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The Age of COVID-19: Fear, Loathing, and the "New Normal" [1]

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ABSTRACT

In this article, I give some of the history of COVID-19, and review some of the unanswered questions about what is being represented as an extraordinary "pandemic". Foremost among them is whether those "fashioning the narrative", to borrow a phrase from the Stanford mathematician Richard Moore, also had a hand in fashioning the "pandemic" itself. I also introduce the articles in the rest of this issue that follow my own.

Keywords: *contact tracing, flatten the curve, mask efficacy, PCR, polymerase chain reaction tests, shape the narrative, social distancing, social shaming, specific new powers, virtue signaling*

Who defined the crisis and its orthodox meaning?
Those who fashion the narrative.
Why did they choose that meaning?
So the government could claim the right to specific new powers.
Where will this lead?
To the exercise of those new powers.
(Moore 2020)

Introduction to Issue 2 of the *IJVTPR*

This is the second issue of *IJVTPR* where we explore various issues arising from the COVID-19 pandemic from various angles. I take on the problem of providing some recent history, confused as it has been, to set the stage for the fear, loathing, and all the other aspects that make up this "new normal". In our call for papers about COVID-19, the Children's Health Defense Team stepped up to address the *cui bono* question. After that paper (the second in this issue) was peer reviewed and

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accepted for publication in *IJVTPR*, in order for it to reach a broader audience, with written permission from *IJVTPR*, it appeared in *The Defender* on December 14, 2020. That CHD article, which directly follows mine in this issue of *IJVTPR*, recounts the largest transfer of wealth in the history of the world: trillions of dollars were taken from a multitude of middle class citizens and transferred to a tiny cabal of elite power brokers during this unprecedented time.

In the third paper, John W. Oller, Jr. deals with so-called "gain of function" or "dual use" (bioweapons) research leading up to where we are now with COVID-19.

The fourth paper by James Lyons-Weiler discusses the way out-of-balance high cost of false positive COVID diagnoses.

The fifth paper by Russell Blaylock sorts out some of the likely sources of damage from inflammation owed to SARS-CoV-2. His thinking about the cytokine storm and its role in causing, in the most severe cases, dysregulation of the immune defenses leading to catastrophic systems failure and death, is a natural set up for his own suggestions about ways to reduce pathological damage, and for the theoretical thinking of the sixth paper in this issue by Robert M. Davidson and Timothy Winey.

In the sixth entry, Davidson and Winey present some hopeful results of research with L-ascorbic acid and its ubiquitous positive impact on biosignaling systems. Their detailed analysis and review presents L-ascorbic acid (Vitamin C) as doing in living chemistry more or less what oil does in an automotive engine. They suggest that it must aid in rescuing cells from SARS-CoV-2 just as it does from viruses in general.

Then, in the seventh paper in this issue, James Lyons-Weiler proposes "Plan B" for oversight in the public health domain to replace the failed "Plan A" that has led to an out-of-control plutocracy stuffing itself with additional wealth and power while it robs everyone else of the very things, as the regulatory arm of government, it was supposed to preserve and protect on behalf of the people.

The eighth entry of this issue is an amended version of Sin Han Lee's paper: "Toll-like receptor 9 agonists in HPV vaccine Gardasil9" from the first issue of the journal (Lee 2020). It is re-published here with two substantive corrections. Because of the importance of Lee's article to the ongoing lawsuit, *Balasco v. Merck* (2020; also see Baum Hedlund Aristei & Goldman 2020; Hendler 2020), to make certain that the details are right, rather than publish a list of the two errata in that paper, we have re-published the whole of it with changes marked in purple and footnoted by us. In the original setup of that paper, on p. 82 the following line was omitted: "(5/6) were those of HPV 18 and one (1/6) was that of HPV 11 (synthetic)" and on p. 92 "3-60 μm" should have been "3-60 nm". Those content errata are corrected in the version of that paper that appears here and it is republished in its entirety. Corrections are footnoted and are colored in purple.

The ninth and final entry, a very personal statement by John Oller, deals with a patent application that has been referred to frequently in blogposts and in the news as manifesting "The Mark of the Beast" (Grapevine News 2020) — a surveillance system for Microsoft's "cryptocurrency" invention. Its purpose is to enable the elite plutocrats profiting from the still malingering crisis (see the entry by the Children's Health Defense Team immediately following mine in this issue of the *IJVTPR*), to control on a global scale the power of individuals to buy and sell contingent upon the most intimate

details of their bodily actions and mental states as recorded by networks of computers, telecommunications systems, servers, cell phones, tablets, laptops, smart devices (watches and televisions), and "other embodiments", but "not limited" to such computational devices, as will be understood, in the words of the patent holders, by "those skilled in the art to practice the invention" (see Abramson et al. 2020, p. 3, where lines 23 and 24 contain the quoted phrases). Among the "other embodiments" mentioned in the relevant research literature are "quantum dots" emitting infrared signals that were used to track vaccinations injected in a "dye" in one of the studies sponsored by the Bill & Melinda Gates Foundation (McHugh et al. 2019). In an interview by telephone on June 3, 2020, Bill Gates is reported to have said, "I've never been involved [*sic* in] any sort of microchip-type thing" (Brown and Weise 2020). Right. He says this in spite of the fact that the "quantum dots" injected beneath the skin with a vaccine (Trafton 2019) are among the latest computational devices experimented with by MIT researchers in work sponsored by the Bill & Melinda Gates Foundation (McHugh et al. 2019). This particular "embodiment" of a surveillance system is "delivered under the skin at the same time as the vaccine" (Trafton 2019).

Revisiting the Early Days of the COVID-19 "Pandemic"

By now, we've all heard words and phrases about COVID-19 repeated endlessly — words and phrases most of us never want to hear again. Among them is the word *unprecedented* to describe the emerging pandemic; *social distancing*, the notion that you can protect yourself and others by keeping a 2-meter distance from them; *social shaming* and *virtue signaling* indicating the opprobrium that those who don't obey guidelines for social distancing and masks often face from those who do; *flatten the curve*, a concept originally intended to convey the danger of flooding hospitals with too many sick people to handle. There are others.

To understand such additions to the world's lexicon, let's go back to the beginning. The WHO announced "COVID-19" — the name of a new disease attributed to the Corona family of viruses on 11 February 2020 using guidelines previously developed by the World Organization for Animal Health (OIE) and the Food and Agriculture Organization — both of these being subagencies of the United Nations (World Health Organization 2020; https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it). The virus itself was formally dubbed "severe acute respiratory syndrome coronavirus 2", or SARS-CoV-2.

Informally, the name was "Corona virus disease 19", which was soon shortened to "COVID-19". It is closely related to the coronavirus that gave rise to "sudden acute respiratory syndrome" (SARS; Centers for Disease Control and Prevention 2017) in 2003. COVID-19 thus became the newest named member of the coronavirus family (International Committee on Taxonomy of Viruses 2020) — the viruses, incidentally, credited with a large fraction of what we consider to be the common cold (Anon 2020b). Other coronaviruses can be fatal to humans, e.g. "Middle East respiratory syndrome" (MERS; Centers for Disease Control and Prevention 2019f) and, of course, SARS. The COVID-19 virus pandemic, so declared by the WHO on March 11, 2020 (Ducharme 2020), came into being just as the book, from which this article is excerpted (Shaw 2021), was entering a rewrite phase. COVID-19 was not in the original book outline, but events overtook the book just as they upset the world. What we thought we knew about the disease in the early days consisted of scraps of information filtered through the Chinese government and various international media, notably,

backed up by the WHO — see the timeline as reported by the World Health Organization 2020 beginning January 10, 2019 and still being updated daily ever since.

The Web of Science reports 58,635 peer-reviewed papers using the term "COVID-19" published since the beginning of the current "pandemic" and Google Scholar reports about 234,000 articles for a similar search as of the same date (December 15, 2020). Prior to the March 11, 2020 announcement, the WHO Director-General, Tedros Adhanom Ghebreyesus, referred to the looming crisis as "a public health emergency of international concern". He kept his distance, however, even at that late date, from the term "pandemic" (Ducharme 2020).

Naturally Formed or Deliberately Manufactured?

The official story then and now was that COVID-19 is a zoonotic coronavirus that jumped to humans from either bats or pangolins, or both, beginning in a "wet market" selling live animals or their carcasses in Wuhan, China (Anon 2020h). Was it merely a coincidence that the nearby Wuhan Institute of Virology, the first Bio-Safety Level 4 (BSL-4) laboratory of China opened officially in 2018 (Bo 2018) and was experimenting with more coronaviruses than any other laboratory in the world (Anon 2020h)? In 2017, David Cyranoski wrote in the prestigious bioscience journal *Nature* about "concerns" of "scientists outside of China" who worried about the possibility of "pathogens escaping" from the first of the five to seven Chinese BSL-4 labs set to study "the world's most dangerous pathogens". After SARS-CoV-2 had already set off alarms all over the world, the Editor-in-Chief of *Nature* added the following note at the top of Cyranoski's paper:

> **Editors' note, January 2020:** Many stories have promoted an unverified theory that the Wuhan lab discussed in this article played a role in the coronavirus outbreak that began in December 2019. *Nature* knows of no evidence that this is true; scientists believe the most likely source of the coronavirus to be an animal market.

Was it merely another curious coincidence that the Chinese scientists at the BSL-4 laboratory in Wuhan were deeply involved in what is called "gain of function" (GOF) research? That is, in research aiming to alter the genes of viruses to make them more deadly as potential biological weapons (see Oller's article in this issue). Was it also a mere coincidence that many such studies have been paid for by the National Institute of Allergy and Infectious Diseases headed by Dr. Anthony Fauci (Nabel and Fauci 2010; Fauci 2012; Erbelding et al. 2018; Breggin and Breggin 2020; Guterl 2020; Mascola and Fauci 2020; Sellin 2020)? Also, was it just a coincidence that Fauci was involved in funding collaborations between the Wuhan researchers and two US universities, notably the University of North Carolina at Chapel Hill (Menachery et al. 2015, 2016, 2017, 2019; Anthony et al. 2017) and the University of Texas Medical Branch (UTMB) at Galveston Texas (see Breggin and Breggin 2020 and references there), as well as the EcoHealth Alliance based in New York (Sellin 2020; Yan et al. 2020b)?

Even more curious coincidences seemed to be lurking in the background as well: On July 5, 2019, a husband and wife team, Dr. Xiangguo Qiu, her husband Keding Cheng "and an unknown number of her students from China were removed from Canada's only level-4 lab" (Pauls 2019) by the Canadian federal police, the Royal Canadian Mounted Police for reasons that were never fully disclosed. Both Qiu and Cheng, had long-established ties to the Wuhan Institute of Virology.

A Picture-Perfect Simulation Just 53 Days Before the First COVID-19 Death

All of the foregoing background makes events of 2020 seem increasingly dodgier. It gets better, or worse, depending on one's perspective. On October 18, 2019, Johns Hopkins University's Bloomberg School of Public Health, Center for Health Security, hosted a 2-day tabletop simulation exercise about a pandemic that closes down most of the world. This exercise, called *Event 201*, was in large part paid for by the World Economic Forum and the Bill & Melinda Gates Foundation (Open Philanthropy Project 2019).

There were 15 main participants drawn from business, medical, pharmaceutical, and governmental organizations. Of the 15, five stand out: Dr. Chris Elias from the Bill & Melinda Gates Foundation, Prof. George F. Gao, the Director General for the Chinese Centers for Disease Control, Stephen C. Redd from the U.S CDC, and Adriane Thomas, Vice President Global Health from Johnson and Johnson, one of the world's giant pharmaceutical companies. And then there is the fifth party consisting of the central bankers, ubiquitous by their absence, and yet like the proverbial elephant in the boardroom as noted by Catherine Austin Fitts (see her interview with Greg Hunter 2020 at https://robinwestenra.blogspot.com/2020/12/catherine-austin-fitts-on-great-reset.html). These five, based on their credentials and influence, seem to be the main players. As for the other 10, it is not clear why they were there at all. Maybe they are bankers, or were chosen at random to fill empty chairs (https://www.centerforhealthsecurity.org/event201/players/)?

On January 23, 2020, in the face of growing numbers of victims in Wuhan and elsewhere in Hubei province, the Chinese government did a hard lockdown of the city and province (Anon 2020c). The official death tally in China was reported by CNN on that date as 25 with an estimated 800 persons infected in Wuhan, a city of 11 million. A little less than four months later, on Wednesday, April 6, 2020, the pandemic in China was officially declared to be over (Zhong and Wang 2020), but not before it had spread around the world by Chinese and other international travelers from Hubei province, very much as in the *Event 201* scenario.

Now it was the rest of the world that went into escalating reports of infection, followed by various levels of lockdown, and "state of exception" decrees. At the time of this writing, as I get close to finishing my book, most countries are experiencing a "second wave" of infections. Whether these are real or not will be addressed below. In the meantime, in this article I address a number of things we don't fully know, although more reports appear daily, albeit many of them preliminary, speculative, or already known to be just plain wrong.

Unanswered Questions Remain

In this essay, I will try to fill in some of the answers to questions such as: Where and how did COVID-19 really originate, particularly was it a natural virus or one modified by researchers as a gain of function (GOF) manipulation? What is the actual pathophysiology of the disease, including impacts on the CNS? What are the age, sex, national and ethnic demographics of COVID-19 infection? What are the real numbers, a question that ties directly to the question of ways to test for the virus and/or the surrogate markers of prior infection? How many really died in China versus the US? And why have COVID-19 deaths not had a major impact on refugees in various camps? How effective were and are measures taken by various medical authorities, e.g., masks, social distancing,

lockdowns, etc.? In the following sections, I will take these on one at a time where answers are known.

The Origins of COVID-19

A number of studies have suggested that COVID-19 arose as a zoonotic virus that jumped from other species to humans first in the animal "wet" market in Wuhan (Andersen et al. 2020; Lam et al. 2020; Zhang, Wu, and Zhang 2020). This remains the dominant narrative. Various more recent studies, however, cast doubt on the natural zoonotic origins view. Among them is the work of Zhan et al. featured in an article by Rowan Jacobsen in early September 2020 entitled *Could COVID-19 have escaped from a lab?* (Jacobsen 2020; https://www.bostonmagazine.com/news/2020/09/09/alina-chan-broad-institute-coronavirus/). The Zhan paper titled , "SARS-CoV-2 is well adapted for humans. What does this mean for re-emergence?" (Zhan, Deverman, and Chan 2020; see the version posted May 2, 2020. at https://doi.org/10.1101/2020.05.01.073262doi: bioRxiv preprint) notes some oddities about what the authors term "evolutionary dynamics". The article has not apparently been peer-reviewed so this is an obvious concern for credibility, but the authors certainly have the credentials for their work to be taken seriously, at least once some of the panic about COVID-19 wears off: First author S. H. Zhan was at the Department of Zoology and Biodiversity Research Centre at my own university (UBC) before moving over to a company called Fusion Genomics Corp.; second author B. E. Deverman is a professor at the Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard. The senior author is Y. A. Chan, formerly a Ph.D student also at UBC and now a postdoctoral fellow at the Broad Institute with Deverman.

In the abstract, the authors write:

> In a side-by-side comparison of evolutionary dynamics between the 2019/2020 SARS-CoV-2 and the 2003 SARS-CoV, we were surprised to find that SARS-CoV-2 resembles SARS-CoV in the late phase of the 2003 epidemic after SARS-CoV had developed several advantageous adaptations for human transmission. Our observations suggest that by the time SARS-CoV-2 was first detected in late 2019, it was already pre-adapted to human transmission to an extent similar to late epidemic SARS-CoV. However, no precursors or branches of evolution stemming from a less human-adapted SARS-CoV-2-like virus have been detected. (Zhan et al. 2020)

In other words, COVID-19 showed up in the human population already too well adapted to humans to be a virus that had recently jumped from some other species. Further, there seemed to be no earlier variants which would be typical of the new virus. The authors suggest several ways this might have occurred. While they don't dwell on it and indeed are very cautious in how they interpret their data, one of these ways might be if COVID-19 were deliberately engineered as part of a GOF study, perhaps at the BSL-4 facility at the Wuhan Institute of Virology.

Jacobsen (2020) explores all of this. He opens his discussion with the following:

> The world's preeminent scientists say a theory from the Broad Institute's Alina Chan is too wild to be believed. But when the theory is about the possibility of COVID being man-made, is this science or censorship?

It's a good question. Jacobsen considers the often hostile responses that the Zhan paper received and how Chan as senior author handled it. Unsurprisingly, given the orthodoxy in vaccine research, the possibility that COVID-19 arose in a laboratory clashes with the story that many scientists and much of the media prefer to believe and repeat. But which narrative is correct? Both cannot be correct because they contradict each other. If the virus was created in a BSL-4 laboratory it was not

a natural zoonotic occurrence that leaped from bats to pangolins to man, or by any other natural pathway.

The zoonotic narrative, however, keeps changing. Denmark was soon reporting that COVID-19 jumped from humans to farmed mink and expressed fear that it might jump back again to humans (Hart 2020; Kevany 2020), perhaps a not trivial concern. Chan and her colleagues are following this story and await the latest developments. What is sure, however, is that the pangolin origin study is simply not correct: no COVID-19 precursors have been found in that species (Chan personal communication; also see Latham and Wilson 2020b; Segreto 2020; Segreto and Deigin 2020; Yan et al. 2020).

It is worth considering that GOF research is nothing new and has gone on for the better part of 100 years in the US and increasingly in other countries that compete with the US for world dominance, China being only one such. The stunning illogic of GOF research to create more pathogenic viruses in order to protect against them is discussed by Oller in this issue. As he notes, such research is the logical equivalent to the fire department of a major city setting large parts of the city alight in order to prepare for a potential conflagration. Rather than actually being protective, such a research program virtually assures that the deliberately constructed GOF virus will find its way into the human population either by accidental release or by a deliberate action by "bad players" — as anticipated in the *Event 201* simulation at Johns Hopkins University.

Pathophysiology of COVID-19 by the Organ Systems Impacted

For the discussion in this section, I rely heavily on Mokhtari et al. 2020, "COVID-19 and multi-organ failure: A narrative review on potential mechanisms", published in the *Journal of Molecular Histology*, *51*(6), 613–628 (https://doi.org/10.1007/s10735-020-09915-3).

Respiratory

When the victims of COVID-19 first started to fall ill, first in Wuhan, and then in the West, the initial medical response was aimed at the most obvious symptoms, that is primarily those of the respiratory system. For many people these symptoms were at about the level of a common cold or even yearly influenza: cough, sore throat, fever and so on. In some of those affected, primarily the elderly and those with significant comorbid respiratory and cardiovascular conditions, their condition rapidly progressed to acute respiratory distress syndrome, ARDS. This was similar to other acute deadly coronavirus infections of the past: Middle East Respiratory Syndrome (MERS; Centers for Disease Control and Prevention 2019f) and Severe Acute Respiratory Syndrome (SARS; Centers for Disease Control and Prevention 2017). In each case, the virus' "spike protein" seemed to attach primarily to epithelial cells in various part of the respiratory system as well as epithelial cells on veins and arteries of the respiratory system at a receptor binding site termed ACE-2 (angiotensin converting enzyme 2). In turn the infection triggered severe inflammatory responses and cell death leading to fluid build up in the lungs. Moreover, the infection often provoked what was termed a "cytokine storm" in which the immune system overreacted and released inflammatory cytokines such as IL-6, TNF-α, and others that actually damaged lung alveoli cells (Miller and Blaylock 2017; especially the introduction by Blaylock). The result was often lung failure leading to multi-system organ failure followed by death in severe cases.

