VOLUME 1

A GENETICALLY GIFTED CORONAVIRUS HAS EMERGED WITH PERFECTED PANDEMIC POTENTIAL

Weaponized Virus Meets Domesticated Humans

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INTRODUCTION

The Covid-19 pandemic is the story of a novel animal coronavirus, ***CoV-2***, so perfectly mutated that it infected humans around the world within a few months and will likely never be eradicated.

This is not the first time it has tried. The first two corona outbreak attempts failed.

Third-time-lucky clever changes to CoV-2's genetic code confer two critical upgrades. How both of these adaptive versus gain of function changes came about in one virus before it ever met a human remains unsolved. Although there is a short list of intermediate host suspects that include pangolins and snakes, it is more likely that humanized ACE2-expressing mice in secret laboratory served as the breeding ground.

That such an outbreak has occurred three times in just the last 20 years, each time producing a virus better suited to infect humans, should raise a few legitimate questions before the next mysterious outbreak occurs, as promised by the World Health Organization.

WHAT IS A VIRUS?

Viruses are critical moving parts in the complex puzzle of Life. They have been integral to evolution.

Eons ago, small pieces of RNA code moving between bacteria developed ways to "survive" and are now called *viruses*.

Viruses are stripped-down, bare-bones pieces of genetic code, suitably packaged for transfer between living host cells. They depend on a cycle of infection, replication, and subsequent passage to the next host. It is a simple strategy that infects all known life forms, influencing evolution and species survival in ways that we have yet to appreciate.

We have our own very similar gene-code messages communicating internally between our cells. Called ***micro-RNA***, these snippets of code produced in one cell enter other cells and influence their function. They have similar gene-activating messenger capabilities as hormones, influencing gene transcription into protein formation. Most of us had never heard of micro-RNA until the new RNA vaccines came to the rescue las year.

We portray viruses as if they have taken on a "life of their own", seemingly more intent on their own survival than ours. One could compare them to pieces of computer software code that seemingly go rogue and infect themselves into other susceptible computers connected by the internet. It's no surprise that we call those infectious self-replicating pieces of code '***viruses***'.

A virus is just a stray piece of fragile genetic code packaged in a protective protein envelope which must get into a host cell if it is to replicate itself. Most viruses simply disintegrate once they leave their host cell nursery. They cannot be said to die, as they are not alive.

In a stable long-term relationship, the life cycles of a virus and its host enable both to persist.

There is no benefit to a virus to kill its host, especially if death occurs rapidly, before the virus can replicate and spread. A rapidly lethal virus runs the risk of killing off it hosts, ruining any hope of a long-term relationship. Unstable relationships happen when a virus emerges in a new biological. A newly emerged virus that does not kill off its new host and can spread between them has a good chance of forming a stable, long-term relationship. In a successful relationship, the virus becomes less lethal as the surviving host species becomes less susceptible.

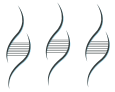
Cells need to make an effort to defend themselves from being overwhelmed by an infecting virus if they are to survive. All living cells, even bacteria, are equipped with innate defense strategies against viral infections. Life is impossible without an adequate viral defense strategy that enables viral detection and the production of substances that destroy or impede the virus. This defense must prevent unlimited viral replication which would exhaust the cell and kill it.

The viral strategy entails entering the host cell where it safely unwraps its delicate genetic code and replicates itself, while also using the cell's own protein-making machinery to make the structural proteins to re-wrap copies of itself. Some viruses are able to temporarily disable the host cell defenses long enough to replicate and escape in great numbers.

There are millions of different viruses. Some use ***RNA*** as their genetic code, while others use ***DNA***. Since genetic codes are made up of two "opposite" strands that match each other, they can use either of the "mirror images" of the code: the (-) or (+) side. It doesn't seem to matter which coding system a virus uses. What is far more important are the strategies each virus uses to perpetuate itself - regardless whether it uses DNA or RNA code.

Two key principles to understanding viruses involve figuring out their host cell-entry and replication strategies.

CoV-2 has two main gain of function genetic alterations that greatly increase its ability to spread throughout the human race.



