent) line of cells (called a "hybridoma") produced one kind of antibody, specifically targeted at the antigen recognized by that B cell! The discovery of these *monoclonal antibodies* resulted in a Nobel Prize in 1984.



It was only a short step to learn how to use human B cells instead of mouse cells. These days every pharmaceutical company has produced a variety of monoclonal antibody drugs to fight cancer and other diseases, typically with tightly-held procedures. Two of these companies have directed their attention of combating COVID-19 with monoclonals.

Lilly/AbCellera. A small privately-held Canadian biotech company, AbCellera, set out in 2018 to create rapid-development protocols for monoclonal antibodies directed at emerging pandemic diseases. They first ran a trial with monoclonals aimed at pandemic influenza. Obtaining encouraging results, AbCellera was set to start a second trial directed this time at SARS when the COVID-19 pandemic began. On February 25 the company received a blood sample from one of the first U.S. patients who recovered from COVID-19. Separating the cells in the blood sample so that every cell was in a separate chamber, the researchers tested the chambers for ability to produce antibody that would bind to COVID-19's spike protein. In this way they were able within three days to identify over 2000 B cell lines producing antibodies directed at COVID-19. The best of these lines were then passed on to partner Eli Lilly, a much larger American publicly-traded drug company with considerable experience running clinical trials. It took Lilly only three months to develop and compare the monoclonal antibodies from the lines – this is blazing fast. On June 1 Lilly announced it has begun a double-blind placebo-controlled phase 1 clinical trial of the best of the monoclonal antibodies, which they have named LY-CoV$_{555}$. Directed against the spike protein of COVID-19, LY-CoV$_{555}$ will (hopefully) block viral attachment and entry into human cells, thus neutralizing the virus. Should work. We will see.

Regeneron. A parallel effort, promoted strongly by our government, is being marshalled by another publicly-traded American biotech company, Regeneron. This company has produced two anti-COVID-19 monoclonal antibodies that bind to different parts of the virus spike protein, and mixed them together to form a drug the company calls REGN-COV2. Using two different monoclonals is a good idea. It prevents the escape from treatment of any future COVID-19 with a spike-gene mutation that makes the virus able to evade one antibody. Such mutations are rare but not unheard of. Two such mutations simultaneously would be like lightning striking twice. Not going to happen.

The REGIN-COV2 monoclonal antibody mixture began a phase 1 clinical trial involving 30 COVID-19 patients on June 1, the same date on which Lilly's phase 1 trial began. Regeneron's speedy phase 1 trial showed the treatment to be safe. Regeneron's phase 2 trials will involve 1,850 hospitalized patients and 1,050 non-hospitalized patients at 150 sites in the United States, Brazil, Mexico and Chile. Phase 3 trials, to be conducted simultaneously, will involve some 2,000 patients at around 100 hospitals around the this country. Both trials begin as I write this. I am not a pharma guy, but I have never heard of running phase 2 & phase 3 trials simultaneously.

Not ones to be bashful, the federal government's Operation Warp Speed has awarded Regeneron a $450 million contract to manufacture and supply its monoclonal antibody treatment. The Department of Defense says it wants to be able to make REGN-COV2 immediately available if its clinical trials are successful and if it receives emergency use authorization from the FDA. Wow. A lot of very big "ifs."

That's enough for this week. Stay safe. Mom and I are planning a few car trips in coming weeks, so we shall soon be able to rub noses, if only one at a time.

Dad