The initial response was to place severely ill patients on respirators, a response we now realize often did more harm than good.

Cardiovascular

Work coming out of Italy made it clear that the infection was not confined to the respiratory system, but also involved the cardiovascular and other systems. Once again, the ACE-2 receptor seems to have been a molecular target for the virus, inducing direct cell death on its own, as well as indirect cell death by inciting a cytokine riot in the lungs. A key vascular feature in some of the affected persons was a coagulopathy, defined as an abnormal blood flow with either excessive bleeding *or* clotting.

Renal and Liver Infection

Significant negative impacts of COVID-19 viruses have also been reported on both the kidneys and liver, once again through ACE-2 receptors. However, it should also be clear that even without direct infection, serious impacts on respiratory and cardiovascular function will in turn damage both other organs.

Nervous System Effects

A surprising feature that began to emerge in some patients seemed to involve the nervous system, where initial phases of the disease seemed to be associated with the loss of smell or taste, headache, and dizziness as features of early phase infections. Other consequences can include stroke, multiple sclerosis, Guillain-Barré, and encephalitis (Montanari and Gatti 2016; Wang et al. 2016). COVID-19 can impact different parts of the nervous system, including the CNS, the peripheral nervous system, and the musculoskeletal system. Overall, 3.46% of patients with COVID-19 infection were found in one Chinese study to have CNS outcomes — 24.8% of those with overall nervous system involvement (Sheraton et al. 2020). Sometimes such deficits seemed to remain after other symptoms had abated, including cognitive dysfunctions.

The nervous system outcomes have not to date been as extensively investigated as those for other organ systems as cited above but it seems clear that there are multiple pathways by which the virus can access the nervous system, including through the olfactory epithelium (Baig et al. 2020; Bilinska et al. 2020) and by transport along the vagus nerve from the GI system (Pereira 2020). This latter is perhaps particularly concerning given the emerging speculation that the origin of Parkinson's disease involves the same route from the GI system, up the vagus nerve and into the brain (Visanji et al. 2013; Ubeda-Bañon et al. 2014; Braak and Del Tredici 2017). Such features may be taken to indicate the serious potential for triggering longer term progressive neurological disorders (Wilson and Jack 2020) through a range of mechanisms, including inflammatory processes triggered by binding to ACE-2 receptors, direct impacts on astrocytes and microglia and the cytokine storm (Sultana and Ananthapur 2020).

How Severe Is COVID-19?

The above will serve to make clear that COVID-19 infection can be extremely severe in some individuals and can lead to death and may have longer term impacts insofar as the nervous system may be permanently damaged. It should not therefore be assumed that the disease is trivial for all people in its manifestations. However, there are still fundamental questions which remain to which there are, at this time, no conclusive answers. These include the following: What is the percentage of the population affected by the virus; how do age, sex, ethnicity/race impact infection by the virus; how severe is it overall for most people?

Percentage of the population affected

A now dated early summary of the number of infected was provided by reporter Ben Swann of Truth in Media (2020; at https://www.youtube.com/watch?v=ohO8eAwi_po&feature=share&fbclid=IwAR0KWh1GbnJrt_908uYrXnLGPozOV26xBSyAWX6Ij4Ys5k0gMyd-qapl0_Q). Basically, Swann takes the WHO's own COVID-19 case numbers and shows how they were manipulating data claiming a deadly pandemic many times worse than seasonal flu — .1% as against 3.4% for a death threat from SARS-CoV-2 34 times greater than from seasonal flu. In doing so they created a level of panic in society that has rarely been seen in peacetime. As Swann noted, the implications for the economy of the world were already daunting and have only become more so as I write these words today. And that was only the first "wave" of the disease. At this writing, most of the world, less China, seems to be fully into the second wave, in some countries already a third wave.

Part of the panic that the WHO, various governments and the mainstream media spawned arose from two main things: The first was how the number of deaths per case infected were calculated. Problem one within this arose from trying to determine how many people had actually died from COVID-19.

In the early days of the pandemic, there was clearly a tendency to attribute any death for someone who showed any of the respiratory symptoms of the disease as a COVID-19 case (Yeadon 2020). Later, the definition of a "case" would be extended to anyone who got a positive reading from the incredibly sensitive real time polymerase chain reaction (RT-PCR) testing for practically any viral RNA that has ever infected the individual tested; also see the first of James Lyons-Weiler's papers in this volume). This procedure, often accompanied by dubious laboratory analyses (as shown below) was all it took for all fatalities in anyone who tested positive by that method to be classified as a COVID-19 death. The distinction between "dying from COVID-19" versus "dying some time after a positive result from the super-sensitive RT-PCR testing for COVID-19" remains highly relevant. For example, if one has COVID-19 and it impacts organ systems as described above, in severe cases up to the point where death occurs, this may be a *bona fide* COVID-19 fatality. More indirectly, if one has a significant and documented respiratory or cardiovascular disorder and the disease triggers the cascade of events that further damages an already stressed system leading to death, then it is also legitimate to call that a COVID-19 death. So what are the real fatality numbers? It depends on various unknown factors, such as how many different RNAs trigger a positive RT-PCR result. The answer, therefore, must be assumed that we don't really know what the percent of deaths is relative to the number of genuine SARS-CoV-2 infections.

Problem 2 arose from trying to determine how many people had actually contracted the disease regardless of any overt symptoms, if any at all (the so called "asymptomatic" cases) unique to COVID-19. And the only way to assess this is to do the mass screening by either RT-PCR or blood sampling, serology. In the early phases, blood tests were not reliably done and as discussed below for RT-PCR the excessively high number of positive cases is probably grossly misleading with respect to determining the total number of actual SARS-CoV-2 infections.

For all these interrelated reasons, if you don't know the numerator (the number of actual SARS-CoV-2 fatalities) and you are forced to guess the denominator (the total number of people actually infected with SARS-CoV-2 as contrasted with some other corona virus, or even a flu virus) you can't calculate the rate of fatalities in the population. Professor John Ioannidis ran some antibody tests on April 3-4, 2020 in Santa Clara, California on 3,324 persons and came up with infection rates that were much higher than the medical authorities in California were claiming (Bendavid et al. 2020). By May 2020 researchers in Japan, using a similar method for measuring seroprevalance of SARS-CoV-2 antibodies, found that the number of infected persons in Kobe, Japan was 396 to 858 times greater than had been previously estimated. The consequence of such numbers was to greatly increase the denominator and thus to reduce the ratio of deaths to infections from SARS-CoV-2. Earlier estimates, it seems, based on the far less reliable method of RT-PCR testing, had inflated the death rate from SARS-CoV-2 infections beyond all reason. This is not to minimize the importance of any deaths, but to say that our understanding of the COVID-19 "pandemic" has been distorted out of proportion much as Ioannidis predicted early on (Ioannidis, Cripps, and Tanner 2020).

The media, of course, grabbed such numbers and ran with them, thus vastly inflating public panic and turning COVID-19 into the modern equivalent of the Black Death. In some sense, the erroneous modeling that came out of Imperial College in London, funded by none other than the Bill & Melinda Gates Foundation, notoriously (and predictably) overestimated the expected number of deaths (Chalmers 2020; Dayaratna 2020; Reynolds 2020).

Reported Numbers

So, let's look at the actual reported numbers by age, ethnicity, and sex where possible broken down by demographics for both the U.S and Canada. The current data for the Demographics in the US are found here: https://covid.cdc.gov/covid-data-tracker/#demographics For Canada the data are reported here: https://health-infobase.canada.ca/COVID-19/epidemiological-summary-COVID-19-cases.html The statistics, however, do not evaluate the accuracy (validity) of the data reported. That aspect is particularly relevant given the issues for diagnosis and testing already mentioned and those to follow in this section.

A fast glance of the numbers for the U.S shows evidence for the observations that have been made from the beginning of the pandemic. Namely that most of those diagnosed with COVID-19 (CDC, as of Dec. 4, 2020) are concentrated in the 18-64 age range (75.6%) with very few cases under age 4, 1.8%, and only 8.2% in the 5-17 age bracket, confirming that those under 18 are not the main disease vectors. Somewhat surprisingly, the elderly above 65, considered in some reports to be the most at risk of catching the disease, are at 14.5%. However, those above 56 are most likely to die with the peak at those above 85 at 32.4% with total deaths attributed to COVID-19 of 198,788, oddly a number about 70,000 less than usually reported at this time by the media.

These COVID-19 death numbers reflect what has been seen in various western countries and may reflect either greater mortality due to age, to living conditions as in care homes, or both.

The male/female ratio is pretty close at 47.9 versus 52.1, respectively. In terms of ethnicity, white non-Hispanics make up the bulk of cases at 52.5%, followed by Hispanics at 24.2% and 14% for Black Americans. These latter numbers, however, cannot be taken to be definite because they are not adjusted for proportion of the overall population, nor does the CDC consider reporting consistent by state and community.

Canada during the same period reported 372,409 cases (with the same problems already noted for testing in general) and approximately 19,900 deaths. There was a relatively even case spread until after age 60, after which the infection rate declines. Male cases predominate over female from ages above 39. Canada did not report on ethnicity.

Assays to evaluate COVID-19: PCR versus serology

A key concept to keep in mind in the following is that viral infection in an uninfected person largely depends on both the amount of virus they are exposed to and the time period over which they are exposed. There are other factors such as the virulence of the virus. For details see the Pathogenesis of Virus Infections as explained by (Burrell, Howard, and Frederick A Murphy 2017) in Fenner and White's Medical Virology (Fifth Edition):

> Viral virulence is influenced by viral genes in four categories: (1) those that affect the power of the virus to replicate, (2) those that affect host defenses, (3) those that affect tropism, spread throughout the body and transmissibility, and (4) those that encode or produce products that are directly toxic to the host.

Testing protocols

PCR

Most jurisdictions around the world have been using variants of testing by polymerase chain reaction (PCR) to determine if someone is infected with COVID-19. In this approach, a researcher can take a very small sample of genetic material, for example from a virus in an infected person's nasal pathways, and run this through a series of chemical steps in a device termed a thermal cycler. Each cycle is one amplification of the original signal. In British Columbia, as elsewhere, the preferred PCR method of many is called "reverse transcriptase PCR (RT-PCR; Anon 2020d). There are numerous ways this protocol can go wrong, but in the hands of qualified researchers such problems should be minimal.

In order to detect a RNA nucleotide sequence, for example that which gives the spike protein of COVID-19, multiple amplification cycles are typically undertaken. The threshold for detecting viral RNA that might be from infectious viruses is called the cycle threshold or "Ct." Typically, researchers use 25 to 35 cycles. Going toward the higher end and beyond increases the risk of rejecting a true null hypothesis, that is, of getting a false positive answer, finding a "case" where none exists (Type I error); going too low risks failing to reject a false null hypothesis, thus missing a "case" of actual infection (Type II error). The relative dangers applied to COVID-19 testing are that a false positive might characterize a person as infectious when they are not (and quarantining that

person unnecessarily, and at considerable expense; per the first paper in this issue by James Lyons-Weiler), while a false negative risks missing someone who is infectious (someone who perhaps ought to be quarantined but will not be). Writing in *Focus on Victoria*, Alan Cassels, a Victoria-based journalist, took a look at potential PCR testing problems here in British Columbia in an article titled, "With the COVID-19 test, positivity doesn't mean infectious" (Cassels 2020). Referring to disease numbers and deaths since March 2020, he asked: "What stands out from these numbers [of number of active cases, hospitalizations, deaths, etc.]? An extremely low likelihood of death by COVID-19 in BC. Certainly lower than any annual toll of the flu. Certainly lower than the numbers of people who have died from cancers, heart attacks, overdoses, suicides and the myriad of other things that take life every single day. If you take 2019 as an average, 132 people per day die in BC, from all causes. That was the last full year without a pandemic virus." And, he continues: "With less than one person per day dying of COVID in BC, one is tempted to ask if we're making a mountain out of a molehill. I'm increasingly surprised by the general subservience of the populace and the absence of thoughtful dissent against emergency measures that are undoubtedly causing all kinds of other suffering, wreaking long-term havoc on our society, our livelihoods and our economy."

Cassels takes the view that serious COVID-19 illness and death, while tragic, tends to focus our health professionals on one disease and thus one health outcome. In the process, both they and the province's politicians, may neglect others suffering from a range of health related problems, for example, the increasing impacts of drug use with the attendant mortalities, spousal and child abuse, and increasing poverty due to COVID-19 economic impacts. In regard to this latter situation, false positives tend to make politicians go to extreme measures to control disease spread, as they are now doing in various countries, while exacerbating the other issues that have long ranging implications for overall health. Cassels goes on to elaborate about the crucial issue of false positives,

> I consulted a molecular biologist (who asked me to withhold her name as she works as a provincial government biologist) who said that we have to be very cautious in interpreting these tests because the reverse transcriptase enzyme has poor efficiency in converting RNA to DNA. She told me that if we do over 30 to 35 cycles "we can't culture a live virus from the sample." Basically, she added, "a high cycle threshold means we're finding meaningless fragments that say nothing about the infectivity of the patient."
>
> This is an expert who uses the RT-PCR test everyday in her work doing forensic science, so I trust she knows its limitations. She was quite forthright in saying that possibly as many as 90 percent of those testing positive for COVID-19 are probably not infectious. Which is to say they may have had "fragments" of the virus, but they couldn't possibly spread the virus to anyone else.

These comments are backed up almost precisely up in a recent study by Jaafar et al. (2020) titled, "Correlation Between 3,790 Quantitative Polymerase Chain Reaction–Positives Samples and Positive Cell Cultures, Including 1,941 Severe Acute Respiratory Syndrome Coronavirus 2 Isolates", which appeared in the journal *Clinical Infectious Diseases*, and can be viewed at https://doi.org/10.1093/cid/ciaa1491. The authors compared active virus recovery from cell culture experiments compared to the Ct at which the samples were retrieved. At 25 cycles, the real positive rate was 70%; at a Ct of 30 it was down to 20%; at 35 cycles it was less than 3%. This means that running at 35 cycles, the false positive rate is about 97%.

To add to this, an article that came out last year shows just how incorrectly British Columbia, and likely a host of other testing states/provinces/countries, were performing their PCR tests to determine case numbers. In British Columbia, for example, not only do they test samples with 35

cycles, they are also apparently not consistent in the number of cycles used. Ryan et al. noted the first two major mistakes *not* to make with PRC:

> Mindful of the recommendations contained in series of existing review papers on eDNA…we offer the following suggestions for standardizing eDNA techniques in light of our own findings. *To maximize diversity detected with a given primer set, minimize PCR cycles, preferably fewer than 35; Keep PCR protocols strictly consistent across samples you wish to compare* [italics, mine]. (Kelly, Shelton, and Gallego 2019).

In other words, to get accurate measurements, one needs to do the exact opposite of what the health authorities in British Columbia have done to date. As cited above, the British Columbia Centre for Disease Control which does PCR testing for COVID-19 for the province, runs their PCR tests at 35 cycles. From solely a perspective of knowing who has had COVID-19 and thus getting a better grip on numbers to date this might be useful in calculating the true overall death rate due to infection. However, from the perspective of determining how many might still be infectious and thus require more severe population control measures by the authorities, this is simply nonsense. False positives cannot infect anyone else and, as noted by Cassels, identifying positive PCR outcomes as COVID-19 "cases" when they are clearly not is sloppy science and a foolish basis for governmental decisions.

To confirm what I had heard from Cassels in person, I also asked the BC CDC directly. Here is what came back:

> PCR testing
>
> The cycle threshold number used to diagnose COVID-19 may vary based on the test used but we typically use a cutoff of 35 cycles and simultaneously detect two targets (the RDRP and E gene) and certain assays use cutoffs of 40 or even more cycles.
>
> Cycle threshold represents how many rounds of amplification are required to detect COVID-19 RNA in a sample. More cycles mean less copies of virus in the sample hence there are concerns about being overly sensitive.
>
> However, this is a very complex issue. There is good evidence that when more than 24 to 30 cycles are required to detect virus the virus concentration is so low that it becomes difficult to cultivate the virus. However the cells used in the laboratory to cultivate the virus aren't equivalent to the cells in the *nasopharynx or the lungs in people. So just because one can't culture the virus in a laboratory that does not mean that it won't transmit. Many believe that with low copy numbers (high CT) values the virus is not likely to be transmitted.*
>
> But it is also important to understand that it is not that the test sensitivity is being inflated, rather having a very sensitive test helps address missing infected people because of poorly collected samples (collecting adequate samples is difficult, and samples such as saliva typically have less virus especially in outpatients).
>
> In the literature and first hand we have seen a number of cases of COVID-19 in British Columbians where the person is early on during their infection course and the initial sample had a very high CT value ~35 (low virus RNA concentration) and the next day the CT was ~14 (high virus RNA concentration). Setting the detection threshold to [*sic*] low seems appealing until one misses that early case that can transmit infections to multiple people. [italics, mine]

So, in other words, BC CDC recognizes that they are on the very high end of detection, but feels they can balance the resulting high false positive rate by their worries about going too low and by their reliance on a particular cell culture method.

As for the statement that the cell cultures used by some researchers may not reflect the ability of low levels of actual virus to infect cells of the nasopharynx or lungs, it's a simple problem to solve: Go to a cell culture repository, such as American Type Culture Collection (ATCC; at

https://www.google.com/search?q=atcc&rlz=1C1CHBF_enCA816CA816&oq=atcc&aqs=chrome..69i57j0i67l4j0l3.4847j0j7&sourceid=chrome&ie=UTF-8) and get the right kind of cells. It's easy and I did it in five minutes: Open the website, go to Cell Lines for COVID-19 Research, find the section on Primary Cells you want, then take your pick. It is literally about that hard. All of this again is begging the question of why BC CDC chooses not to find the cell types that they claim they need.

It is worth noting in regard to the overall discussion about PCR that the co-inventor of the PCR, Nobel Laureate Dr. Kary Mullis, completely agreed that running too many cycles allows one to find anything that one wants to find, whether it is meaningful or not (Mullis et al. 1986).

All of the above raises the next question: Does the Provincial Health Officer, Dr. Bonnie Henry, really not know the broader literature, such as the Jaafar et al. study, or is there something else here, apart from a rickety bureaucracy, that the rest of us are missing? Wouldn't a better Ct have been in a sweet spot of detection within acceptable false positive and false negative levels, for example, somewhere between 20 and 25?

Serology

Another way to test for COVID-19, or any other disease, is to use antibody methods. In other words, to look at antibodies created by your immune system in response to infection with some pathogen, such as a virus. However, this approach is, at best, a surrogate marker because positive antibody levels do not tell you if you are immune, merely that your immune system has responded at some level. Antibody serology also does not measure the power of response of the body's immune memory cells. In context to COVID-19 case evaluations, serology can, however tell you if the person has encountered the pathogen. Antibody screening does not tell whether the person has an active infection. It can only detect whether there has been one in the past.