CELL ENTRY

A virus is defined by the company it keeps: where it hangs its hat at the end of a dangerous journey between host cells and how it replicates itself in preparation for another escapade.

Living cells are contained by strong and flexible fatty membranes that prevent the free flow of water and dissolved substances. While oxygen dives through cell membranes like a ghost through a brick wall, most nutrients such as glucose and electrolytes must use entry portals known as ***channels***. These protein structures can be opened and closed on command. Some of these channels act as pumps, literally forcing ions across the membrane, against their will (concentration gradient).

Another class of cell membrane proteins act as receptors, binding outside molecules which alter the receptor as a way to deliver a message to the cell.

Another class of membrane protein cuts up protein messages outside the cell to change the message the altered protein delivers. We shall learn a lot about this type of membrane protein in the section dealing with how CoV-2 enters human cells.

Once a stem cell is chosen to become a certain type of cell, it sets about positioning itself and making the proteins that it needs to perform the functions of its chosen "career". Precise communication causes the cell to open, photocopy and export the pages of its DNA library in the form of identical RNA copies to make the proteins that it needs to be the cell that it is destined to be.

Some of these proteins are posted on the cell membrane to enable communication and interaction with the rest of the body. Cell membranes are literally studded with an array of proteins, like billboards along a busy highway, or signs and parking spaces along a strip mall. Each cell expresses the membrane proteins that are involved in the work that its cell is engaged in.

Cells do not make membrane proteins to intentionally enable viral entry. Viruses may have driven evolution and have other miraculous long-term effects, but being infected by a virus has no immediate benefit to a cell. Viruses must use the host cell's own infrastructure to its own ends, including an entry mechanism.

Viruses have many different host membrane proteins to choose from to get into the cell. Each virus has its own specific entry trick. Although a particular membrane protein can be found in many or all different species, they are usually different enough to prevent viruses that are adapted to one species from using them to gain entry in a different species. This is how viruses are prevented from crossing into another host species, except closely related species such as between humans and primates.

Each time a virus transfers from one species to another it is ground zero for emergence into a new host species.

Zoonotic transfers are happening increasingly to humans because we are arrogant enough to study viruses by collecting them from diverse animals in remote locations. Someone is ordering and paying scientists go into caves, catch bats and swab their mouths and anuses to collect viral samples. There are government-funded projects doing this around the world, even now, after Covid-19.

Successful zoonotic transfer of a virus into a new species results in the emergence of the virus in its new host population. Most of the time, the introduced virus is not well adapted to the new hosts and for many reasons, it fails to form a stable relationship. Sometimes, a newly infected population that has never been exposed to the virus, or has been isolated from it for a long time, will not fare as well as the rest of its species that has developed a stable relationship with the virus.

Successful emergence comes down to whether a virus can gain entry into cells of its new host to survive, replicate itself and then spread to another host of the same species. In January 2020, it dawned on the world that the newly emerged bat virus, Cov-2, was frighteningly capable of human-to-human transmission.

WHY IS COV-2 SO GOOD AT SPREADING?

The most common way that infected material is shared between animals is through shedding of material from their bodies: respiratory fluids, fecal matter, urine, semen, etc. Any time part of one animal gets into another, it is likely contaminated with viruses or other organisms – enabling spread.

The most common and easiest way for a virus to spread between modern humans is through breathing. We have improved sanitation to virtually eliminate spread of fecal matter between humans in comparison to just a few hundred years ago when gastrointestinal diseases were responsible for most childhood diseases and deaths.

Once we understood how those diseases were spread, humans designed and built homes and cities to keep drinking water and wastewater separate. Subsequent reductions in housing density with improved ventilation went a long way to reducing respiratory-mediated illnesses.

As did societies in the past, we have learned to accept our current level of respiratory disease burden and we rely on 'Medicine' to keep treating those infections. Tuberculosis remains endemic in many regions, while influenza and pneumonia (viral and bacterial lung infections) continue to be common end-of-life, and therefore life-ending infections.

We humans have taken control of our living conditions to such a large extent that disruptive forces of Nature such as hurricanes are seen as an assault on our way of life. We have created home and work environments that are increasingly safe and comfortable. We strive to provide clean water and food for everyone, at all times. Our shelter are climate controlled and we travel great distances while seated. We do the same for our domesticated animals, those that we keep as pets or raise for food.

Today, domesticated humans and animals outnumber ***wild humans and animals***. We, and our food animals, often live in very close quarters, albeit clean quarters. This makes human-to-human spread of infection by breathing – respiratory route – the most likely viral strategy to succeed. Sharing our breath with complete strangers from all parts of the world had become quite normal and acceptable. Before 2020, one could fly into London overnight from anywhere in the world and be watching a live music concert in Wembley Stadium the very next night, shouting and cheering and spewing exotic viruses over everyone.

Every year we are told how a new strain of influenza virus is spreading around the world in a predictable way during the winter months. Society accepts 0.1% mortality from influenza in the vulnerable members of the population. It remains mostly and end-of-life occurrence – affecting those already near the end of their lives - just as we are seeing with Covid.

A new influenza virus strain that either spreads better or is more harmful periodically upsets this stable relationship.

It was not hard to predict that a new (novel) respiratory virus could upset this balance. Bird flu viruses have been knocking at our cell membrane protein doors for decades. A few of them got in, but while they could wipe out whole flocks of domesticated chickens and ducks, they could never sustain a human relationship by spreading between humans. Some poultry workers got sick, but it ended there.

Maybe we got complacent or maybe we figured that the limitations of viral adaptation would continue to protect us, all the while we built societies that increasingly favored a respiratory pandemic. Bill Gates and the WHO have been warning of this for years.

A virus that is suited to one mammal species may not do well in another type of mammal. To make the leap, called a ***zoonotic transfer***, one of two events needs to occur.

A mutated variant of the virus in the primary host could get transferred to a different species that it just happened to be perfectly suited to. Those are long odds, unless the primary and secondary hosts spent a lot of time together such as a farmer and his flocks.

Alternatively, the virus could survive in an intermediary host, enabling it to develop a relationship long enough to allow yet another random mutation to make it successful in yet another host, after it is passed on. Again, those are long odds that don't happen very frequently when compared with the vast array of viruses and their potential hosts on the planet.

CoV-2 is a member of the coronavirus family that is characterized by having a very large genome that codes for the infamous spike proteins that stud its protective envelope and are used to gain entry into its host cell.

Humans have stable relationships with a few other coronaviruses that cause a "cold": a runny nose, fever, chills and a cough. If we don't get a secondary bacterial infection in our lungs, we get over it in a few days. We may not even make antibodies to this virus for more than a few years. It may be such a low threat that it's not worth the effort, or an occasional mild cold may be good for us, exercising our immune responses and keeping them battle ready. Not all infections are harmful.

In 2001 a new coronavirus emerged in humans in China called ***SARS-CoV***. I shall call it ***CoV-1***. This virus had close relatives that were found in bats and other mammals in China. The bat shouldered the blame for being the primary host, while the exact intermediate host remained obscure. The list of suspects remains: civets, pangolins and pigs. It doesn't really matter now.

What was so different about this novel coronavirus was its entry strategy. It had never been seen before in humans. This virus uses a membrane protein called ***ACE2*** to gain entry.

ACE2 was first discovered and published in a scientific journal just a few years before CoV-1 emerged from hiding in Chinese Horseshoe bats. At that time, scientists were still figuring out why ACE2 was there and we certainly did not know what it did. Just as researchers in the field were trying to figure it out, the CoV-1 jumped to humans and used our ACE2 similarity to bat ACE2 to cause a brief and brutal outbreak.

ACE2 is a membrane protein expressed (made) by cells in our respiratory tracts – our airways – from our noses and tongues right down to the cells lining our alveoli (air sacs). All humans express ACE2 throughout their lives. The virus just has to get into our nose to enter a host cell and reproduce. Newly minted viruses are then breathed in or out, spreading deeper into our lungs or outwards to other humans.

The spike protein entry mechanism is quite intricate and beautifully adapted to get past our defenses.

The spike protein ACE2-entry key is a short sequence of about a dozen amino acids that fits tightly onto the ACE2 protein, as if it were a magnetized. It has a perfect shape and electric charge distribution that matches a binding site on human ACE2. Called the ***Receptor Binding Domain (RBD)***, the actual protein locking sequence (domain) is carefully protected by being folded into the spike protein envelope.