A key concern with antibody testing is that the testing "kits" have high sensitivity (that they have the power to detect relatively small numbers of antibodies to the pathogen in question) and specificity (that they have the power to focus on antibodies addressed to a particular pathogen). However, a test that is sensitive to every conceivable pathogen, to many of them, is relatively useless for identifying infections by a particular virus such as SARS-CoV-2. Both sensitivity and specificity are required for valid tests and are not easily, and certainly not always, achieved (Deeks et al. 2020).

What this means is that to have any valid predictive value, any such test needs to detect the particular antibodies to some disease with high levels (*sensitivity*) and not confuse them with antibodies to some other pathogen (*specificity*). Both are important but the latter is crucial. As a matter of fact, the power of any serology antibody test to detect a particular type of infection as distinct from many others that may be involved is relatively unimpressive (Mboumba Bouassa et al. 2020). Serology can easily give false results. Some antibody detection products are better than others and finding those that give reliable outcomes is not easy, particularly in the COVID-19 pandemic.

One particular example, as cited above, involved the much criticised antibody tests conducted by John Ioannidis and colleagues in their initial screening for antibody levels for COVID-19 in an attempt to derive the correct percentage of the population affected by COVID-19 (Bendavid et al. 2020). The criticisms of this work seemed to arise mostly from a disagreement with the ongoing mainstream narrative about how deadly COVID-19 was, rather than the methods employed. In

another study, one comparing results of serological tests with confirmed PCR cases of persons infected with SARS-CoV-2 but not hospitalized — to avoid the bias of selecting only severe cases of infection — the results were not reassuring:

> Of LFIAs [lateral flow immunoassays, a kind that can be used on a world-wide scale] assessed in both clinic and laboratory, finger-prick self-test sensitivity varied from 21% to 92% versus PCR-confirmed cases and from 22% to 96% versus composite ELISA [enzyme linked immunosensitive assay; test kit] positives. Concordance between finger-prick and serum testing was at best moderate (kappa 0.56) and, at worst, slight (kappa 0.13). (Flower et al. 2020)

Given that the "finger-prick" testing and "serum testing" both involved the blood drawn from the same individuals the degree of "concordance" between the distinct methods was incredibly weak. Whereas it should be nearly perfect (kappa = 1) — because the same individuals were tested — in fact the measured level of kappa suggest actual agreement at about 50% to 55% of the assays (Anon 2020a).

To Halt the Spread of COVID-19, How Effective Are the Measures Taken?

Different countries chose different strategies to halt the spread of COVID-19. Typically, these involved various levels of lockdowns of movement and association, mandates for masks, and other health measures. One fairly fierce debate is whether Sweden, which did a minimalist protocol for COVID-19 containment fared better than other Western European countries which opted for harsher measures. The initial results seemed to suggest that Sweden had failed compared to other countries in the region which had more stringent measures (Habib 2020; Pearce, Lawlor, and Brickley 2020). That view is now up for debate, especially if Sweden got the entire pandemic over at once and is not now facing a serious second wave unlike their neighbors (Habib 2020a). At the time of this writing, these results are still not available.

A similar question can be asked about China where the pandemic began. How many died and did they get control of the pandemic with a harsh lockdown regime? The answer is that we don't really know.

Masks

The key question here to ask is this: Does wearing masks by the population at large help slow COVID-19's spread, or can it hurt the individuals who do so?

The common wisdom, and that promoted heavily by the mainstream media and health officials, is that mask wearing definitely helps and can't possibly hurt. This leads, in turn, to members of the public "virtue signalling" or even actively shaming those who won't, or can't, wear masks with a comment that many of us have heard over the last year: "Just wear the damned mask already."

But is it even true that mask wearing actually helps slow transmission. The answer is maybe yes, maybe no, and it depends.

This is confusing to say the least and much of this confusion arises from assuming that all masks are equally effective at blocking viral transmission in either direction. In the following, let's look at the main types of masks in order of effectiveness, from lowest to highest, where the main criterion is

viral permeability due to the materials used in mask construction. The second criterion is how the masks are worn.

The most common mask types seen in public are the varieties of cloth masks that now come in a variety of designs and colors. These are typically made of one or two cloth layers of various types. Depending on the weave of the cloth mask, these might diminish viral transmission in either direction by blocking large droplets or even phlegm. That, of course, would be good. Is that, however, how most COVID-19 is transmitted? No, it's rather mostly transmitted by the smaller, longer traveling droplets called aerosols. Cloth masks do pretty much nothing for these latter droplets and the viruses that might go in either direction, that is from wearer to someone else, or vice versa. Canada's federal health officer, Dr. Teresa Tam, recently suggested that people who wear cloth masks sew an additional third layer of some material, such as diaper material, into their mask (Perreaux, MacDonald, and Walsh 2020; Possamai 2020).

Next up are surgical masks. As with cloth, these are several layers thick, usually of 3 layers as described in an advertisement on the web: a melt-blown polymer, such as polypropylene (which though it may not be harmful to human wearers, is not precisely environmentally friendly over the long term), in the middle between an inner and an outer non-woven fabric. Is this sort of mask able to stop viral transmission? No. The very same conditions apply as for cloth masks: a surgical mask is not designed to stop viral transmission in either direction. As the name implies, these masks are worn during surgical operations to keep material from the wearer out of the sterile field of the patient's open wound; it also serves to keep blood and tissue from the patient out of the mask wearer.

KN95 masks resemble surgical masks. These are Chinese knockoffs of the N95, discussed below. As the name implies they are listed as being 95% effective in stopping viral transmission. This may not, always be correct, though N95 masks are about 95% effective at stopping viral transmission to the wearer if they are fitted properly. Since these masks allow the wearer to breathe freely out, they do not stop viral release to the outside. Like the cloth masks and surgical masks, they will stop large droplets/phlegm from coming out.

Finally, there are the more elaborate masks and face shields, and full body covering sealed at hands and feet, much like Hazmat suits, designed to keep pretty much everything out. These will do just that, but are obviously not realistic for COVID-19, but are rather intended for a BSL-4 containment facility.

One thing to remember with masks of those described above is that covering one's nose and mouth will prevent bacterial and some viral transmission, but since both can also enter through the eyes, this protection is limited far more than most proponents claim. In addition, if one touches any fomite — object or surface containing the virus — and then touches the mask, the entire benefit, if any, of the mask is compromised.

An argument can be made that, just like the usually low effectiveness of influenza vaccines, anything is better than nothing. Well, maybe not: in their paper about the granting of emergency use of COVID-19 vaccines, Singh and Upshur (2020) noted that studies of efficacy of the influenza vaccines have actually never been done at all.

> Despite influenza vaccination becoming routinely recommended for people aged 65 years or older in the USA, whether it lowers mortality is not certain because randomised trials measuring this outcome have never been done.

The argument that low levels of efficacy might be tolerable, could conceivably be true if there were no potential harms associated with the vaccines themselves, but that cannot be correct (Children's Health Defense 2020; Smout 2020). It certainly has not been with the influenza vaccines (Eaton et al. 2018; Oller 2020). Also, in the fear of the moment we should not forget the lessons of Thimerosal and the synergistic interactions of that compound and others, including, for instance, aluminum adjuvants (Luján et al. 2013; R. F. Kennedy 2014; Anaya et al. 2015; Kennedy et al. 2016).

Are there any possible health consequences to mask wearing? For the surgical, KN95 and N95, probably not, apart from whatever psychological issues a person may have now or in the future (Szczesniak et al. 2020). However, with the cloth masks the harm is more physical than purely psychological: As you breathe into a cloth mask over the space of hours you are depositing your respiratory system's bacteria into the warm, moist inside of the mask. Bacteria love such environments and will happily start to breed. You now inhale these bacteria, some of them pathological and in more abundance than before. What might be a consequence? A greater colonization of your respiratory system seems likely. It may be important to observe that the primary cause of death in the "Spanish flu" 1918-19 pandemic involved secondary bacterial pneumonia (Brundage and Shanks 2008; Morens, Taubenberger, and Fauci 2008).

It gets worse: virus infection also increases as described in a 2015 article (MacIntyre et al.) in the *British Medical Journal* (*BMJ*). The editor of *BMJ* decided to add an editorial note to the original article showing that the authors had decided in the face of COVID-19 that any kind of mask against the virus was better than nothing:

> The authors of this article, published in 2015, have written a response to their work in light of the COVID-19 pandemic. We urge our readers to consider the response when reading the article. (see the article at https://bmjopen.bmj.com/content/5/4/e006577.responses#COVID-19-shortages-of-masks-and-the-use-of-cloth-masks-as-a-last-resort).

In other words, forget what the original article said, that was then, this is now, and COVID-19 hysteria trumps previous data if it doesn't conform with the current official panic levels.

Is there other evidence from the medical literature that most mask wearing actually diminishes viral, or particularly COVID-19, spread? Apart from the above, no, not really. The Mayo clinic released a document called *COVID-19: How much protection do face masks offer?* (Mayo Clinic Staff 2020), basically reiterating the discussion of mask types and efficacy, stressing that masks are *only part* of the overall process, including hand washing, for stopping viral transmission.

Tom Jefferson and Carl Henegan, both members of Oxford University's Centre for Evidence-Based Medicine recently penned two articles on the subject of mask effectiveness against COVID-19 spread. Jefferson used to be the head of the Cochrane Collaboration's Vaccine Field group that used to take a generally balanced look at vaccine issues (Enserink, 2018).

Jefferson and Heneghan (2020) evaluated the evidence for the utility of masks against COVID-19 and concluded that there is a general lack of evidence in their favor. This doesn't mean that masks might not be effective to some degree as discussed above, just that the evidence is not yet all that

solid. In a more recent article, the same authors reviewed a current small Danish RCT study called DANMASK-19, that failed to find a significance in COVID-19 infection rates between mask wearers and those who didn't wear masks (Heneghan and Jefferson 2020).

Looking at the DANMASK-19 study in more detail (Bundgaard et al. 2020) it is easy to see why Heneghan and Jefferson came to this conclusion. In this study, the authors conducted a gold standard controlled clinical evaluation. In brief, they enrolled 3,030 participants who were instructed to wear a standard 3-ply surgical mask when out and about for 4.5 hours per day. Controls consisted of 2,994 similar persons who did not wear masks. Of the first group, the authors eliminated those who did not consistently wear their masks for the required time or in the right way. At the end of the trial period, all participants were tested for COVID-19 by their symptoms, as well as by PCR and antibody tests. The results: both groups showed about a 2% COVID-19 infection rate. The rate of infection noted here is marginally higher than that observed by Moderna in their second press release on their efficacy trials (Moderna TX, Inc. 2020), and likely reflects phases of the pandemic, as well as what is happening in different countries around the world.

The authors acknowledged a number of limitations to their study, one being that there was no control for what the participants were doing the other 19.5 hours per day. The journal also featured 17 comments by readers, some of which were worth examining. For example, one commentator wrote that there was no control for interactions with family members during those non-masked hours. There are two take home messages here: one, as noted by Bundgaard et al. (2020), mask wearing alone is not going to change the outcomes and indeed this is precisely the problem that has to be acknowledged by governments. Secondly, the number of people infected in both cases, coming in at 2% hardly describes the media's tendency to portray COVID-19 as a massive modern scourge. If the infection rate is about 2% and we take the highest estimated death rate of 3.4% coming from the WHO early in the epidemic (Ben Swann 2020), out of 100,000 persons in the population, on the average, we should estimate about 7 chances in 10,000 of getting and dying from a SARS-CoV-2 infection, regardless of whether or not you wear a mask.

As Jefferson and Heneghan stressed in their first article, the way that medical and lay people evaluate the efficacy of masks, overall, is very much in keeping with politics rather than science. As I argue in my book, when people are thinking about COVID-19, and even more generally when the discussion is about vaccines, the "trust the science" perspective makes the science out to be whatever the politicians and media are reporting. "Science" becomes whatever preconceived beliefs the poloticos and media are serving up today.

Another issue, at least here in British Columbia, is that the masking policies seem capricious: Masks are now required for adults inside any public building, but not for anyone under 12 years old. Are the medical authorities stating that children can't get COVID-19 and thus cannot transmit it? If so, this is a contradiction to what they have said throughout the pandemic.

Social distancing

Social distancing is the notion that if people stay a minimum of 2 meters, roughly 6 feet, apart from each other, then a person infected with a virus can't spread the virus to another. As described in a recent publication (Jones et al. 2020), this 2-meter number, a vast oversimplification of the actual

facts about virus dispersion, arose from an experiment done more than a hundred and twenty four years ago using methods that could not distinguish particle size and distribution accurately (Flügge 1897). More realistically, the actual distance measurements depend on the size of the particles released, that is larger ones as well as aerosols, and ambient conditions such as wind, temperature, etc. Taking a middling position at 2-meters may seem like a reasonable alternative if you want to avoid the most common infection zone, but in reality, the rule is arbitrary. Nor does it take into account virus particles on fomites, or what happens within homes where presumably a family is not expected to observe any such distancing. So on the one hand it seems to be something we can all do to limit the spread of COVID-19, or any other virus, and on the other simply a way for the authorities to signal to all of us that their regulations show that they are on top of the problem. Of course, it should also be noted that the demands for 2-meter spacing tend to be ignored if the same authorities have sympathy with events involving masses of people, such as with the various Black Lives Matter (BLM), demonstrations in the U.S and Canada, or if they don't with groups protesting *the lockdowns*. Accepting that BLM is protesting *en masse* for a very valid reason, the fact that our own health authorities allow them to do so while condemning other groups, simply reveals that the 2-meter policy is quite capricious, with the key variables being politics and the likelihood that enforcing restrictions would lead to protests getting out of control. In other words, this is not about medical practice, it is about population control. The fact that the media generally go along without question merely emphasizes the extent to which the media have become spokespersons for agencies of the State rather than actually doing real journalism.

Lockdowns

This brings us to lockdowns. Do they work? The answer, as with masks, is yes, no, and maybe. How can this be? The yes part is simple: if you keep everyone away from everyone else, any infected people will not be able to infect others. Eventually, those ill who recover will gain at least temporary immunity and not be able to infect others. There are various caveats to this, however. The first obvious one is that the longer you do it, the greater likelihood of economic disruptions that will tend to cascade as we've seen around the world. If you want to crash an economy, then this might be the way to go. A key question is how long do you wait before removing the lockdown? Is it the standard quarantine period of 14 days? If so, how does one explain the second COVID-19 wave in countries like Italy that were completely locked down and whose borders were closed. You can't, unless you also postulate secret reservoirs of virus that are somehow evading the expected timeline for the infectious phase. The standard answer often given for the difference is that in comparing Italy and China, the first was slow to lock down, the latter did it sooner in Hubei province. But Hubei is part of China and once the lockdown there ended, the rest of the population of China could go to Wuhan and those in Wuhan could go out. Maybe, but to accept this one would also have to accept that no one at all outside of Hubei province was infected with COVID-19. This last is patently absurd given that the virus was supposed to have infected the world starting in Wuhan.

What about Sweden? They didn't lock down, but tried to find a middle way. Did they succeed to control COVID-19 with much more modest measures, or not? Did they get a second wave or did they basically get it done all at once? The emerging picture suggests that they did not (Habib 2020a), although more than anything it calls into question the understanding of how herd immunity actually works, either for disease epidemics in general or following mass vaccination.

The next thing to consider with lockdowns is what else happens while people are locked down. For example, the economic costs and the inevitable increase in poverty or in general indebtedness as most North Americans live paycheck to paycheck, and are not even close to parity with government handouts during the lockdowns. Never mind the failure to treat other medical conditions — ironically, including kids not getting other vaccines on the CDC schedule — the psychological impacts on everyone, maybe particularly children and the elderly, the increasing levels of depression and suicide, child and spousal abuse, drug overdoses, and more. If we were dealing with a truly horrible pathogen such as Ebola or Marburg virus, then full lockdown measures might indeed be the better option. But as we aren't, as shown in the above section on real cases versus fatalities, then a full lockdown is not in anyone's best interests, apart maybe from those who sponsored and stand to profit from the upward flow of wealth in the Great Reset (see the next article following mine in this issue).

Monitoring

The monitoring of COVID-19 cases, including by "contact tracing" has been a train wreck from a scientific perspective. Contact tracing involves determining if someone has COVID-19 and then locating and testing everyone that the "infected" person has been in contact with, including their families. At a superficial level, this seems like a straightforward way to control the pandemic before it spreads further. But, as cited above, if your confirmation is an RT-PCR test in which you have set the cycle number at or above 35, all you generate are meaningless false positives. If your goal is something besides actual disease control — say, for instance, to scare everyone in the world into taking one of the coming SARS-CoV-2 vaccines — this is peachy. If, however, the real concern *is* disease control, "contact tracing" is expensive, invasive, and is quite certain to do more harm than good. In this connection, consider the cost of false positives from the perspective offered by James Lyons-Weiler in the fourth paper in this issue.

Reporting and snitching

If the authorities are hoping to make ostensibly free societies conform to the former German Democratic Republic model, this is one way to do it. If that is not what you want, then such recommendations are not for the benefit of anyone but the State. Does what happened in Germany leading up to and during World War II ring any bells?

Vaccine Passports

This idea is increasingly being floated by various entities, including governments, airlines, and others. The idea here is that you will have some sort of electronic device that has recorded your COVID-19 health status: either you have had a vaccine for the disease, or you have had a negative PCR test. If you are listed as "green" you are good to participate in "normal" life. If you aren't, or will not comply with the vaccine or the test, then you will have a "yellow" or "red" status and you won't be allowed to buy or sell, or travel.

The obvious flaws in such a health passport scheme are the following: First, since vaccines tend to have limited effectiveness over time (secondary vaccine failure), how often do you need to get tested? What about whether the vaccine didn't work in the first place (primary vaccine failure). Will

you now have to have an antibody test to see? Will you have to be revaccinated if not? How often will your "Health passport" have to be updated? This is the sort of thing that various corporations will love, as well as State bureaucrats whose lives revolve around making their fellow citizens functional prisoners. Since the above flaws in testing will be huge, it clearly is not a health measure and cannot accurately tell us who is infectious or not. Rather, this is clearly a control measure.

Legislation

British Columbia recently passed Bill 19 in the provincial legislature — providing "broad new emergency powers" measures allowing the government to "change any legislation during an emergency, without any oversight form the public and without approval from the legislature" (Macauley 2020 — mirroring similar legislation in other jurisdictions (Kate Ryan-Lloyd, Clerk of the Legislative Assembly 2020; Macauley 2020). Here we have the purest expression of the phrase "state of exception".

COVID-19 vaccine mandates

In response to the "pandemic", the clarion call for vaccine mandates rings out in various legislatures and in the media. As I point out in my book, in a chapter dealing with the ideology of vaccination, one way we know that we are dealing with a cult religion is that *everyone* joins the cult either freely, or they are compelled to join if they don't want to do it. Either way, they must join. As an aside, I have never once heard those opposed to any aspect of vaccines take a similar extreme position on the negative side: That everyone absolutely must refrain from being injected, or that all vaccines must be banned. This is a fundamental difference between cult behavior and free choice.