The delicate RBD is exposed when one of our defensive proteins that literally cuts invading proteins to render them ineffective, snips open the spike protein of the invading virus.

One of our first-line defensive protein is called ***TMPRSS2***. TMPRSS2 hangs around our ACE2 expressing cells, taking care of business. When a coronavirus shows up, TMPRSS2 slashes the spike protein. But instead of harming CoV-2, it arms it!

The exposed ACE2 key sequence binds hard to ACE2, creating a tight ACE2/spike protein complex. While the open arms of the spike protein bind to the cell membrane to form a protective shield around the ACE2/RBD complex.

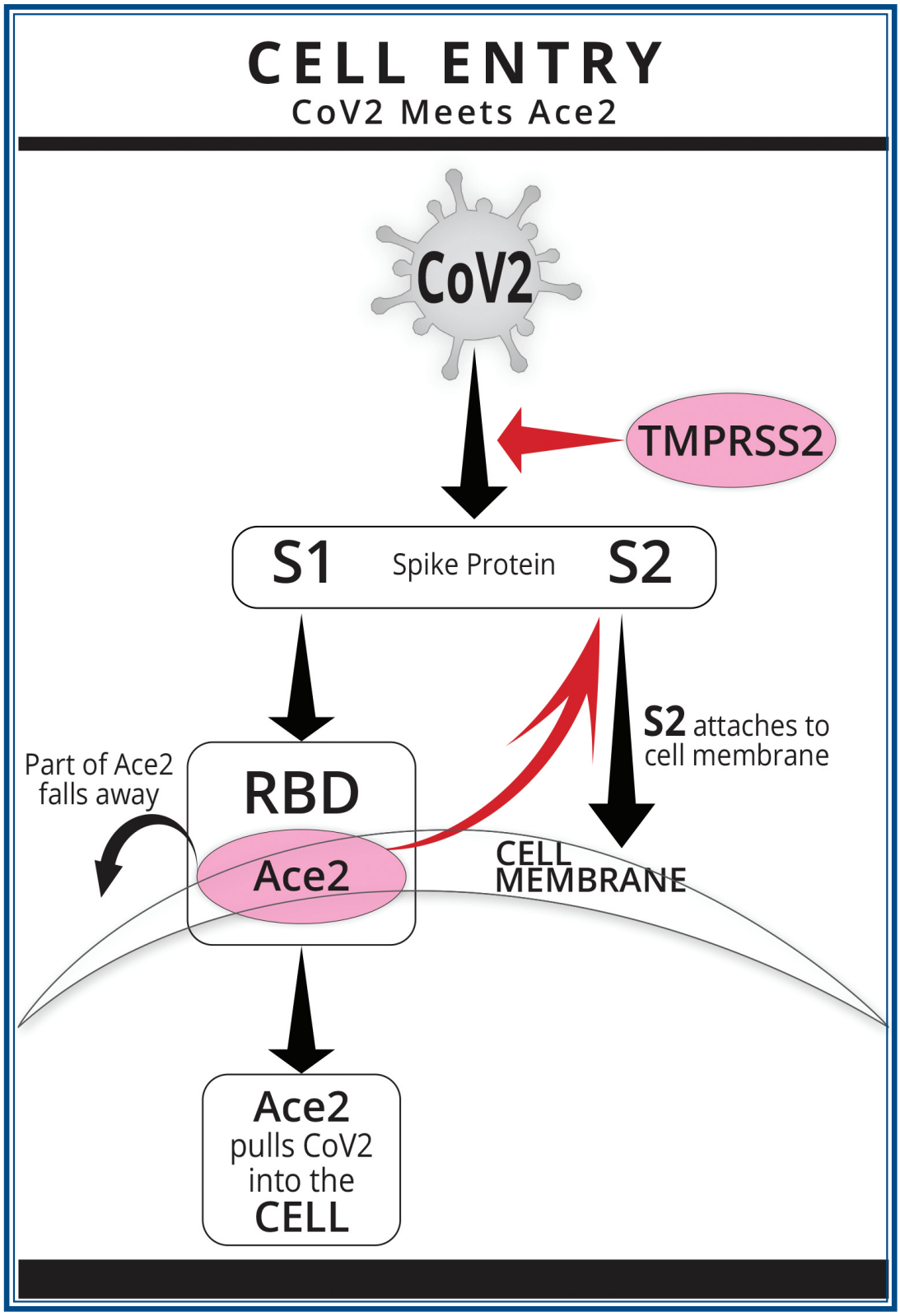
The spike protein then induces another protease, called ***TACE***, this time to slash off the piece of ACE2 that is outside the cell membrane. The remaining piece of ACE2 within the membrane, with the virus still clinging on for all it is worth, pulls back into the cell.

Altered or damaged membrane proteins are known to retreat into their cells when they are damaged or bound by a particular substance. Our opioid receptors retreat back into our sensory nerves when bound by the highly potent and dangerous opiate called *fentanyl*.

A virus close to a TMPRSS2/ACE2/TACE cell membrane group will gain access to the cell and the ACE2 protein will be destroyed in the process. TMPRSS2 and TACE are tricked into aiding viral entry. The more TACE and TMPRSS2 is expressed, the more effective the welcoming committee. People with chronic lung disease and smokers, who express more of both proteins as a result of inflammation, are made more susceptible to being infected by CoV-2. This is an example of how a host defensive strategy can be used by an adapted virus to improve its infectious ability.

It's easy to imagine this infection unfolding as newly made viruses spread around the lungs – moved by the ebb and flow of our breathing – to infect all ACE2-expressing cells. If ACE2 was only found in our lungs, then the virus would have to settle for that and either leave the body or face annihilation when the immune system figures out that it was in the lungs and destroyed it.

ACE2-expressing cells throughout our lungs are the primary entry gateway. However, ACE2 is expressed widely throughout our bodies and is especially so by the cells lining our blood vessels – vascular endothelial cells - which then ensures widespread viral dispersion.


CELL ENTRY
CoV2 Meets Ace2
CoV2
TMPRSS2
S1
Spike Protein
S2
S2 attaches to cell membrane
Part of Ace2 falls away
RBD
Ace2
CELL MEMBRANE
Ace2 pulls CoV2 into the CELL

Vascular endothelium makes up a very large organ – as big as our livers – when all lumped together. These endothelial cells regulate blood flow to every part of our bodies. This explains why Covid-19 can be such a confusing disease, seemingly targeting different organs at random.

Any cells expressing ACE2 are now fair game for the virus. It can reach anywhere through the blood stream and get across the endothelial barrier by using ACE2 for entry, replicating in the endothelial cell and then exiting out the other side of the cell into the tissue.

GAIN OF FUNCTION #1 - Cell Entry

How Is The CoV-2 Entry Strategy Different From CoV-1?

By now, most of us are familiar with the term "***gain of function***". This is used to describe a modified virus that is better than its parent at a particular function.

Sloppy replication of RNA-viruses can be advantageous to the long-term survival of the virus by creating slightly different offspring with each replication cycle. One such offspring will occasionally be a more successful version of the virus in that host. This is how a virus adapts, albeit unconsciously by random modifications. Most of these modifications are unlikely to help, but, as most of the viruses produced are destroyed anyway, only one slightly improved virus needs to survive to drive evolution of the virus

Although the complex spike protein cell-entry mechanism that CoV-2 uses seems to be much the same as CoV-1, it is a lot more successful.

Early on in the Covid-19 outbreak, genome sequencing showed that although CoV-2 was closely related to CoV-1, it had a few strategic improvements. One change was to a few amino acids in its RBD 12-amino acid sequence that binds to ACE2. These changes greatly increased the attraction between the RBD and ACE2. If the RBD was a drug, we would say that it was much more *potent*. The new virus was hundreds of time more potent than CoV-1, enabling a much smaller "dose" of the virus to establish an infection.

How Does One Dose A Virus?

Viruses escape from our bodies in our body fluids. If a smaller dose can infect another person, then a smaller aerosol droplet of moisture from our lungs will suffice. When we cough to clear our airways, we expel a shower of large droplets of airway mucus. This mucus is loaded with microbes living in our airways. Most of these are harmless organisms that we co-exist with. When we are infected with a pathogen – a bad bug – we can spread those to others by coughing mucus onto them. If enough of the mucus gets into them, the organisms contained in the mucus may survive and establish a new breeding cycle in their new host – infecting them.