The 2015 measles outbreak in Disneyland and the later wave of supposed measles outbreaks in 2019 spurred calls for mandatory vaccination, often for infectious diseases other than measles. The panic associated with COVID-19 has amplified the calls, reflecting the near panic that COVID-19 monitors have generated. We can only expect the demands for vaccine mandates to accelerate for two reasons: first the fear generated is contagious and real; and the second reason is that when authorities realize that they are not achieving anything close to "herd immunity" (because nowhere near the 80% infection rate predicted by Neil Ferguson of Imperial College in London is occurring), they will impose laws or constraints on buying and selling that will force the uptake of vaccines. To hell with voluntary uptake. In fact, any actual "herd immunity" in human populations is never possible with vaccines at all because of secondary vaccine failure — whatever fraction of the population has yet to be infected in order to develop natural immunity is always prevented from acquiring it by forced vaccination programs with a significant rate of secondary failure.

It is obvious, however, from the brief history laid out in this paper that no COVID-19 vaccination program was ever intended to be only for kids. Whatever shape it may take in terms of the number and types of approved vaccines, the program will be for the whole population. Once the authorities see that they can't get there with the carrot, out will come the stick. As I've discussed, this will not likely be represented as forced vaccination, but rather the withdrawal of your freedom to enjoy your routine daily life at restaurants, bars, movie theaters, and malls, getting on an airplane, riding in a taxi, or just driving about and buying gasoline in your own car and in your own country, etc. The hope by those in authority is that the withdrawal of your privileges will force those on who might

prefer to wait and see, or simply to say no thanks to the vaccine(s), to comply with the global technocratic surveillance systems that are now in the phase of being patented and manufactured.

But do the same authorities not realize that all of the current vaccine candidates — two of them coming off the shelves and into the marketplace from Pfizer and Moderna as we speak — already demand at least two shots initially and then likely will require boosters at some unknown interval for the rest of a person's life. The manufacturers selling the vaccines, of course, will love this.

What will be less to like is the almost certain increase in adverse reactions that can be predicted. What then? It will be Gandhi's march to the sea paradox in that any action taken by the authorities using their meager understanding of the disease will be the wrong one: in attempting, certainly with limited success judging by viral vaccines of the past, to reduce the spread of the pathogen of the day — something that is about as likely to change tomorrow as the weather — they are virtually certain to accelerate the number and severity of autoimmune reactions and chronic noncommunicable diseases (Calitz et al. 2015). Pick one; or better yet, don't go down this path at all, but telling that to a politician or medical bureaucrat is about as useful as talking to a wall, maybe less.

Social and medical consequences of COVID-19 control measures

In addition to the above control measures, medical and political authorities in large measure have relied on fear to drive many otherwise decent people to act as *de facto* medical guardians of everyone else. Aspects of this were seen in what was termed "social shaming" to blame people not fully complying with the regulations *du jour* for any COVID-19 surge or even death all the while virtue signalling by mask wearing — regardless whether the mask worn did anything positive at all. This last was common.

What were the impacts of such actions? As fully predictable, these included making children more fearful of others and their world, a feature that will surely come back to haunt us in the future. They including making addicts so fearful of other people that they neglected to use so called "safe injection" monitored sites, at least here in British Columbia, leading to a significant increase in overdose deaths (Rodda, West, and LeSaint 2020); increases in spousal and child abuse (Brown et al. 2020; Thomas et al. 2020); increased morbidity and mortality due to people not feeling safe or being willing to access medical care (Dave, Seoudi, and Coulthard 2020; Devi and Kostova 2020; Sher 2020); and the impact of social isolation on the elderly (Robb et al. 2020). In addition, the increased levels of financial distress much of the population suffered, including job loss with loss of income, exacerbated much of the above (Witteveen and Velthorst 2020).

Gaslighting the "proles" for fun and especially profit

A widely stated view by the medical and political establishments is that "normal" returns once a vaccine is available (and taken by most people). Note that the companies making the COVID-19 vaccines — Moderna (mRNA-1273), Pfizer (BNT162), AstraZeneca (AZD1222), and Johnson and Johnson (Ad26, Cov2.S) — have all received liability protection from various governments as part of the price for making their future vaccine available to those countries (US Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research 2020; Singh and Upshur 2020).

The first two SARS-CoV-2 vaccine producers (of the previous paragraph) are using messenger RNA (mRNA) platforms for their vaccine. Basically, mRNA platforms are novel, largely experimental, means of immune stimulation in which the mRNA for the crucial COVID-19 spike protein (the part that allows the virus to attach to ACE-2 receptors) is encapsulated in lipid nanoparticles. The vaccine containing this construct is injected into the muscle and is meant to move into cells, come out of its lipid envelope, bind to organelles called ribosomes and thus cause the mRNA/ribosome complex to generate the spike protein. From there, the protein is expected to migrate to the surface of the cell where it will trigger an immune response, ideally by both B and T cells, as well as eventually creating neutralizing antibodies.

Earlier human mRNA vaccine studies have demonstrated a range of issues in humans and animals. In earlier human trials Alberer et al., (2017) of CureVac used an mRNA vaccine against rabies, and conducted and reported on a Phase 1 trial with 101 human volunteers examining the safety and tolerability of that vaccine. The study ran from 2013 to 2016 and reported only mild to moderate adverse effects and good immunogenicity, but not if the vaccine was injected intramuscularly. The researchers did not examine the volunteers over an extended time period for safety. Bahl et al. (2017) from Moderna looked at an mRNA vaccine for influenza across a range of species, including humans, primates, ferrets and mice. In all cases they found a strong initial immune response. In the animals used, no evaluation of any impact on organ systems was reported. Similar results were found by Edwards and colleagues in two different studies (Abu Raya et al. 2017; Edwards et al. 2017) from Sanofi-Pasteur, but again no safety data were reported.

Other animal studies, in general, made similar claims: high levels of immune response, but there were some concerning aspects in relation to safety. Among them were acute respiratory syndrome (ARDS), migration of the construct from the injection site, and antibody dependent enhancement (ADE). For example, Moderna's recent rhesus macaque monkey study used 24 male and female animals divided into groups of 3. In the vaccinated groups they used either the 10μg or 100μg dosage of the mRNA vaccine. Animals were injected twice at time 0 and 4 weeks later, then challenged by being exposed intranasally to live COVID-19 virus. The study claimed that the vaccinated groups showed effective prevention of infection of the lungs in both groups put only in the nose with the 100μg dose. In both cases, the claim was that effective production of neutralizing antibodies occurred along with increases in T1 helper cells. However, the study also noted that monkeys do not get severe COVID-19 disease. In addition, the study did not examine any possible adverse effects beyond presumably the animal's behaviors, assuming that was done prior to sacrifice (Corbett et al. 2020). A prior mouse study (Corbett 2020) also from Moderna and only posted to a pre-release journal website (i.e., not peer reviewed), reported the same high antibody response, but again no long range safety data were obtained.

Another problem with mRNA vaccines is that they require extreme cold storage before injection in the range of at least -20C° to -80°C. This makes it difficult, albeit not impossible, to transport effectively *en masse* to those who may want it, or for whom the government wants it. This also calls into question how labile the vaccine may be, both the mRNA itself and the lipid covering, in the long run inside the human body. This may be one reason why various entities including the NIAID have suggested that multiple booster doses may be required (Jaimie Etkin 2020; Woodward 2020).

The vaccines being developed by the other companies above, as well as the Chinese company Sinovax and the Russian vaccine Sputnik V, are so-called viral vectors vaccines. Viral vectors vaccines, as discussed in my book, take a weakened virus for another disease and incorporate the protein that you want to generate the immune response, in the case of COVID-19 the spike protein, into it to trigger an immune response. These vaccines are more stable than the mRNA vaccines, but are also largely experimental.

Human Trials: Efficacy Data for Moderna

The first mRNA vaccine efficacy data coming out of Moderna's Phase 3 study and similar claims by Pfizer have been widely touted in the media and by people like Anthony Fauci. For this reason, it is important to realize just how such numbers can be manipulated to make outcomes seem more favourable and thus palatable to the public in an attempt to boost future vaccine uptake.

In the initial data cited in a press release on November 16th, Moderna claimed an efficacy of 94.5% of the vaccine in preventing COVID-19 infection. The Phase 3 trials had enrolled 30,000 people in a 1:1 ratio of treated versus controls in what Moderna claimed was a double-blinded study. A double-blinded study is one in which neither the participants or the experimenters know who gets the placebo or the treatment.

Let's assume for a moment that there were 15,000 in both the control arm (the claim is that the controls actually received a saline placebo, rare as that is in vaccine trials) and 15,000 in the treatment arm of the vaccine mRNA-1273 given at the middle dose regime of 100μg based on their Phase 1 trials. Two weeks after the second injection, Moderna monitored the participants for 2 months out in the real world and recorded those who became infected with COVID-19 (https://investors.modernatx.com/news-releases/news-release-details/modernas-COVID-19-vaccine-candidate-meets-its-primary-efficacy). The primary endpoint of this monitoring gave 95 total infections, 90 in the control group, 5 in the vaccine group. How the infection was determined was not specified in their press release, but would be useful to know in light of issues discussed in the earlier sections of this paper. One would also like to assume that diagnosis was not simply by a physician's subjective observation of symptoms.

If the numbers are correct, and remember this is science by press release with no raw data included, then the RR indeed comes out at 94.5% efficacy. Put into percentages, the controls had a rate of infection of 0.006% and the vaccinated group 0.00033%. How about severe cases of COVID-19 found in the control arm? In the same approximately 15,000 control subjects, 11 were diagnosed as having a severe case of COVID-19 or 0.0007%, or about 12% of the total group of the controls were infected.

Two weeks later in their November 30th press release, Moderna updated the previous report for a new efficacy calculation of 94.1% with 196 cases of COVID-19. In the control group, the number was 185 cases (0.012%) and 11 cases in the vaccinated group (0.00073%). Severe cases in the control group were 30 (0.002%) and included 1 death (0.000067%), compared to the number of U.S deaths (269,000 as of December 2020) in a population of 328.2 million: 0.00082%, the latter number suggesting once again that the CDC's death rates from COVID-19 may be inflated, in this case by at least a factor of 12.

In the space of two weeks, the rate of infection in the control group had gone from 0.006 to 0.01; in the vaccinated group the number of cases had doubled, thus accounting for the decreasing efficacy reported. The severe cases in the control group had gone from 0.00073% in the first report to 0.002% in the second.

It all sounds very dramatic at first glance, but it may also be smoke and mirrors given the comparison of the percentages at the two time points in the two groups: The infection rate in the controls hovered around the level of influenza of a mild to moderate year, in this case the year 2018 to 2019. Using this year so as not to confuse any influenza cases with COVID-19, to get a rate of influenza infection in the US population (328.4 million of 0.01% (https://www.cdc.gov/flu/about/burden/2018-2019.html#:~:text=vaccination%20uptake11.-,Conclusion,2012%E2%80%932013%20influenza%20season1).

In the control group the severe cases had almost tripled, but were still a tiny part of the total. The only real bright spot actually here for Moderna is that their vaccinated group had no severe cases as yet. It is also important to keep in mind that these data do not reflect certain populations who may be included in a general vaccine program: pregnant women, infants, children, and adolescents.

One thing that may be emerging from these numbers is that they may actually show us the real percentage of the population at risk overall from COVID-19 at about 0.01%, as well as those who will become severely ill and/or die. But in order to save that 0.002% of the population, how many people would one have to vaccinate and what would be the tradeoff against possible adverse effects?

Looked at from a more skeptical perspective, both groups had a rough doubling of COVID-19 infection, which may lead to speculation that the vaccine does not actually prevent the disease but merely slows down its expression. Peter Doshi, an Associate Editor of the *British Medical Journal*, writing in a medical blog about the Phase 1 data (https://blogs.bmj.com/bmj/2020/11/26/peter-doshi-pfizer-and-modernas-95-effective-vaccines-lets-be-cautious-and-first-see-the-full-data/) urges: "Let's Be Cautious": Pfizer, Moderna Need to Release More Data to Back Up Claims of "95% Effective" Vaccines. Doshi states also the obvious:

> Let's put this in perspective. First, a relative risk reduction is being reported, not absolute risk reduction, which appears to be less than 1%. Second, these results refer to the trials' primary endpoint of COVID-19 of essentially any severity, and importantly not the vaccine's ability to save lives, nor the ability to prevent infection, nor the efficacy in important subgroups (e.g. frail elderly). Those still remain unknown. Third, these results reflect a time point relatively soon after vaccination, and we know nothing about vaccine performance at 3, 6, or 12 months, so cannot compare these efficacy numbers against other vaccines like influenza vaccines (which are judged over a season). Fourth, children, adolescents, and immunocompromised individuals were largely excluded from the trials, so we still lack any data on these important populations.

Doshi is right, of course, and his critiques equally apply to the efficacy studies of Pfizer which claimed a ratio of 162 COVID-19 infected people in the control group versus only 8 in the vaccinated group in a total of 44,000 people, 0.007% versus 0.00036%, both numbers remarkably close to those of the first Moderna report (Moderna TX, Inc 2020). He also raises the concern about the blinding in the study given that the adverse effects reported by actual vaccine recipients could have clued them to which group they were in and thus modified their behaviors.

Efficacy Data Claimed But Not Published

The truth is that we won't be able to independently review the efficacy data until they are provided in peer-reviewed publications, ideally with raw data supplied.

Efficacy data for Pfizer

Pfizer's combined Phase 1 and 2 data claimed high antibody titres after both doses with antibody levels rising higher after dose 2. In the later Phase 3 study, their calculations of efficacy of greater than 90+% were based on approximately 18,000 people in each of the vaccinated and control arms (and the nature of the placebo injection is still not known). In this report Pfizer claimed that after following for 2 months, 8 of the vaccine-treated group developed COVID-19 compared to 162 in the control group.

These ratios resemble those of Moderna and are the basis of their efficacy report. As it currently stands, at least from a regulatory viewpoint, such data allow Moderna and Pfizer, and no doubt eventually the other companies, to hype the efficacy of their vaccines while smoothly side stepping their actual dangers for potential short and long term adverse effects on account of novelties in this disease. In actuality, those who have been saying that COVID-19 infection is at about the same level as influenza seem to be correct.

Johnson and Johnson

From this company we receive more "science" by press release: they claimed 98% seroconversion but with no efficacy calculations as of October 4, 2020 (https://www.jnj.com/johnson-johnson-posts-interim-results-from-phase-1-2a-clinical-trial-of-its-janssen-covid-19-vaccine-candidate).

AstraZeneca

In a press release on November 23, 2020 the AstraZeneca company claimed: AZD1222 vaccine met primary efficacy endpoint in preventing COVID-19" the company claimed (AstraZeneca 2020; https://www.astrazeneca.com/media-centre/press-releases/2020/azd1222hlr.html):

> One dosing regimen (n=2,741) showed vaccine efficacy of 90% when AZD1222 was given as a half dose, followed by a full dose at least one month apart, and another dosing regimen (n=8,895) showed 62% efficacy when given as two full doses at least one month apart. The combined analysis from both dosing regimens (n=11,636) resulted in an average efficacy of 70%.

As it currently stands, at least from a regulatory viewpoint, data not peer-reviewed by persons outside the employ of Moderna (and Pfizer), and no doubt eventually the other companies, to puff efficacy of their vaccines while underestimating the dangers of the disease, as well as the potential adverse effects of their remedies for recipients of the vaccines. In other words, those who have been saying that COVID-19 infection is at about the same level as influenza seem to be correct, while the potential dangers from the vaccines remain clouded.

Could all of these calculations be wrong? Sure, they could be, but then we would also have to reject all of Moderna's claims of efficacy for their vaccine. You can't really claim both, at least not honestly. Could the number of infected persons change with longer surveillance? For sure, and this

seems to be happening, but so too do the efficacy data. We will only know in the future if Moderna keeps sending these updates.

What other evidence might suggest that this is not wrong? One thing that supports the above numbers is a recent report from Johns Hopkins University that came out in an article on November 22, 2020 in the student paper, *The Johns Hopkins News-Letter* titled, "*A closer look at U.S death rates due to COVID-19*" (https://www.jhunewsletter.com/article/2020/11/a-closer-look-at-u-s-deaths-due-to-COVID-19].[Appendix). The article was retracted by the university on November 27th for potentially providing "misinformation" (https://www.jhunewsletter.com/article/2020/11/a-closer-look-at-u-s-deaths-due-to-COVID-19).

In the original article, writer Yammi Gu (2020) interviewed the author of a study by the director for the Master's in Applied Economics, Genevieve Briand. Briand had presented her data in a PowerPoint webinar. In compiling the data, she had used CDC data from mid March 2020 to mid September. Her conclusion was that the impact of COVID-19 on mortality across all age groups had not changed from previous years. Oddly, what had changed was the cardiovascular death rates along with other diseases. Briand had wondered why this might be so and came to the conclusion that somehow some disease numbers put out might have been "misleading". Could Briand have been wrong in her analysis and conclusions? For sure. But how is it misinformation when a scientific report varies from an official narrative? The same sort of response, weaponizing the peer-review process with retractions, should hardly come as a surprise (Shaw 2020). The Briand material was judged as apostasy and the newspaper report got retracted by those in control. The November 27th retraction notice was quick to point out that "*Briand is neither a medical professional nor a disease researcher."* If they cannot dispute the facts, they can always attack the messenger.

As of this writing, the death toll in the US cited above was somewhere near 269,000 people or 0.00082% of the population; in Canada, it comes out to be 12,470 deaths in a current population 37,742, 154 or 0.00033. Are these numbers reliable and valid with respect to the named "COVID-19 pandemic"? Maybe not in a statistical sense, but surely for the families of the dead they are significant in the usual way. Comparisons between influenza epidemics of the past, however, and the present "COVID-19 pandemic" are both subjective and dependent on many factors that have to be taken into account. Shifting the diagnosis, how significant are the cases of Alzheimer's disease in the U.S, for example? Turns out these are 0.0177, thus involving vastly more "cases" than even the highest estimates of infected persons with SARS-CoV-2. Apart from the families of those impacted by Alzheimer's, together with the physicians and researchers working on the disease, does anyone really care all that much? No, but why not? Are Alzheimer's deaths less significant than those attributed, validly or not, to SARS-CoV-2? One notable difference is that there is no expectation on the part of the media and big pharma of a vaccine for Alzheimer's prevention.

All that taken into account, the efficacy data for COVID-19 vaccine results still say nothing about the safety record of recipients of the experimental vaccines of Pfizer, Moderna or the other companies in the race to capitalize on the pandemic.

mRNA Vaccine Safety Studies: Moderna

Moderna's Phase 1 safety data, produced in a two-volume report of 1,015 pages were released to Aaron Siri following a Freedom of Information Act (FOIA) request to the US Department of Health and Human Services. It is titled *Safety Summary Report, Phase 1, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults* and was published by Moderna on June 2, 2020. Data were derived from the post vaccine medical surveillance of 85 participants of both sexes divided into 7 cohorts. There were no controls, as is typical for such "safety" studies.

Distinct cohorts in small numbers

All participants received two injections of mRNA-1293, one on the first day, the second 29 days later. All patients were followed up by physician visits on days 1, 2, and 4 after each dose, and afterwards at 3, 6 and 12 months after the second dose. Forty-five of these 85 individuals, ages 18 to 55, were divided into 3 cohorts with dosages of 25μg, 100μg, and 250μg of the mRNA construct. There was also a 56 to 70-year old group with 20 people and one at more than 71-year old age group with the same numbers. These latter groups received only the 25μg or 100μg doses.