Highly infectious viruses are spread by very small aerosol size particles.

Much smaller droplets from our lungs are more capable of infecting someone else because they can navigate obstacles a lot better than larger ones that simply splatter on a surface, instead of going with the flow of air around it. The smallest droplets that we produce while breathing can get through or around ineffective face masks, remaining suspended in the air for longer periods and be breathed in and navigate past physical airway defenses to be deposited deep in the lung of the new host.

In this way, increased viral potency enables more successful spread between hosts and makes it harder to contain.

This explains why health authorities appeared to flip-flop on facemasks and social distancing guidelines. The best way to stop spread is to wear an I-95 quality mask and stay far away from other humans. Full surface contact precautions such as gloves, surface cleaning and hand washing would prevent picking up mucous that had already landed on a surface.

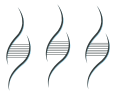
There must have been a lot of heated discussions around the world as administrators at all levels tried to negotiate feasible behavioral mandates that their people would adhere to following. Anything too onerous would have been rejected. While changes to these mandates are often derided as "***flip-flopping***", they really reflect leaders trying to make the best of a bad situation and getting the highest compliance for a range of onerous practices. Compliance and understanding take time and conditioning, enabling leaders to gradually up the ante as we collectively comprehended what was required of us.

The newly altered Receptor Binding Domain of CoV-2 provides a gain of function that vastly enhances its spread. Remember, we were already living in a manner that supports respiratory spread though our communities and all around the globe in a matter of days. We have steadfastly increased the potential to spread aerosolized viruses between ourselves over the past 100 years.

Co-V2 is found in feces, so it can spread by the fecal-oral route, but so few of us get infected that way anymore that this method of spread does not have the ability to cause a global pandemic in a matter of weeks. The virus is found in sewage and some cities are monitoring sewage as a means of tracking the virus. Don't be thrown off by stories of gastrointestinal involvement and fecal spread as adding to the mystery and frightening power of this virus. Fecal spread is just not that important right now.

Any future changes in the RBD sequence that improve its affinity for ACE2 may further increase spreadability. Such a viral strain would quickly dominate the pandemic.

What if this new more infective virus also lost its other gain of function, its stealth mode? At that point, the pandemic would start to wane. This is how outbreaks progress, with the virus evolving itself into a stable relationship with its hosts, or dying off completely as has happened with CoV-1.



GAIN OF FUNCTION #2 - CoV-2 in Stealth Mode

As we have seen, CoV-1 was not as 'potent' as CoV-2, so masks and barriers and isolation strategies may have been more effective back in 2002. Another important reason for the downfall of CoV-1 is that its stealth mode, the ability to silence its host while it replicates, was not very effective. The virus set off alarms before it was ready to leave the host cells. Immediate isolation when symptoms appeared in an infected person helped stop spread.

Some viruses benefit from a ***replicate-and-escape strategy*** that is executed long before they are detected by their host cells.

CoV-1 was going to have to buy itself more reproduction time if it was going to be pandemic-worthy.

Every living cell in nature has some ability to defend itself against a viral infection. This intrinsic cellular defense is called the ***Innate Immune System***. It has three main parts:

1) detection of the invader,
2) ability to destroy or impede the virus, and
3) a means to self-destruct the infected cell by imploding from within (apoptosis) or from outside by activating local innate immune cells patrolling in the neighborhood to literally kill the cell for the good of the whole organism. Cells that form a barrier the outside, epithelial cells, have an early detection and self-destruct system that will result in cell death if it does indeed get heavily infected.

Once CoV-2 enters its host cell, it uses its large array of protein tools to commandeer the cell for its own ends. It first uses its own RNA code to make 2 large proteins that are then cut up into 16 smaller

active proteins that set about replicating and packaging new RNA units for new viruses. The host cell is simultaneously blocked from making its own RNA instructions and therefore cannot make proteins to defend itself, even though it may have detected the infection. Another viral protein prevents ***cell apoptosis*** (suicide) in response to the heavy workload of making the proteins for the new viruses.