In the first cohort of 45 participants, 32 (71%) had some "possible" adverse reaction(s) to the vaccine. They ranged from "mild", to "moderate", or "severe". At 25μg, 5 of 15 had adverse events; with the 100μg group 10 of 15; and in the 250μg group 12 of 15 had an adverse reaction at some level. In the 56-70 age cohort, 14 of 20 (70%) had "possible" adverse effects; in the 71+ age cohort had 10 of 20 (50%) of participants had potential adverse effects.

Moderna physicians decide which observed reactions were caused by the vaccine

Moderna physicians then decided which of the "possible" adverse effects were really from the vaccine. How they did so was not clear from the report and without knowing these details there is not much point in trying to evaluate non-related from vaccine-related events.

In this mass of data there are some take away messages: First, as the dose of the mRNA increases, the percentage of real adverse vaccine events appear to go up, an outcome that is not really a surprise in any dose-response function. The higher adverse effects in the 250μg group is likely a reason that this dose was dropped in the Phase 3 trials.

Crucial groups were not studied

The second point is that there were so many moderate and severe reactions overall, an outcome that will be far from trivial if Moderna's vaccine is put out to the general population, including to groups not studied in this study, namely pregnant women, infants, children, and adolescents.

In general, small sample sizes, as in these Phase 1 safety data, are prone to suffer from potentially large errors in interpretation. Some of this may be resolved by Moderna's Phase 3 trials, which will likely not be available for review prior to the expected roll out of the vaccine in the last month of 2020.

Based on the results of Moderna's Phase 1 safety study and the above cited efficacy data, Moderna recently applied for a Emergency Use Application (EUA) for the mRNA-1293 vaccine from the FDA. The EUA guidelines can be found at this URL, https://www.fda.gov/media/142749/download and they include the following conditions for application for an EUA:

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2. • The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

Pfizer has done the equivalent EUA to the British authorities based on their initial efficacy studies.

Safety Data from Pfizer

Two reports have come out on the safety of Pfizer's BNT62 mRNA vaccine. The first is by Mulligan et al. (2020; https://pubmed.ncbi.nlm.nih.gov/32785213/) published in July as a preprint (not yet peer-reviewed). The second was a Phase 3 safety and efficacy report (Pfizer and BioNTech 2020), not yet published, but put out to the FDA for EUA approval. This document was evaluated by FDA scientists. Let's look at each of those reports in turn.

Mulligan et al. on Phase 1/2

The study looked at 45 male and female participants, 18 to 54, in approximately equal numbers Safety and tolerability were followed for 14 days after the second of two doses: 10μg, 30μg; at 100μg there was only 1 dose. The groups are therefore small, particularly the placebo group (N=3 per dose group) and it is not clear what the placebo actually was.

Injection site pain was reported for all vaccine groups, some of it categorized as severe. Some placebo volunteers had minor localized pain at the injection site. The vaccine also induced fever in 75% of treated patients after the second dose with two participants experiencing high fever in the 30μg group. Some in these treated groups also experienced sleep disturbances, joint pain, headache, and fatigue. Also, lymphadenopathy (enlargement of lymph nodes) and four cases of Bell's palsy (inflammation of cranial nerve 7 (facial) were found in the vaccine groups versus none in the control group.

Pfizer's FDA Briefing document

Many of the same adverse effects were seen in the Phase 3 data as in the initial safety evaluation by Mulligan et al. The resulting tabulated Phase 3 data are summarized in their Tables 17/18 (18-55 age group and greater than 55 group, respectively) listing a range of adverse effects including fever,

fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, new or worsened joint pain, and lymphadenopathy (enlargement of lymph nodes). In a potentially serious twist, four cases of Bell's palsy were found in the vaccine groups versus none in the control group.

The latest interpretation of some of the adverse effects seen in the trials from both companies has all the flavor of trying to spin the outcomes to make them somehow seem like good results. Specifically, statements now coming out in the media quoting physicians is that any observed adverse effect simply shows that "the vaccine is working and your immune system is responding as it should". This might be true to some extent in that many conventional vaccines with live or attenuated viruses do have the capacity to create a mild version of the disease with the view that your immune system response will prevent a worse real response to a pathogen. This follows from Edward Jenner's original work and makes some sense. However, such cannot apply to an mRNA vaccine where no real infectious agent is present to give you the targeted disease.

The alternative explanation is not that the vaccine is effectively activating an immune response to fight a future COVID-19 infection, but rather that your body is responding to something toxic, and/or triggering an abnormal immune response, such as an autoimmune reaction. A suggestion of this comes from the Pfizer trials in which four of the vaccine recipients developed Bell's palsy, a weakness or even paralysis of the 7th cranial nerve pair (facial) that controls facial muscles. The impact on there is the result of inflammation that compresses the nerve. Bell's palsy has several triggers, including viral infection, and although it is usually temporary, it is not always so. These results, combined with higher levels of joint pain and headache in the vaccine recipients suggest that the mRNA vaccine used by Pfizer can have cartilage and neurological consequences in the CNS, both of which should alert us to the prospect that other longer-term consequences may arise with longer surveillance.

Pfizer also applied for, and received the equivalent EUA to the British authorities based on their initial efficacy and safety studies, both from Phases 1-3. Since then, their EUA equivalent from the UK and then a US EUA were granted before the New Year.

What Could Go Wrong with mRNA Vaccines?

In principle, not much, if we stay with the mainstream Crick model for DNA triggered protein synthesis. A laboratory created mRNA based on the genome of the COVID-19 virus should be simple: The injected mRNA now binds to ribosomes, the complex makes protein, and that protein is extruded from the cell to trigger the immune response. After this, the mRNA-ribosome complex is supposed to come apart, the mRNA is degraded and that's the end of it.

All good, and maybe apart from the adverse effects seen in both Moderna and Pfizer phase trials that's all there is to it.

What, however, if there is another, more accurate, model of how DNA transcription to protein works, one in which there are "recursive" feedback loops in what the Crick model considers to be a linear process, that is DNA to RNA to protein. What if instead, as in the Pellionisz (2008) model, feedback occurs at all levels: DNA to RNA and back, RNA to protein and back, and then protein back to DNA? Could the artificial mRNA have an impact on DNA? What then? It must certainly be

the hope — maybe prayer would be the better word — of the molecular biologists at Moderna and Pfizer that Crick was right and Pellionisz was wrong.

Insider Trading?

In a move that raised media and public eyebrows and even got the Securities and Exchange Commission involved (Derysh 2020; Durden 2020), executives at Moderna and Pfizer began dumping their shares as their press releases praised the emerging data and various health officials such Dr. Anthony Fauci, NIAID director and much of the corporate media piled on. As Children's Health Defense documented in a detailed evaluation of the COVID-19 pandemic (see the Children's Health Defense Team article in this issue of *IJVTPR* immediately following my article), such stock sales seemed to herald the foreknowledge of some greater plan. The CHD Team writes:

> … a few intrepid journalists have begun calling attention to Big Pharma's pandemic profiteering, even pointing out that "insiders at companies developing experimental vaccines and treatments . . . aren't waiting until they finish the job to collect their reward" (Wallack, 2020). An October piece in the *Boston Globe* cited the example of Moderna, one of the companies that has rushed a candidate vaccine into clinical trials (Wallack, 2020). It took Moderna a mere three weeks after Bill Gates' initial funding installment to send its first batch of experimental vaccine to research and patent partner, the National Institute of Allergy and Infectious Diseases (NIAID), leading to an immediate surge in share price of 28 percent (Lee, 2020; Loftus, 2020). By early April, Moderna's CEO had become an overnight billionaire, and by October he had sold nearly $58 million in stock (Tognini, 2020; Wallack, 2020). Meanwhile, Moderna's chief medical officer has been "systematically liquidating all of his company stock" — about $70 million — "in a series of pre-planned trades that have made him roughly $1 million richer each week" (Wallack, 2020). Thus far this year, company insiders have sold $309 million in stock versus under $2 million in 2019, fueling suspicion that they may be "downplaying possible obstacles to goose stock prices — and increase their personal profits" (Wallack, 2020). Also among those who sold Moderna stock options was Moncef Slaoui, the former Moderna board member and former GlaxoSmithKline executive who now heads up Operation Warp Speed (Rozsa & Spencer, 2020).

With all of the above, it is best to remember the quote usually attributed to Mark Twain: "If you tell the truth, you don't have to remember anything." How much more complex it seemingly becomes when one is trying to bolster a story built on a collection of almost absolute misinformation and collusion at a massive level?

The Trajectory of Past Viral Pandemics

According to various sources including the epidemiologists associated with the Great Barrington Declaration (Kulldorff, Gupta, Bhattacharya, et al. 2020) and other similar statements (for example the suddenly banned YouTube by renowned epidemiologist, Knut Wittkowski (Levine 2020), the world is handling the COVID-19 pandemic in a way that is not consistent with what has been learned, supposedly, from the history of such pandemics. Essentially, viral pandemics have predictable phases, an initial spike of disease cases, following by a dampening in cases and fatalities, in turn followed by later waves. Eventually, a viral pandemic achieves some sort of natural "herd" (make that "generalized") immunity with many of the infected never becoming in the least symptomatic. In June 2020, the WHO lead on COVID-19, Maria Van Kerkhove, announced that about 40% of "asymptomatic" persons could pass the virus to others, but within 24 hours of that statement she was forced to backtrack and admit that "in the real world" transmission from asymptomatic persons is actually a rare event, making thinking persons wonder if it can happen at all

(Boseley 2020; Spano 2020). One could indeed write a very long book about the various conspiracies alleged in the development or use of vaccines.

Triangulating the WEF and the "Great Reset"

The World Economic Forum (WEF) consists of a number of major corporations in various fields including the pharma, fossil fuels, technology, especially internet and artificial intelligence technology, and governments. Headed up by Klaus Schwab, a man who seems to firmly believe that the future of human kind lies in transhumanism (Harris 2020), WEF and the Bill & Melinda Gates Foundation money appear to be the main drivers of what has been called, by Schwab and others, the "Great Reset." The idea is that with COVID-19 as the "accidental" driving force, the pandemic has forced on humanity the need to restructure economies and societies and essentially rearrange the world.

For whose benefit are they proposing to do so? While the claim is made that the Reset will balance out economic and social inequalities, the actual reality is that it represents a push for greater economic wealth transfer and social control that only flows in one direction: upwards toward the collection of billionaires and their corporate interests at the top of the food chain. Watching various governments adopt the motto of the WEF, "build back better" is not only curious but betrays the extent to which a variety of politicians and governments have been utterly corrupted.

Some of those on the right tend to see in such measures a form of socialism or communism, but those who think so need to go back to Political Systems 101. What we have here with the Great Reset is nothing other than true fascism in its purest 21st Century form, not that much different than the Nazi version in the 20th Century, where major corporations and governments collude to take capital and decision making from below and concentrate it upwards into the hands of those already rich and powerful beyond measure.

What we are seeing with the "new normal" of COVID-19 is nothing more or less than a rolling global *coup d'état* created by those same special interests: "big data, big telecom, big oil and chemical, big finance and [the] global public health cartel" as documented here in this issue of *IJVTPR* (the next entry) by the Children's Health Defense Team (CHD). The role of the US military-intelligence apparatus in all of this cannot be ignored. As the CHD Team writes:

> The Pentagon's involvement in coronavirus-related efforts goes well beyond DARPA-funded research. Four-star General Gustave Perna is serving as chief operating officer of Operation Warp Speed alongside chief advisor Moncef Slaoui (see below). General Perna, in charge of U.S. Army Materiel Command, oversees the global supply chain for over 190,000 U.S. Army employees (HHS, 2020b). For the first time ever, the distribution of the eventual coronavirus vaccines is being planned as a "joint venture" between the CDC and the Pentagon, with the latter overseeing "all the logistics of getting the vaccines to the right place, at the right time, in the right condition…

As the article by CHD makes clear,

> In fact, global financial patterns and pronouncements point to a seismic overhaul of governance and financial systems that is playing out beneath the surface of the pandemic, reaching far beyond the health domain. These developments highlight a disturbing push for global technocracy — a form of centralized, expert-led control over resource production and consumption that the *Wall Street Journal* characterizes as "anti-democratic rule by elites who think they know better".

Who is driving the COVID-19 vaccine faster and further: this may shock some of the right wing types who may read this book, but it is none other than Moncef Slaoui, a former Moderna board member and GSK executive who is now in charge of Operation Warp Speed, the Trump administration's last effort to fast track vaccine development for COVID-19 (Thacker 2020).

And, citing *The State of Our Currencies* and other pandemic-related writings by Catherine Austin Fitts (see her on Hunter 2020; at https://robinwestenra.blogspot.com/2020/12/catherine-austin-fitts-on-great-reset.html) CHD quotes her as saying,

> [re the pandemic] emphasizes the importance of accepting that what is transpiring in the financial, tech, and biopharmaceutical sectors is interconnected. Part of this involves recognizing that the coronavirus vaccines currently dominating the headlines represent something likely to go far beyond the simple health intervention being held out by scientists and officials as a panacea. Instead, the evidence suggests that COVID-19 vaccines are intended to serve as a Trojan horse to transport invasive technologies into people's brains and bodies. These technologies could include brain-machine interface nanotechnology, digital identity tracking devices, technology that can be turned on and off remotely, and cryptocurrency-compatible chips.

Some may ask how such a conspiracy on such a grand scale could even be possible. It's actually not all that hard to imagine: Just think of the existence of any Mafia grouping or drug cartel. None of this is to say that all members of the cartel always get along or even like each other. None of what is happening is about like or dislike, rather it is all about power and control, plus wealth for those at the top, with less for those below.

Did it take a long time to put together this plan? Undoubtedly: the coordination of all the moving parts across sectors demonstrates with little doubt that the plan has been in the works for years, vastly longer than we have been led to believe as the rapid response to COVID-19. In brief, COVID-19 is not the cause of the Great Reset, merely the excuse for it to launch.

Viewed in this way, we can see that the actual reality of COVID-19 and COVID-19 vaccines, let alone other vaccines, is not the whole beast, merely the "pointy end of the spear', behind which stands an array of special interests pushing the spear forward for their joint and individual interests.

Triangulation is the process by which one finds a point or source by observing, and triangulating, from three separate locations. Where the vectors all converge is the source. We now are close to that. The Children's Health Defense Team has produced a remarkable evaluation (in the article following this one in this issue of *IJVTPR*) that lines up almost completely from the Weston A. Price Foundation (see https://www.westonaprice.org/health-topics/COVID-19-pursuing-truth-to-protect-our-liberties/) and the work of an independent journalist, Tessa Lena, in New York City (Lena 2020).

The location given is to Davos, Switzerland, headquarters of the WEF. The main commanders, in my view the truly "bad actors" here, are Schwab, Gates with his vast wealth, and some other "captains" of industry. The next level down members of the cartel who make the trains run on time, as with the Nazis to deliver the Jews and Roma to the death camps, are Tedros Greybryesus of the WHO, and Moncef Slaoui, mentioned above, the czar of Donald Trump's Operation Warp Speed, the program to promote vaccine candidates for COVID-19 as rapidly as possible and to distribute them across America. The other middle ranking entities are GVAP, CEPI, GAVI, the Wellcome Foundation and the Vaccine Confidence Project, all with Gates Foundation money in their pockets. Lower down the food chain are the myriad politicians and medical authorities who go along out of

ignorance or fear. And, of course, the mainstream media with its endless "psychic driving", are among this group and "only following orders", as well.

The Essential Role of the Captured Media in the Great Reset

In regard to the latter, the following transcript pretty much fill out all the details on how the media sees its role. We've already explored some of this in early chapters, but the following makes the nature of a captured media crystal clear, if it wasn't already. Speaking on the dangers of the "antivaxxers", Anthony Fauci carries on with the notion that such people are the true enemy:

> "We've got to do a considerable amount of community engagement and community outreach because there is this reluctance to get vaccinated.
>
> "I think it has to do with a lot of things that we can clarify. We're moving at a very rapid speed because of the urgency of the situation to develop a vaccine. We want to make sure that we're very transparent, that people appreciate that that speed is not compromising safety, nor is it compromising scientific integrity.
>
> "In addition, superimposed upon that is something that we have to face the reality of. It's true, it's unfortunate is the general anti-vaccine feeling among certain segments of our society.
>
> "Then there's the issue of people not wanting to be told what to do by authority. It's a bit of the anti-authority, anti-science approach in this country.
>
> "Those are all obstacles we have to take head on and we've got to make as much open, honest and transparent outreach to the community to convince them that getting vaccinated is for their benefit and the benefit of the community. And everything about the vaccine development and implementation will be transparent. (Fauci 2020)

Later, Fauci also appeared on PBS News Hour to discuss the rapid spread of the virus as well as to give hope to others about the development and eventual rollout of a future COVID-19 vaccine (PBS NewsHour 2020; July 17, 2020, PBS News Hour FULL INTERVIEW at https://www.youtube.com/watch?v=8Su5C_YefBU).

This is how some of the interview went, with Fauci responding to the PBS interviewer's questions:

> Fauci: "…Generally that would take a couple of years to get to that point. We're already there. We're going into a phase three trial at the end of the month. …
>
> When you're dealing with vaccines you can't guarantee things, but you can say based on the science and the way things are going, that I'm cautiously optimistic that we can meet that projection that I made months ago. And that is, by the end of this calendar year and the beginning of 2021, I feel optimistic that we will have a vaccine, one or more, that we can start distributing to people. Because if you look at the infections going on right now and phase three trials that are now starting at the end of the month, we could get a signal of safety and efficacy by as we get into the late fall and early winter.
>
> "If we do, by the beginning of 2021, we could have a vaccine."
>
> PBS: "Available to hundreds of millions of Americans?
>
> Fauci: "…Start making doses before you know that the trial works. Which means that if it works, you've saved months. …
>
> "We think we can start getting doses in the beginning of 2021, and the companies have said hundreds of millions of doses within that year. …"
>
> PBS: "Do you have a worry though Dr. Fauci that the anti-vaccine movement could interfere with this timetable?"

> Fauci: "Yes, I do because we have to admit and realize that there is an anti-vaxx movement that we've had to struggle with in this county. I believe the solution to that is community engagement and community outreach, to get people that are trusted by the community to go out there and explain to them the importance of not only getting engaged in the vaccine trial, but the importance of when the vaccine is shown to be safe and effective, to actually take the vaccine because it could be lifesaving and it certainly would be the solution to this terrible pandemic." (PBS NewsHour 2020)

The mainstream media is not the sole player by any means in the attempts to blame vaccine dissidents for a potential failure of the COVID-19 vaccine, or any vaccine for that matter. One of the main cheerleaders is Dr. Heidi Larson, who heads up the Vaccine Confidence Project which is replete with Bill & Melinda Gates Foundation money (LSHTM 2019). This is also the group that has joined the chorus claiming "antivaxxers" are a major hazard to public health.