When RNA duplicates itself, it must become double–stranded for a brief moment. Host cells have sensor proteins that recognize this foreign double-stranded RNA, as its own RNA does not duplicate itself and is never double-stranded. These ***dsRNA sensors*** activate gene transcription factors that instruct the cell to make defensive proteins such as interferons and cytokines, putting the cell into an anti-viral state. The spike protein of CoV-2 has yet another trick up its sleeve. It blocks the recognition of double-stranded viral RNA and prevents the cell from activating this powerful anti-viral response.

Cells make a protein, called ***MHC-1***, which binds to any foreign viral proteins, antigens, which may be in the cell. MHC-1 is continually made and moved out onto the cell membrane. If it picks up an antigen before it is hung out on the cell membrane, the antigen will be shown to the outside world and trigger the interest of cytotoxic-T lymphocytes patrolling the area. These small resident white cells will kill a cell whose MHC-1 protein declares that its cell is infected. Killing the cell prevents the virus from gaining a foothold and prevents an invading virus from successfully establishing a base at the start of its invasion.

Viruses such as ***HIV*** that have stealth capability are able to make a protein called ***ORF8***. This protein binds to MHC-1 and routes it away from the cell membrane into a lysosome, where it is destroyed. This is one way in which the HIV virus is able to infect cells and keep the immune system from finding out. The HIV-infected patient remains remarkably asymptomatic largely on account of ORF8 activity.

Somehow, CoV-2 chanced upon the genetic code for ORF8 and included it into its genome. The ORF8 code is the most altered piece of code in CoV-2, the most different from CoV-1 and its relatives. It is the also the most significant genetic change to CoV-2 and accounts for its ability to spread quietly before it is detected – addressing the very weakness that helped us shut down the SARS outbreak.

This RNA sequence that codes for ORF8 is literally the CoV-2 ***murder weapon*** and the key to the origin of this virus lies in finding where this murderous gene sequence originated.

This is how, during the early stage of an infection, while CoV-2 is quietly replicating and spreading throughout the ACE2-expressing cells in the body, the innate immune system remains remarkably quiet. The infected person may not even know they have been infected.

Stealth is the other critical feature required for pandemic spread in addition to potent, small droplet, respiratory transmission.

Coronaviruses, with their large genomes that make a team of proteins to interfere with many aspects of the host defense system, are well equipped for stealth. CoV-2 took it to the next level.

How A Viral Infection Ends

A viral infection ends when:

1) ***the virus has used up all its host cell entry portals and is unable to enter any more cells to replicate. Depleted entry portals may have a harmful effect on the host cell.***

and/or

2) ***the host mounts an effective immune response, destroying the virus and the cells they are infecting. This response may kill the host, taking the virus with it.***

Both of these events likely play out in unison and likely contribute to the inflammatory events seen in Covid.

Since we survive most viral infections, our immune systems are extremely effective at protecting us from viral infections. We would not be here otherwise. Viral infection is a part of life for every living creature on Earth.

Our immune systems have the ability to remember a virus and build a defensive position to protect against it again. Repeated infections with the same virus would weaken us and our species as a whole, so we must literally drive them off and be able to defend ourselves until we recover fully.

The long-term defensive strategy is based on making antibodies to the virus and then putting those trained cells into our immune memory banks, to be called up for duty should that same virus return.

This induced response, called the ***Adaptive Immune System***, entails more than putting an antibody recipe into deep storage. The lymphocyte cells involved in the adaptive system are also programmed to respond in a range of ways, from a killing and repairing response to an inflammatory response, referred to as ***Th1*** and ***Th2*** responses, respectively.

When we are healthy and are blessed with a well-balanced immune system, replete with all the minerals it needs (especially zinc) and one that has not been interfered with, we are capable of mounting a strong and life-long immune response to that virus.

This is quite well demonstrated by our response to the measles virus. Newborns, protected by antibodies gifted from their immuned mothers, naturally contract measles around the age of five and never get infected again. Although the infection is harmful to malnourished children, especially with vitamin A deficiency, healthy children get over it remarkably well and are left with a stronger zinc-dependent Th1-balanced system that might even reduce inflammatory-biased responses to other challenges, resulting in fewer allergies.

A whole virus response is well recognized to provide a stronger and more effective and prolonged immune response in healthy people than a response induced by vaccination. Vaccines are ideal treatments when given to individuals at risk of sickening and dying from a particular infection, should they get it.

The risk from the vaccine should be lower than the risk from the infection. There are very seldom cost/risk free interventions in medicine.

WHAT IS HERD IMMUNITY?

While on the subject of agriculture and herds of domesticated animals and humans, it's time to discuss herd immunity and the drive to have all of us vaccinated for the greater good of population immunity.

Vaccines are useful to protect a vulnerable population from a viral threat that cannot be contained. In the case of herds of farm animals, their dense living situation makes rapid spread of a new outbreak almost impossible to contain. A vaccine that protects most of the animals for the short duration of their lives and does not adversely affect their ability to convert food into body mass is useful. Owing to their low genetic diversity, once a vaccine is found to be safe in tests, it is not unreasonable to extrapolate that safety to the whole herd. Even if the vaccine did turn out to be harmful in some breeds, the cost to society is small and such events would not likely be significant.

Vaccines are useful for providing limited duration protection for at-risk populations, where the risks of vaccination are lower that the risks associated with infection.

This may not extrapolate to the situation we are now embroiled in, where politicians are advocating mandatory vaccination of every human, regardless of individual circumstances and we need to be vigilant.

We know that:

1. ***Both a virus and the vaccine against it may harm an equally small but significant portion of the human herd.***

   As with any new illness, we need to identify the characteristics of those harmed by the vaccine and those by the virus. They may not be the same group of people. Then

we must decide if the vaccine risks are lower than the risk of getting the infection in all sub-groups of the herd.

It is disingenuous (aka deceitful) to ask those people who are at increased risk from the vaccine and much lower risk from the infection to take one for the team because they are possibly contributing to herd immunity. Vaccine risk and infection risk are not related. Individual protection is not the same as herd immunity, and the two may be mutually exclusive.

2. ***Vaccines provide limited (efficacy and duration) protection that may well increase survival in certain well-defined at-risk groups of the herd. The influenza vaccine is a well-known example and may be worth providing to those individuals who are at risk of contracting the virus when the threat from the virus is considerable to them.***

In order to make best use of our vaccine defense strategy against this pandemic, we need to determine not only how the virus spreads between us but how it makes us sick. Once we know this, we can determine who is at risk from severe illness and death and only then we can decide on treatment strategies to protect that group of people.

Maybe, those of us who are not at great risk from Covid-19 should be turned out to pasture to get on with life, get the infection and develop the best herd immunity of all by engaging our own immune systems directly with the virus to develop life-long immunity.

We now know that people who survived SARS, CoV-1 infections, almost twenty years ago, are now immune to CoV-2. Maybe, this is how we are going to have to earn herd immunity!! Time will tell. It's a great big experiment now and we must not allow any of us to forget this until the outcomes are further tabulated.

SUMMARY

CoV-2 is a coronavirus with a particularly large RNA genome that has resided in bats until 20 years ago when it emerged in humans. Its main difference from our own endemic coronaviruses is the mode of cell entry that it uses, our ACE2 membrane protein.

CoV-2 is a genetically improved version of CoV-1 with spectacular gain of function in two critical aspects of its life cycle: cell entry and stealth.

The ACE2-binding protein found in the tip of the spike protein has a higher affinity for ACE2, which translates into much higher ability to infect cells. This makes it more contagious because a smaller droplet size of (aerosolized) fluid in our exhaled breath can infect a new host.

The virus has the usual coronavirus stealth abilities encoded in its large RNA genome that subvert the cells innate immune system from mounting an internal response to infection. It also has a new piece of code, acquired from a different virus altogether, that codes for the protein ORF8. ORF8 effectively shuts down the infected cell's ability to alert outside help from resident immune cells such as killer T-lymphocytes to destroy the infected cell before the virus can replicate and spread.

These simultaneous mutations account for two gain of function abilities that have enabled this emerging virus to instantaneously become a pandemic champion, without the need for any further evolution in humans.