On Mandates and Lawsuits

The restrictions on daily life imposed by politicians across the world are not abating. Indeed, they seem to be accelerating. What started out in the early COVID-19 days as full or partial lockdowns to "flatten the curve" and intended for several weeks, have largely been maintained. Some of these that may have been suspended in part or in whole when COVID-19 case loads seemed to be diminishing, have now come back in force in countries or regions facing a second or third wave of the disease. For example, here in British Columbia and other parts of Canada, we were experiencing gradual easing of social distancing and other restrictions, but when cases started to rise again, the public health officers began to panic yet again. Our own Dr. Bonnie Henry looked at the rising false positive numbers, ignored proper PCR testing methods and decided, as has become her wont, to treat British Columbians as social lepers. She has been allowed to do so care of Bill 19, an Orwellian piece of provincial legislation that allows her to dictate the lives of 4 million people. Here in B.C, many continue to see her as a heroine; increasing numbers think she is a petty bureaucrat whose power of the executive diktat has gone to her head.

Spain and Italy locked down hard again; Sweden also increased their relatively soft restrictions. Around the world, politicians, left, right and center clamor for much anticipated vaccine to arrive to deliver that most magical of imaginary beasts, herd immunity. For this reason, it seems virtually inevitable that mandates for COVID-19 vaccines will soon become the norm. These will be enforced not by overt force, but by escalating restrictions on those who won't comply, that is by taking away the "privileges" of people who are now awakening to the notion that this is all they really have ever had.

There are, however, some reasons for hope: The Great Barrington Declaration has now been signed by tens of thousands of academics and hundreds of thousand of lay people. This declaration made much of the official left apoplectic, decrying it as an alt-right attempt to punish poor people, an odd critique given that it states precisely the opposite. In brief, the idea is to allow most economic activity to go on as normal while ensuring protection for those most vulnerable to the disease (Kulldorff et al. 2020).

Lawsuits against governments have been filed in Canada and Germany and elsewhere and surely many more will follow.

And, resistance, covert and overt is growing to this world *coup d'etat.*

The Future of COVID-19 and Us

As this section is written and even later when it goes to press, it seems likely that we will still be dealing with this COVID-19 or other diseases like it. Now various entities from the Canadian Army to governments around the world note that there may be future outbreaks of COVID-19, or other viruses, that we need to be prepared to face for months or years to come. We are indeed on the brink of a "brave new world", in which lockdowns, social isolation and distancing and all of the societal changes now proposed will be with us, perhaps forever. And, we will be asked to remember, it is all for the greater good and that "we are all in this together", except of course for the billionaire class whose concept of being in this all together seems remarkably different from people trying hard each month to pay their mortgage. Now we are asked to protect seniors and those with various comorbid conditions. Next time the vulnerable might be children or those in their 20s or 30s. In this new world, there will always be new threats and new things for us all to fear and more things to sacrifice for the greater good.

The response to COVID-19 will have charted the path forward for government working with, or more likely on behalf, of industry to increasingly dictate what we do, with whom, how, and when. And if that is not the sort of world we were warned about by George Orwell and Aldous Huxley, I don't know what is: Trust Big Brother, don't question, don't listen to dissenting voices, do what we tell you for the greater good (and we, the government, will decide what that is).

We have arrived at that new world. It was ushered in by 9/11 and for 20 years, US society has been moved more and more toward a state of perpetual war for the benefit of the defense industry which has increasingly been partnered with big pharma. COVID-19 ushers in the attempted dominance of the pharma cartel teaming with global technocrats seeking control over the entire world. The former could imprison you at will, even kill you. The latter seeks to control your very existence from before birth until after your death.

The world has indeed been turned upside down by the confluence of COVID-19 and the proposed Great Reset. It is hard not to imagine that the latter inspired in principle, if not in reality the former. Regardless of how fatalistic many of us seem to be in the face of the events of 2020, there is always the hope for resistance to the WEF, Bill Gates, and to the other corporate henchmen who may have made this all possible. Some of these options for resistance and renewal are discussed in my book and some useful suggestions are made here in this issue of the *IJVTPR* in the second entry by James Lyons-Weiler.

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Planned Surveillance and Control by Global Technocrats: A Big-Picture Look at the Current Pandemic Beneficiaries

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ABSTRACT

Global financial patterns and pronouncements point to a seismic overhaul of governance and financial systems that is playing out beneath the surface of the COVID-19 pandemic, reaching far beyond the health domain. Increased centralized control has the potential to create an unbridgeable chasm between a tiny handful of winners and a majority of losers. To foster an integrated analysis of the technocratic and financial forces and agendas at play, this rapid review identifies some of the pandemic's principal beneficiaries across the interwoven financial, tech, biopharmaceutical, and military-intelligence sectors, assessing developments in the context of the accelerating global push for technocratic consolidation and control. The evidence suggests that Trojan horse coronavirus vaccines may challenge bodily integrity and informed consent in entirely new ways, transporting invasive technologies into people's brains and bodies. Technologies such as brain-machine interfaces, digital identity tracking devices, and cryptocurrency-compatible chips would contribute to the central banking goal of replacing currencies with digital transaction and identification systems and creating a global control grid that connects the world population to the military-pharma-intelligence cloud of the global technocrats. Moreover, using vaccines as a delivery vehicle for surveillance technologies cancels any legal liability.

Keywords: *biopharmaceuticals; central banks; COVID-19 pandemic; digital identity; Operation Warp Speed; technocracy; vaccines*

Introduction

On March 11, 2020, the World Health Organization (WHO) upgraded a reportedly novel coronavirus from a global health emergency (as of January 30) to a global pandemic, having given the name "COVID-19" to the newly minted disease associated with the virus (Forster, 2020; World Health Organization, 2020a). If one examines actions taken both before and since the WHO's March decree, it seems evident that many highly placed individuals and sectors were able to strategically position themselves to benefit from the declared crisis (Children's Health Defense, 2020b). At the same time, with a "new form of economic shock" being imposed worldwide under

cover of COVID-19 (Lagarde, 2020), it has become apparent that old-fashioned corporate profiteering is far from the whole story.

In fact, global financial patterns and pronouncements point to a seismic overhaul of governance and financial systems that is playing out beneath the surface of the pandemic, reaching far beyond the health domain. These developments highlight a disturbing push for global technocracy — a form of centralized, expert-led control over resource production and consumption that the *Wall Street Journal* has characterized as "anti-democratic rule by elites who think they know better" (Wood, 2018, 2020; Fitts, 2020a; Schinder, 2020; Schumacher, 2020; White, 2020). In the U.S., many of the actions unfolding behind the scenes are also benefiting from a climate of institutionalized secrecy enabled by the October 2018 adoption of a game-changing policy statement (FASAB Statement 56), which turned financial disclosure rules upside-down to allow the U.S. government and its contractors to maintain secret books (Federal Accounting Standards Advisory Board, 2018; Ferri & Lurie, 2018).

As 2020's rapid-fire events suggest, substantially increased centralized control and secrecy have the potential to create an unbridgeable chasm between a tiny handful of elite winners and a majority of upper and lower middle class losers. In early June, CNBC's Wall Street analyst Jim Cramer heatedly pointed out the fact that the pandemic had already produced "one of the greatest wealth transfers in history" (Clifford, 2020). Others have echoed these observations, describing the "monumental transfer of wealth from the bottom of the economic ladder to the top" (Barnett, 2020; Kampf-Lassin, 2020). In comparison to the benefits flowing to large corporations and billionaires, Cramer bluntly observed that pandemic-related restrictions have had a "horrible effect" on America's small-business economy, with a similar pattern on display outside the U.S. (Clifford, 2020). Even the World Economic Forum — which has promoted many of the structural changes now underway at its annual Davos meetings — acknowledges the "asymmetric nature" of COVID-19-related hardships and the "greater ferocity and velocity" of the pandemic's impact on populations already under stress before 2020 (World Economic Forum, 2020).

By early fall, fifty million Americans (many with already high burdens of debt) had lost jobs; financial forecasters were issuing warnings about further layoffs; and millions of the still-employed were earning less than pre-pandemic (Andriotis, 2020). In addition, the bulk of the trillions in federal stimulus (which by early May exceeded the gross domestic product of all but six nations worldwide) had made its way to large corporations; *Forbes* reported that roughly 70 percent of the initial $350 billion intended for struggling small businesses went to large companies (Simon, 2020). Observers suggest that by channeling taxpayer bailouts to the companies that already had the greatest ability to withstand the shutdowns, the largest players have been able to gain even more of a "stranglehold" over the economy (Kampf-Lassin, 2020).

As U.S. billionaires' wealth increased by almost a trillion dollars (a weekly average of $42 billion), weekly jobless claims, requests for food bank assistance, and reports of addiction, overdoses, depression, and suicide began "shatter[ing] all historical records" (Feeding America, n.d.; Alcorn, 2020; Americans for Tax Fairness, 2020; Baldor & Burns, 2020; Community FoodBank of New Jersey, 2020; Dubey *et al.*, 2020; Ettman *et al.*, 2020; Hollyfield, 2020; Lerma, 2020; Prestigiacomo, 2020; Schwarz, 2020; Sergent *et al.*, 2020; Thorbecke, 2020; Wan & Long, 2020). Outside the U.S., the situation is similar (Bueno-Notivol *et al.*, 2020). As a marker of the global surge in hunger, the Nobel Committee awarded its 2020 Peace Prize to the World Food Programme, prompting the

agency's head to warn that the world is "on the brink of a hunger pandemic" that could result in "famines of biblical proportions" in the coming year (Lederer, 2020).

In November, the Centers for Disease Control and Prevention (CDC) released data identifying over 100,000 excess U.S. deaths "indirectly" associated with the pandemic (Rossen *et al.*, 2020), including a "stunning 26.5% jump" in excess deaths in young adults in their mid-twenties through mid-forties (Prestigiacomo, 2020). Commenting on these mortality data — which reflect "a death count well beyond what [researchers] would normally expect" (Preidt, 2020) — the former U.S. Food and Drug Administration (FDA) Commissioner Scott Gottlieb voiced his suspicion that "a good portion of the deaths in that younger cohort were deaths due to despair," including drug overdoses (Squawk Box, 2020). University researchers writing about mortality in *JAMA* concurred that "Excess deaths attributed to causes other than COVID-19 could reflect deaths . . . resulting from disruptions produced by the pandemic" (Woolf *et al.*, 2020), including "spillover effects . . . such as delayed medical care, economic hardship or emotional distress" (Preidt, 2020). Multilateral entities like the Organisation for Economic Co-operation and Development (OECD) emphasize that it will be essential to assess the long-term impact of "confinement and deteriorating financial conditions" on mortality and warn that the social and economic fallout is likely to be "significant" (Morgan *et al.*, 2020).

As an ideology, technocracy is recognized for exalting knowledge and expertise as the principal sources of legitimate power and authority and for asserting that there is "one best way" that only "the experts" (e.g., engineers, scientists, and doctors) can determine (Burris, 1989). However, critics of technocracy have long pointed out that, particularly in crisis situations, the know-how, "discretionary interventions" and seemingly "elastic" power claimed by technocrats can end up blurring the line between useful expertise and "arbitrary rule" (White, 2020). Moreover, technocrats typically resist attempts to make explicit "the non-rational attributes of technocratic decision-making" (Burris, 1989).

With the noticeable absence of any cost-benefit analysis and the increasingly "non-rational" justifications being put forth for COVID-19 restrictions (Handley, 2020; Kristen, 2020; Kulldorff *et al.*, 2020; The Reaction Team, 2020) — as well as the economic, political, social, and cultural changes rolling out at dizzying speed — it is important to try to understand the technocratic and financial agendas at play. Three increasingly interwoven sectors (Big Finance, Big Tech, and Big Pharma) are reaping rewards from COVID-19, benefiting from close relationships with the military-intelligence apparatus (Glaser, 2020; Usdin, 2020). This rapid review seeks to (1) identify some of the pandemic's principal beneficiaries (financial and otherwise) across these sectors, and (2) assess these parties' actions in the context of the accelerating global push for technocratic consolidation and control through invasive surveillance.

Methods

Rapid reviews are used to synthesize evidence in a streamlined manner, abbreviating the timeline and requirements of more involved systematic reviews (Ganann *et al.*, 2010). A rapid review is particularly well suited to emerging current event sequences, and the dynamic COVID-19-related situation certainly qualifies. Though not exhaustive, rapid reviews make it possible to quickly

summarize available evidence across multiple disciplines, whether for the purpose of informing policy-making and decision-making or to identify patterns and take stock of the bigger picture.

For the purposes of this broad overview of current events, we relied primarily on the so-called grey literature as well as media accounts (from both the legacy media and independent journalists) and various online sources. We also consulted relevant peer-reviewed literature. Notably, while the peer-review process is ordinarily slow-moving, COVID-19-related studies have been making their way through the pipeline at breakneck speed (Packer, 2020).

Examples of sources consulted for this review include conventional and alternative financial commentary; webpages and communications from public health agencies, international organizations, and universities; individual blogs and commentary; and peer-reviewed studies cataloguing the impact of COVID-19 restrictions.

Big Finance

Assisted by the media, commentators have had an easy time framing the events of 2020 principally as a health crisis. With each passing month, however, those claims wear thinner (Barnett, 2020). In a comprehensive analysis titled *The State of Our Currencies*, former U.S. Assistant Secretary of Housing Catherine Austin Fitts (2020a) offers a broader and more instructive interpretation. Informed by close attention to financial patterns, Fitts asserts that the "shock doctrine" measures being imposed under cover of COVID-19 are helping lay the train tracks for a new global central banking machine and a technocratic "regulatory and economic model that permits far greater central control".

Fitts calls attention to G7 central bankers' August 2019 approval in Jackson Hole, Wyoming of a plan called "Going Direct" (Bartsch *et al.*, 2019) that makes the case for a novel "blurring [of] the lines between government fiscal policy and central bank monetary policy" (Martens & Martens, 2020). Drafted months before COVID-19, the plan — co-branded by the World Economic Forum (n.d.) as "the Great Reset" — evokes the prospect of a serious economic downturn and "unusual circumstances" that could be used to justify "unprecedented" global measures (Bartsch *et al.*, 2019).

Fitts (2020a) postulates that central bankers have both a short-term aim (to extend the existing dollar-based reserve currency system) and an ambitious longer-term goal: to implement a "new global governance and financial transaction system, and gather the power necessary to herd all parties into the new system". Characterizing these aspirations as nothing short of ending currency as we know it, Fitts suggests that the top-down digital-currency-based model being promoted as a replacement could end up sidelining traditional intermediaries and instead directly furnish populations with something akin to a "credit at the company store". Spelling out the implications of such a model, Fitts notes that with the help of digital surveillance and a social credit system, the central-bank-controlled "credit" could easily be "adjusted or turned off on an individual basis". General Manager Agustín Carstens of the Bank for International Settlements (BIS) — the central bank of central banks — recently acknowledged as much, stating that in stark contrast to cash, a Central Bank Digital Currency (CBDC) would give central banks "absolute control" over CBDC use "and the technology to enforce" CBDC rules and regulations (International Monetary Fund, 2020). With a vaccine-injected digital surveillance program in individuals, the CBDC would have dictatorial power at the level of individual buying and selling.

Fitts' analysis suggests that central bankers began laying the groundwork for the desired global transition well in advance of the coronavirus mayhem. In 2019 alone, G7 finance ministers endorsed a cryptocurrency action plan in July; in August, the G7 central bankers approved "Going Direct"; in September, the U.S. Federal Reserve ("the Fed") started making hundreds of billions of dollars in loans "direct" to Wall Street trading houses; and in October, the BIS issued a major report on global cryptocurrencies (Bank for International Settlements, 2019; Helms, 2019; Fitts, 2020a; Martens & Martens, 2020). In the middle of the frenzy of central bank activity in October, the Bill & Melinda Gates Foundation (along with the World Economic Forum and Johns Hopkins Center for Health Security) held the well-publicized "pandemic tabletop exercise" called Event 201, which played out a global coronavirus outbreak scenario strikingly similar to 2020's actual events (Center for Health Security, n.d.).

In January 2020, U.S. corporations witnessed a record number of CEO departures (Ausick, 2020; Marinova, 2020) — a mass exodus that strategically allowed over 200 departing executives to sell their stock at or near the market high (see Table 1). Other wealthy and influential insiders also engaged in surprisingly well-timed stock market transactions. For example, following a late-January, behind-closed-doors briefing about the virus (which had yet to affect a single American), certain U.S. senators sold hundreds of thousands of dollars of stock, "unloading shares that plummeted in value a month later" (Lane, 2020). The world's wealthiest person, Amazon CEO Jeff Bezos, sold nearly $4.1 billion over an 11-day period in early February after having also sold $2.8 billion in shares in August 2019 (Palmer, 2020).

Table 1. U.S. CEO Departures in January 2020

Fact	**Comments**
219 CEO departures overall	-Record-setting number of departures -40 percent higher year over year -Average age 55.7 years (versus 60.7 years in 2019)
Key sectors affected	-Technology (250% more than Jan. 2019: 35 vs. 10) -Health Care/Products (18 departures) -Hospitals (18 departures)
Selected companies affected	Credit Suisse, Disney, Fastly, Groupon, Hulu, IBM, L Brands, LinkedIn, Mastercard, Match Group, Salesforce, T-Mobile

Sources: Ausick, 2020; ChallengerGray, 2020

As the U.S. government turned on the stimulus spigot in March, the Fed sustained its irregular intervention in the U.S. economy. By the summer of 2020, the Fed had expanded its balance sheet by $2.9 trillion — much of it unaccounted for, according to Fed-watcher John Titus (2020) — and financial observers were warning that "the market is no longer the biggest factor in selecting [economic] winners and losers" (Whalen, 2020). Titus (2020) concurs with this assessment, baldly

characterizing 2020's events as a Fed-led "coup d'état". Titus (2014) has been chronicling major financial forces and legal changes since the 2008 financial crisis, describing how central banks are not only able to "loot" the American people "in broad daylight" but can do so without fear of prosecution — probably because, as Titus and Fitts (2020a) both point out, the Department of Justice depends on Fed member banks for its financial operations.

The coronavirus stimulus has provided abundant financial opportunities advantageous to Fed member banks. Over a two-week period in April, for example, large banks earned $10 billion in fees (ranging from 1 to 5 percent) simply for processing the government's loans to businesses (Sullivan *et al.*, 2020). Class-action lawsuits subsequently alleged that the banks prioritized larger loans (and larger companies) in order to garner the largest fees, while shutting out "tens of thousands" of eligible but smaller businesses (Sullivan *et al.*, 2020). Serving as lender to the parent company of a national restaurant chain, Fed member bank JPMorgan Chase (the largest and most profitable bank in the U.S.) earned a $100,000 fee for a single "one-time transaction for which it assumed no risk and could pass through with fewer requirements than for a regular loan" (Sullivan *et al.*, 2020).

In September, Senator Marco Rubio (Chairman of the Senate Committee on Small Business and Entrepreneurship) wrote to the JPMorgan Chase CEO expressing "alarm" about allegations that JPMorgan employees "may have been involved in potentially illegal conduct" in the distribution of Paycheck Protection Program and Economic Injury Disaster Loan funds (Rubio, 2020). *Bloomberg* later confirmed the possibility of COVID-19-related banking abuse on a wide scale (David, 2020). Importantly, this is not a new pattern of behavior for the U.S. banking behemoth. Since 2002 (and primarily since the 2008 financial crisis), JPMorgan Chase has paid out at least $42 billion in settlements for questionable, unethical, or illegal behavior (Fitts, 2019); its public-facing Wikipedia page lists involvement in 22 different "controversies," including the economically shattering Enron and Madoff scandals ("JPMorgan Chase", n.d.). Nevertheless, JPMorgan continues to earn glowing accolades from the financial community. In June 2020, *Forbes* urged investors to "bank on the best" in the uncertain COVID-19 environment (Trainer, 2020), citing JPMorgan's post-2009 "industry-leading profitability" and asserting that the bank is exceptionally well positioned to expand its market share both during and post-pandemic. In October, JPMorgan rolled out a new smartphone credit card reader designed to compete with Square and PayPal (Son, 2020).

Big Tech

By July 2020, global billionaires' wealth had surged to an all-time high of $10.2 trillion — an increase of 27.5 percent since April, and a 41.3 percent increase for tech billionaires (Phillipps, 2020). U.S. billionaires accrued a significant share of this pandemic wealth bonus, increasing their worth by $845 billion from mid-March to mid-September and prompting the observation that "for American billionaires specifically, things have never looked better" (Lerma, 2020). As a whole, U.S. billionaires' wealth reached the equivalent of almost one-fifth of the U.S. gross domestic product, with four tech billionaires (Jeff Bezos, Bill Gates, Elon Musk, and Mark Zuckerberg) plus Warren Buffett seeing their total wealth climb by 59 percent (da Costa, 2020). Calling attention to Bezos, in particular, the Institute for Policy Studies described his surge in wealth as "unprecedented in modern financial history", requiring "a real-time hour-by-hour tracker" to keep up (Collins *et al.*, 2020).

The companies with which top-tier billionaires are affiliated include Amazon and Amazon Web Services (Bezos), Apple (Tim Cook), Facebook (Zuckerberg), Google/Alphabet (Larry Page and Sergey Brin), Microsoft (Steve Ballmer and Gates), Oracle (Larry Ellison), Zoom (Eric Yuan), and the variety of companies (including Neuralink, SpaceX, and Tesla) spearheaded by Musk (Alcorn, 2020; Collins *et al*., 2020; Toh, 2020). In July, as *Bloomberg* described these companies' "outsized influence on U.S. markets", it noted that they are as well-situated to profit from the U.S. shutdown as they are to take advantage of a recovering Europe and Asia — a "one-two punch" that has already increased FAANG companies' market (Facebook, Amazon, Apple, Netflix, and Google, plus Microsoft) by 62 percent (Ritholtz, 2020). Suggesting that Silicon Valley will go down in history as "the standout sector" (Divine, 2020a), a *U.S. News* analyst unabashedly recommended Facebook as a 2020 "best buy" because "it's gobbling up the world, and reasonable people could argue that if privacy is dying, individual investors may as well profit alongside Silicon Valley" (Divine, 2020b).

COVID-19 has provided Big Tech (and Big Telecom) with an opportunity to bring a range of controversial technologies further out into the open, despite many unresolved concerns about safety and ethics (Boteler, 2017; Gohd, 2017; Ross, 2018; Boyle, 2019; Feiner, 2019; Markman, 2019; Plautz, 2019; Zhang *et al*., 2019; Bajpai, 2020; Goodwin, 2020; Gyarmathy, 2020; McGovern, 2020; Novet, 2020; Reuters, 2020; Tucker, 2020; U.S. Department of Defense, 2020). Singly and in combination, the technologies (some of which are listed in Table 2) have the potential to usher in unprecedented societal changes, strengthening technocrats' ability to control many facets of daily life. Artificial intelligence (AI), 5G, "smart" utility meters, and the Internet of Things (IoT), for example, are rapidly and fundamentally changing the nature of cities, businesses, and homes — what Fitts (2020a) calls the "final mile" — forming an essential part of the strategy to convert the economic model to a technocratic model that uses AI and software to achieve centrally controlled resource allocation.

Table 2. COVID-19 and the Rollout of Control Technologies

Category	**Description**	**Selected Companies Developing or Promoting the Technology**
Artificial intelligence (AI)	Computer (or robot) ability to perform tasks associated with human intelligence	Amazon, Facebook, Google/Alphabet, Microsoft, Tesla
Augmented reality	Computer data (text, 3D objects, video) overlaid onto real-world objects	Apple, Microsoft, Google/Niantic, Snap
Bioelectronics	Application of electronics to biology and medicine	Galvani Bioelectronics (partnership of Verily/Alphabet and GlaxoSmithKline), Synchron
Brain-machine interface	Communication to/from an implanted human (or animal) brain and an external electronic device	Blackrock Microsystems, Neuralink

Fifth-generation (5G) wireless	Wireless technology (new portions of spectrum; civilian/military uses)	Amazon, AT&T, Crown Castle, Ericsson, Microsoft, Verizon
Genetically modified (GM) mosquitoes	Male mosquitoes programmed to produce female mosquitoes that die before adulthood	Oxitec and Gates Foundation
Internet of Things (IoT)	Network of physical objects connected to the Internet and other devices, including "smart" meters	Amazon, Apple, AT&T, Cisco, Google, IBM, Intel, Microsoft, Samsung, SpaceX
Lab-grown "food"	Synthetic biology ("cellular agriculture") approach making products marketed as "food"	Sergey Brin (Google), Bill Gates (Microsoft), Peter Thiel (PayPal)
Molecule printers	RNA "microfactories" for mRNA vaccine production	CureVac, Tesla
Nanotechnology	Manipulation of atoms and molecules to control chemical properties (numerous applications)	Apple, Google, Intel, Microsoft, Neuralink
Robotics	Programmable machines performing autonomously or semi-autonomously, sometimes using AI	Amazon, Microsoft
Satellites (video surveillance)	Advanced imaging satellites delivering real-time, continuous video planet-wide	EarthNow (Gates-funded)
Smart cities	IoT sensors and technologies collecting data and connecting components city-wide	Amazon, Google, Microsoft, Tesla

In October 2020, the World Economic Forum — the Great Reset's front-row marketer — released a report on the future of jobs, describing the significant displacement of workers resulting from the pandemic and the related global restructuring that the organization has been taking the opportunity to promote (Petzinger, 2020). With automation and COVID-19 causing a "double-disruption" that is not only accelerating job destruction in the short term but "shrinking opportunities" in the longer term, the report solemnly pronounced a "new division of labour between humans, machines and algorithms" (World Economic Forum, 2020). Well before the pandemic, Amazon had established a robot-centric system at its fulfillment centers, with a process focused on "limit[ing] movement of people [and] let[ting] robots move everything" (Masud, 2019). This downsizing of humans has apparently served Amazon well; by May 2020, Amazon's e-commerce business had shot up by 93 percent compared to the previous May (Klebnikov, 2020).

A September 2020 survey showed that many other companies plan to substantially boost their spending on AI and machine learning, citing COVID-19 as their rationale for prioritizing "the adoption of new technologies that enhance and enable automation" (Shein, 2020). Observers also predict, however, that the AI gold rush will lead to even more market consolidation and control by Amazon and three other big COVID-19 winners — Alphabet, Facebook, and Microsoft. These four companies, according to *Forbes*, have the "scale to push the envelope", the "talent and the technology to perfect [AI]", and the computing power to dominate the field (Markman, 2019). Amazon already controls nearly 46 percent of the worldwide public cloud-computing infrastructure that is a key backstop for AI functions such as parallel processing and the digestion of Big Data (Atlantic.Net, 2018; Nix, 2019).

Before COVID-19, consumer rejection of 5G wireless technology had been growing (Castor, 2020). However, the imposition of social distancing measures, remote learning, and online work requirements has provided the telecommunications industry with a ready-made pretext to fast-forward 5G's deployment while attempting to burnish the industry's unfavorable public image. Taking advantage of virus fears, Big Tech and Big Telecom are claiming that 5G can help enable "a future in which business, health care and human interaction must be at more than an arm's length" (Wasserman, 2020). *Forbes* has praised communication service providers for responding to the coronavirus lockdowns "with a sense of urgency, purpose and empathy" (Wilson, 2020). Describing areas requiring more "advanced connectivity", a technology expert at Deloitte Consulting cited the example of "cameralytics" (video surveillance) "to help worker safety and social distancing" (Howell, 2020). Whatever the rationale, the reality on the ground has been a massive increase in U.S. telecom companies' capital spending on 5G and a "full steam ahead" rollout of spectrum and infrastructure that has placed the U.S. "ahead of schedule" (Knight, 2020; Ludlum, 2020). The European Commission is now attempting to follow the U.S.'s lead by pushing for the removal of "regulatory hurdles" and making the case that 5G will aid the region's post-coronavirus economic recovery (McCaskill, 2020).

COVID-19 has also brought another of Big Tech's interests into sharper focus: food. Billionaires such as Bill Gates and Peter Thiel have, for some time, been investing in biotech start-ups that aim to produce, in a lab, stem-cell-based "meat", "fish", "dairy", and "breastmilk" (Kerr, 2016; Kosoff, 2017; Beres, 2020; Wuench, 2020). These start-ups and their investors have been only too happy to position the burgeoning industry as a partial solution to pandemic-related food insecurity and supply chain interruptions (Galanakis, 2020; Pereira & Oliveira, 2020; Yeung, 2020), welcoming COVID-19 as an "accelerator" as well as an opportunity to overcome consumer skepticism (Siegner, 2019; Morrison, 2020). In addition, as the coronavirus breathes new life into the term "sustainability" — long used by technocrats as a cover term for more centralized control (Wood, 2018) — global partners like the United Nations and the World Economic Forum are making the improbable claim that the complex, high-dollar, lab-created food substitutes (which require genetically stable cell lines, bioreactors, "edible scaffolds", and cell culture media) are a "sustainable" option (Whiting, 2020). The biopharma giant Merck is also getting in on the "cultured meat" action, offering to make its "extensive knowledge of the relevant science and biotechnology" available to companies seeking to overcome "critical technological challenges" (Whiting, 2020). Merck frequently collaborates with the Gates Foundation, including in the development of COVID-19 vaccines (Lardieri, 2020).

Big Pharma

In September 2019, an annual Gallup poll reported that the restaurant industry was America's top-ranked and most-liked among the 25 industries regularly assessed by the polling group (McCarthy, 2019). Sadly, less than a year later the Independent Restaurant Coalition predicted the permanent demise of up to 85 percent of independent restaurants (Jiang, 2020). In contrast, the pharmaceutical industry came in "dead last" in the 2019 poll, despite $9.6 billion spent annually on direct-to-consumer advertising and another $20 billion on marketing to health professionals (McCarthy, 2019; Schwartz & Woloshin, 2019). The U.S. is one of only two countries in the world that allows drug companies to market directly to consumers and, in non-election years, roughly 70 percent of news outlets' advertising revenues come from pharma (Solis, 2019).

The pharmaceutical industry's history of "fraud, bribery, lawsuits and scandals" is well known (Compton, n.d.), and no less a figure than Bill Gates has suggested that the public perceives Big Pharma as "kind of selfish and uncooperative"; however, Mr. Gates and *Fortune* magazine propose that COVID-19 may offer the industry an opportunity for "redemption" (Leaf, 2020). The stage may have been set for Big Pharma's year of opportunity in January, when JPMorgan Chase held its 38th annual invitation-only health care conference. The business press describes the yearly conference as "one of the biggest biotech dealmaking events, often setting the tone for funding rounds, partnerships and mergers and acquisitions" (Leuty, 2020). Thus, just when the coronavirus ball was getting rolling, the conference brought an estimated 20,000 venture capitalists, investment bankers, and drug development executives and entrepreneurs to San Francisco to hear keynote addresses by JPMorgan's and GlaxoSmithKline's CEOs and to stoke expectations of a strong year for the biotech-plus-pharma chimera known as "biopharma" (JPMorgan, n.d.; Leuty, 2020; Lipschultz, 2020). In 2014, McKinsey & Company described the investment opportunities in biopharmaceuticals as "big and growing too rapidly to ignore", with an annual growth rate more than double that of conventional pharma and a 20 percent share of global pharmaceutical revenues (Otto *et al.*, 2014).

A few weeks after the JPMorgan conference — and well before any COVID-19 deaths in the U.S. — the Department of Health and Human Services (HHS) helped ensure that significant pandemic benefits would flow into the biopharma and medical space. HHS did so by issuing a declaration (on February 4) making vaccines and all COVID-19-related medical countermeasures immune from legal liability (HHS, 2020a). On March 6, roughly a week after the first reported coronavirus death, President Trump sweetened the pot by signing into law the first in a series of emergency stimulus packages, earmarking 40 percent of the $8.3-billion bill for vaccines and drugs under terms the pharmaceutical industry openly dictated (Karlin-Smith, 2020).

Following the February 4 HHS declaration eliminating legal liability, Bill & Melinda Gates instantly pledged $100 million in funding for coronavirus vaccine research and treatments, followed by another $150 million in mid-April (Bill & Melinda Gates Foundation, 2020; Voytko, 2020). When Operation Warp Speed followed, making untold billions available for research and development of therapeutics and vaccines at taxpayer expense (see Table 3), dozens of biopharma companies jumped into the fray (HHS, n.d.). Catherine Austin Fitts notes that a system that exempts from liability anything labeled as a "vaccine" amounts to "an open invitation to make billions . . . particularly where government regulations and laws can be used to create a guaranteed market

through mandates" (Fitts, 2020b). Moreover, each time the CDC's Advisory Committee on Immunization Practices (ACIP) adds a given vaccine to the CDC schedule, it is not only the equivalent of a "golden ticket" for the vaccine manufacturer but also directly benefits the CDC, which owns dozens of vaccine-related patents and routinely shares licensing agreements with manufacturers (Taylor, 2017; Children's Health Defense, 2019).

Currently, there is one injury for every 39 vaccinations administered (2.6%), often resulting in a "disastrous outcome of life-altering iatrogenic illnesses" (Harvard Pilgrim Health Care, n.d.; Kennedy Jr., 2019; Kristen, 2019). A CDC study published in *JAMA* in 2016 reported that one in five young children (19.5%) under age five who were admitted to emergency rooms for drug reactions were suffering from vaccine injuries (Shehab *et al.*, 2016). Early clinical trial results and COVID-19 vaccines' use of an array of experimental, never-before-approved technologies suggest that comparable (or worse) levels of injury could follow the rollout of coronavirus vaccines (Children's Health Defense, 2020a, 2020c, 2020d, 2020e). The Moderna and Pfizer vaccines, for example, feature mRNA molecules that are known to be "intrinsically unstable and prone to degradation", with an inflammatory component that risks dangerous immune reactions (Feuerstein, Garde, & Joseph, 2020; Jackson *et al.*, 2020; Wadhwa *et al.*, 2020). Assuming the same vaccine injury rate of 2.6 percent, Operation Warp Speed's projected vaccination of roughly 25 million Americans per month (Owermohle, 2020b) could conceivably result in 3.9 million injuries over just the first six months. (Given that the leading vaccines will require two initial doses and probable boosters thereafter, this figure could even be an underestimate.) If Bill Gates and other technocrats succeed in their declared aspiration to manufacture billions of doses of coronavirus vaccine and "get them out to every part of the world" (Gates, 2020), the scale of injury would not only be unprecedented but could open a lucrative, long-term gateway to the wider drug market to manage the injuries (Kristen, 2019).

Table 3. U.S. Taxpayer Monies Awarded to Pharmaceutical and Other Companies via Operation Warp Speed† (March–October, 2020), in Millions (M) or Billions (B) [Source: https://www.hhs.gov/coronavirus/explaining-operation-warp-speed/index.html]

Date	**Amount**	**Company**	**Funding Focus**
March 30	$456M	Johnson & Johnson/Janssen	Vaccine
April 16	$483M	Moderna	Vaccine (Phase 1)
May 12	$138M	ApiJect	Syringes
May 21	$1.2B	AstraZeneca/University of Oxford	Vaccine
June 1	$628M	Emergent BioSolutions	Vaccine/drug manufacturing
June 11	$204M	Corning	Glass vials
June 11	$143M	SiO2 Materials Science	Glass-coated plastic vials

July 7	$450M	Regeneron	Antiviral antibody treatment
July 7	$1.6B	Novavax	Vaccine
July 22	$1.95B	Pfizer	Vaccine
July 26	$472M	Moderna	Vaccine (Phase 3)
July 27	$265M	Fujifilm/Texas A&M University	Vaccine manufacturing
July 31	$2B	Sanofi/GlaxoSmithKline	Vaccine
August 4	$160M	Grand River Aseptic Mfg (GRAM)	Vaccine/drug manufacturing
August 5	$1B	Johnson & Johnson/Janssen	Vaccine (manufacturing)
August 11	$1.5B	Moderna	Vaccine (manufacturing)
August 14	n/a	McKesson (existing contract)	Vaccine distribution
October 9	$486M	AstraZeneca	Monoclonal antibodies
October 13	$31M	Cytiva	Vaccine "consumables"

† **HHS note on Operation Warp Speed funding:** "Congress has directed almost $10 billion to this effort through supplemental funding, including the CARES Act. Congress has also appropriated other flexible funding. The almost $10 billion specifically directed includes more than $6.5 billion designated for countermeasure development through BARDA and $3 billion for NIH research."

By mid-October, 44 candidate vaccines were in clinical evaluation worldwide, with another two hundred or so in the pipeline (Agrawal *et al.*, 2020; World Health Organization, 2020b). Furnishing predictably uncritical coverage ensured by the pharmaceutical industry's strategic entanglements with the media, scientists, and medical journals, the press has been telling the public that the vaccines will play "an important role in most response scenarios", including "'sav[ing] the world' in worse scenarios" and serving as an "insurance policy against continued health and economic shocks" (Agrawal *et al.*, 2020). Only a handful of journalists have called attention to Big Pharma's pandemic profiteering, pointing out that "insiders at companies developing experimental vaccines and treatments . . . aren't waiting until they finish the job to collect their reward" (Wallack, 2020).

An October piece in the *Boston Globe* cited the example of Moderna (Wallack, 2020). It took Moderna a mere three weeks after Bill Gates' initial funding installment to send its first batch of experimental vaccine to research and patent partner, the National Institute of Allergy and Infectious Diseases (NIAID), leading to an immediate surge in share price of 28 percent (Lee, 2020; Loftus, 2020). By early April, Moderna's CEO had become an overnight billionaire; by October, he had sold nearly $58 million in stock, followed by another $2 million in mid-November, just ahead of the company's intended filing for vaccine Emergency Use Authorization (Nagarajan, 2020; Tognini, 2020; Wallack, 2020). Meanwhile, Moderna's chief medical officer has been "systematically liquidating all of his company stock" — about $70 million — "in a series of pre-planned trades that

have made him roughly $1 million richer each week" (Wallack, 2020). Thus far this year, company insiders have sold $309 million in stock versus under $2 million in 2019, fueling suspicion that they may be "downplaying possible obstacles to goose stock prices — and increase their personal profits" (Wallack, 2020). Also among those selling Moderna stock options is Moncef Slaoui, the former Moderna board member and former GlaxoSmithKline executive who now heads up Operation Warp Speed (Rozsa & Spencer, 2020).

From Moderna's perspective, the COVID-19 vaccine represents a lifeline, rescuing the company from a shaky bottom line due to its prior inability to bring any products to market (Garde, 2017; Nathan-Kazis, 2020). Other biopharma companies formerly on the skids are likewise poised to make record profits from the coronavirus (Webb & Diego, 2020). Characterizing the business model for COVID-19 (and other) vaccines as a "great scheme" — particularly given the HHS-guaranteed, risk-free environment — a watchdog group spokesman told the *Boston Globe*, "Taxpayers cover the upfront investment costs and shoulder any downside, while their [biopharma's] executives and shareholders can capture the upside if their drugs pan out and are shoveling obscene amounts of money into their pockets throughout the process" (Wallack, 2020). In the words of a business school professor, "You announce a sliver of positive hope about a product and your stock price goes up," even though "the chances of that product panning out might be relatively low" (Wallack, 2020). In 2020, the company Vaxart saw its per-share stock price rise from 27 cents to a high of $17.49 (Wallack, 2020).

Rolling Stone journalist Matt Taibbi (2020) describes COVID-19 as "the ultimate cash cow", a "subsidy-laden scam", and a legal opportunity for "giant-scale gouging", quoting a legislator who admits that while the public is paying for the research and manufacturing, "the profits will be privatized". Writing in August about how the government-subsidized business model played out for Gilead's drug remdesivir, Taibbi (2020) recounted: "Gilead, a company with a market capitalization of more than $90 billion, making it bigger than Goldman Sachs, develops an antiviral drug with the help of $99 million in American government grant money. Though the drug may cost as little as $10 per dose to make, and is being produced generically in Bangladesh at about a fifth of the list price, and costs about a third less in Europe than it does in the U.S., Gilead ended up selling hundreds of thousands of doses at the maximum conceivable level, i.e., the American private-insurance price — which, incidentally, might be about 10 times what it's worth, given its actual medical impact".

Always a major lobbying presence on Capitol Hill, the pharmaceutical industry has been more lavish than usual with its political spending in 2020, donating over $11 million to individual candidates involved with health care policy and related political action committees (Facher, 2020a). Although the overall amounts represent a pittance for companies earning tens of billions a year, pharma and its lobbying groups recognize that "small chunks of corporate change", when strategically allocated, "can have a significant impact" (Facher, 2020b). Coronavirus vaccine frontrunner Pfizer, the second-largest drug and biotech company in the world and the fourth-highest earner of vaccine revenues (Statista, n.d.; Hansen, 2020), has been the top political spender, likely laying the groundwork for its November 20 filing for Emergency Use Authorization for its coronavirus vaccine (Chander, 2020; Children's Health Defense, 2020d). Pfizer has also benefited from repeated endorsements from the financial community and self-proclaimed spokesmen like Bill Gates (Speights, 2020a, 2020b).

The Military-Intelligence Complex

Traditional vaccines have their fair share of safety problems, but coronavirus and other 21st-century vaccines promise to challenge bodily integrity and informed consent in entirely new ways, particularly given their strong reliance on various forms of nanotechnology (Health and Environment Alliance, 2008; Li *et al.*, 2009; Chauhan *et al.*, 2020; Children's Health Defense, 2020a). Many of the technologies being rolled into COVID-19 vaccines and their delivery systems originated in the military sphere or benefited from Defense Advanced Research Projects Agency (DARPA) funding. DARPA has had a Biological Technologies Office since 2014 and, since the emergence of COVID-19, has specifically directed many of its pandemic-related efforts toward coronavirus therapeutics and vaccines (Gallo, 2020). Far from being suspect, the military's role has been celebrated. A BioCentury report optimistically suggested in March that as an agency "that specializes in turning science fantasies into realities", DARPA might offer the "best hopes" for COVID-19 biotech solutions due to its willingness to pursue "high-risk, high-reward technologies", set goals "that defy conventional wisdom", and go after its goals with a "laser" focus (Usdin, 2020).

One of the principal DARPA-incubated vaccine technologies to gain prominence in the COVID-19 era are the nucleic acid (mRNA and DNA) vaccines that turn the human body into its own "bioreactor" (Ghose, 2015; Usdin, 2020). Vaccines using mRNA (such as Moderna's and Pfizer's) — which developers compare to "software" (Garde, 2017) and praise for their "programmability" (Al-Wassiti, 2019) — target the cell's cytoplasm and rely on delivery technologies such as lipid nanoparticles to "ensure stabilization of mRNA under physiological conditions" (Wadhwa *et al.*, 2020). DNA vaccines (such as Inovio's) are intended to penetrate all the way into a cell's nucleus and come with the risk of "integration of exogenous DNA into the host genome, which may cause severe mutagenesis and induced new diseases" (Zhang, Maruggi, Shan, & Li, 2019). Describing the scientific community's early doubts about nucleic acid vaccines — arising from the potential for "many things" to go wrong — a DARPA program manager recently noted, "It was something that was much too risky for groups like the NIH to fund" (Usdin, 2020).

Risks aside, DARPA and vaccine manufacturers are attracted to one chief benefit of nucleic acid vaccines: They can be developed much more quickly and cheaply. Other military-initiated technologies are also coming into view with COVID-19 vaccines. These include electroporation, which applies a high-voltage electrical pulse to make cell membranes permeable to a vaccine's foreign DNA (Inovio Pharmaceuticals, 2020); syringe-injected biosensors that enable continuous wireless monitoring of vital signs and body chemistry (Peer, n.d.; Profusa, n.d.; Diego, 2020b; Tucker, 2020); and the quantum-dot-based infrared detectors that are under discussion as a tool for tracking vaccination status (Johnson, 2011; Trafton, 2019). DARPA has also played a leading role in developing and funding technologies that "blur the lines between computers and biology", including brain-machine interfaces and neuromonitoring and mind-reading devices (CB Insights, 2019; Gent, 2019; Tullis, 2019).

Some of Moderna's earliest funding came from DARPA, which awarded the company $25 million in 2013 to develop the mRNA platform that has become a key feature of its coronavirus vaccine (Usdin, 2020). Other DARPA beneficiaries now involved in efforts to develop COVID-19 vaccines or therapeutics include AbCellera Biologics, CureVac, Inovio Pharmaceuticals, Regeneron

Pharmaceuticals, and Vir Biotechnology; some of AbCellera's partners include major players like Pfizer and Gilead (Usdin, 2020).

The Pentagon's involvement in coronavirus-related efforts goes well beyond DARPA-funded research. Four-star General Gustave Perna is serving as chief operating officer of Operation Warp Speed alongside chief advisor Moncef Slaoui. General Perna, in charge of U.S. Army Materiel Command, oversees the global supply chain for over 190,000 U.S. Army employees (HHS, 2020b). For the first time ever, the distribution of the eventual coronavirus vaccines is being planned as a "joint venture" between the CDC and the Pentagon, with the latter overseeing "all the logistics of getting the vaccines to the right place, at the right time, in the right condition" (Owermohle, 2020a). In a CBS "60 Minutes" appearance in early November, General Perna indicated that Operation Warp Speed already had doses of (currently unapproved) vaccine and syringes stockpiled and protected by armed guards, and intends to get them out the door "within 24 hours" of vaccine approval and delivered "to every zip code in this country" (Martin, 2020).

The Pentagon has indicated that private-sector involvement could be a key feature of the distribution strategy, and the private sector is positioning itself to participate. Merck, for example, is testing drone delivery of vaccines in partnership with Volansi, Inc., a company that provides "on-demand" drone services for the military (Landi, 2020; Simmie, 2020). In July, Merck's CEO set the stage for its logistics involvement by describing vaccine distribution as "even a harder problem" than the "scientific conundrum of coming forward with a vaccine that works" (Murray & Griffin, 2020).

Outside the pharmaceutical arena, technological transformations that are speeding the world toward more centralized control also reveal the influence of the military-intelligence sector. For example, Amazon Web Services has held cloud-computing contracts with the CIA since 2013, with the original $600 million contract extending to all 17 intelligence agencies (Konkel, 2014). In October of 2019, the Department of Defense awarded the $10 billion JEDI cloud computing contract to Microsoft, a decision that Amazon has unsuccessfully disputed in court (Sandler, 2020). In early 2020, the U.S. Navy awarded a cloud computing contract to Leidos (Leidos, 2020).

5G, too, relies in part on the high-range millimeter-wave spectrum previously used almost entirely by the military for "non-lethal" crowd dispersal weapons (Joint Intermediate Force Capabilities Office, n.d.). In October, the Department of Defense announced it would spend $600 million to test "dual-use" applications of 5G to enhance the U.S. military's "leap-ahead capabilities", including applications such as 5G-enabled augmented/virtual reality, 5G-enabled "smart" warehouses, and 5G technologies "to aid in Air, Space, and Cyberspace lethality" (U.S. Department of Defense, 2020).

Both 5G and cloud computing are critical components of the Big Data and IoT build-out that is enabling the conversion of individual data into the "new oil" (Fitts, 2020a), and both have exploded in 2020 (Howell, 2020; Klebnikov, 2020). The technologies are essential to the "centrally controlled digital financial transaction systems" envisioned by central bankers, who plan to rely on seamless data flows to and from "every smartphone, community, and home without exception" (Fitts, 2020a).

Discussion

As more individuals and organizations connect the technocratic dots and look beneath the coronavirus pandemic's seductively simple surface, it should become increasingly apparent that the pandemic profiteers do not have people's best interests at heart. In *The State of Our Currencies* and other pandemic-related writings, Catherine Austin Fitts (2020a, 2020b) strongly emphasizes the importance of accepting that what is transpiring in the financial, tech, biopharmaceutical, and military-intelligence sectors is interconnected. Part of this involves recognizing that the coronavirus vaccines currently dominating the headlines represent something likely to go far beyond the simple health intervention being held out by scientists and officials as a panacea. Instead, the evidence suggests that COVID-19 vaccines are intended to serve as a Trojan horse to transport invasive technologies into people's brains and bodies. These technologies could include brain-machine interface nanotechnology, digital identity tracking devices, technology that can be turned on and off remotely, and cryptocurrency-compatible chips (Fitts, 2020b).

In Fitts' (2020a, 2020b) view, this type of intimate access — achieved "without notice, disclosure, or compensation" — represents the "final inch" of interest to technocrats. Together with external technologies to control behavior (Max, 2020), such access could permit the achievement of several goals: (1) replacing currencies with a digital transaction system, digital identification, and tracking (an "embedded credit card system"); (2) creating a global control grid that connects the population to the military-intelligence clouds; and (3) obtaining continuous access to valuable individual data on a 24/7 basis (Fitts, 2020b). Countries in West Africa are already piloting a venture by the Gates Foundation, the Gates-funded GAVI vaccine alliance, and Mastercard that "marks a novel approach towards linking a biometric digital identity system, vaccination records, and a payment system into a single cohesive platform" (Diego, 2020a). As Fitts (2020b) summarizes, "Just as Gates installed an operating system in our computers, now the vision is to install an operating system in our bodies and use 'viruses' to mandate an initial installation followed by regular updates". The "neat trick", as Fitts sees it, is that the use of vaccines as the delivery vehicle cancels out legal liability.

It is noteworthy that Bill Gates announced that he was stepping down from the Microsoft board of directors on March 13 — the same day that President Trump declared the pandemic a national emergency (Haselton & Novet, 2020). That same month, the Pentagon reaffirmed its intention for the JEDI cloud-computing contract to go to Microsoft (Rash, 2020; Sun, 2020). By distancing himself from the appearance of conflicts of interest with Microsoft's Defense Department commitments and the Pentagon's subsequent role in Operation Warp Speed, Mr. Gates had more freedom to make the rounds and begin promoting worldwide vaccination and digital certificates (Haggith, 2020). Gates has been less successful in distracting attention from other potential conflicts of interest. An exposé by *The Nation* (ironically also published in March) showed that the Gates Foundation gives billions to corporations in which the foundation holds stocks and bonds — including all of the major pharmaceutical companies — creating a "welter of conflicts of interest" (Schwab, 2020). A dozen years ago, around the time of the 2007-2008 financial crisis, the *Los Angeles Times* outlined the Gates Foundation's numerous holdings in a number of notoriously "destructive or unethical" companies (Piller *et al.*, 2007).

Mr. Gates is not the only party strenuously promoting digital IDs and "no-escape" financial tracking (marketed under the benevolent guise of "financial inclusion"). In October, Kristalina Georgieva,

the International Monetary Fund's (IMF's) Managing Director, evoked "a world in which digital *is* the way in which financial transactions take place" and made it clear that she views universal digital IDs as a non-negotiable requirement for moving in the "right direction" (International Monetary Fund, 2020). Georgieva has, not unhappily, described COVID-19 as a "once in a lifetime pandemic" (Bello, 2020).

Georgieva's remarks should be examined in the context of a proposal by the U.S. House of Representatives to bestow the IMF with $3 trillion "no-strings-attached" U.S. dollars as "coronavirus relief aid" (Huessy, 2020; Roberts, 2020). A U.S. taxpayer-funded gift of this magnitude would be unprecedented and would increase the IMF's lending resources (called Special Drawing Rights or SDRs) by as much as 10-fold (Roberts, 2020). 2020's events (including global debt entrapment and actual or potential food shortages) and the IMF's bullying track record (Bello, 2020) suggest that the IMF could then wield the $3 trillion as a weapon, strong-arming countries into accepting an array of unwanted measures such as digital identities, forced vaccination, and eventually (as the World Economic Forum predicts), the relinquishment of private property (World Economic Forum, 2016). As a step in this general direction, the IMF has strongly praised India's leadership in biometric identification systems. It celebrates the "delivery of social benefits through direct electronic payments to eligible bank account holders", but glosses over the systems' vulnerability to "unauthorized access" and the data breaches that are already rampant (Jha, 2018).

While current prospects for ordinary citizens certainly appear challenging, nothing is a foregone conclusion. Large-scale protests against the curtailment of civil rights have occurred and continue to occur in many countries, most notably in Germany (Depuydt, 2020). The Great Barrington Declaration — a statement crafted by public health scientists from Harvard, Stanford, and Oxford — has garnered signatures from over 12,000 scientists, over 35,000 medical practitioners, and nearly 639,000 citizens from around the world, all concerned about "the damaging physical and mental health impacts of the prevailing COVID-19 policies" (Kulldorff *et al.*, 2020). Similarly, an Appeal authored in May by Archbishop Carlo Maria Viganò, former Apostolic Nuncio to the United States, gathered 40,000 signatures within a few days, with the signatories (religious leaders, doctors, journalists, lawyers, and other professionals) all seeking to draw attention to the threats to sovereignty and freedom that pandemic-related mandates have unleashed (Tosatti, 2020). Archbishop Viganò has also penned severe critiques of the Great Reset, describing its architects as "a global elite that wants to subdue all of humanity, imposing coercive measures [and a health dictatorship] with which to drastically limit individual freedoms and those of entire populations" (Viganò, 2020).

One of the signatories of Archbishop Viganò's Appeal is attorney Robert F. Kennedy, Jr., founder and chief legal counsel of Children's Health Defense, an organization dedicated to ending childhood epidemics by working to eliminate harmful exposures, holding those responsible accountable, and establishing stronger safeguards. In late October, Kennedy recorded a 19-minute video message to people around the world, describing the "coup d'état by big data, by big telecom, by big tech, by the big oil and chemical companies and by the global public health cartel" (Kennedy Jr., 2020). In his closing remarks, Kennedy also indicated that citizens who wish to maintain their freedoms cannot afford to remain complacent: "You are on the front lines of the most important battle in history, and it is the battle to save democracy, and freedom, and human liberty, and human dignity from this

totalitarian cartel that is trying to rob us simultaneously, in every nation in the world, of the rights that every human being is born with."

Competing Interests

The author declares no competing interests.

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Weaponized Pathogens and the SARS-CoV-2 Pandemic

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ABSTRACT

This review zeros in on the aspect of vaccine theory, practice, and research that is the most dangerous, the most controversial, and that is at the epicenter of the alleged SARS-CoV-2 "pandemic". Regardless whether the "pandemic" itself is real or an illusion manufactured out of fear by vested interests, it is central to ethics and policy discussions seeking to understand bioweapons research in general. The official involvement of the USA in civilian bioweapons research dates at least from World War II under President Franklin Delano Roosevelt. The historical records, cloaked in secrecy until after the Anthrax mailing of 2001, reveal an intimate connection to vaccine research and development, its governmental protection from public scrutiny, and from citizen initiated lawsuits. It is an industry that has released dangerous weaponized pathogens by accident and by sinister designs supposedly compensated in the peace-loving nations by unrealistic hopes in non-existent counter-measures for outbreaks, including epidemiological tracking after the fact, vaccines being researched to counter the weaponization of pathogens being studied, immunity enhancing drugs, and downstream hoped for blood sera containing antibodies. Critical questions concern the ratio of real-risks to hoped-for-benefits, the "mitigating" measures "governments" (especially in the USA) have supposedly established to prevent pandemic outbreaks from bioweapons research, and how all that has played out in the instance of SARS-CoV-2.

Keywords: *avian influenza (HPAI), bioweapons research, coronaviruses, COVID-19 pandemic*, *chronic noncommunicable diseases, dual use research, flu vaccines, gain of function*, *H1N1, H5N1, H7N9, Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), SARS-CoV-2*, *weaponized pathogens*

The Path to the Present Pandemic

In 1942, the War Research Service — the USA's official bioweapons research program — was established as a "civilian" agency in Franklin D. Roosevelt's "New Deal". It was headed by George W. Merck (2020), the second President of Merck Pharmaceuticals in the USA, an off-branch of the oldest pharmaceutical company in the world. It is still largely owned by the Merck family dating from 1668 in Darmstadt, Germany (Anon 2020d; Staff at Manager Magazine 2006). Merck remains

one of the world's leading manufacturers of vaccines and one of the 10 largest pharmaceutical money-makers in the world (BizVibe 2020).

Bioweapons Research and Vaccines

Figure 1. George Merck in 1952. Public domain.

Bioweapons and vaccine research may seem somewhat like the opposite sides of the same coin. On the bioweapons side the goal is to make certain disease agents more harmful, and on the vaccine side the objective is to make potential infections less harmful. But no matter how we turn the coin, the two sides are natural cognates — the two faces of a single industry. Developing remedies for microbial pathogens requires knowledge about their genetic construction which is also necessary for increasing the power of selected pathogens to do harm.

From its inception, bioweapons research has been regarded as the evil twin lurking in the shadows while vaccine research has basked in the sunshine of public approval. Meanwhile, fear generated by the threat of offensive bioweapons has motivated a wall of protection around the world's vaccine industry (College of Physicians of Philadelphia 2018). Legal barriers protecting manufacturers of vaccines are especially strong in the USA (Rovner 2005a; Hensley 2011b; USLegal 2016) — the world's largest importer of pharmaceuticals at $99.7 billion (BizVibe 2020) — and in Germany (Picheta 2019), the world's largest exporter of them at $84.7 billion (BizVibe 2020). However, the titanium bubble protecting the vaccine producers racing toward one or more SARS-CoV-2 vaccines (Andrews 2020) is becoming a little more transparent, certainly to much of the whole world through open access academic (peer-reviewed) journals enabling critical discussion of theory, practice, and experimental research.

Fort Detrick, Maryland

The US bioweapons program was originally housed at Fort Detrick, Maryland and in 1944 its oversight was shifted to the US Army's Chemical Warfare Service created during World War I. During that conflict, it was discovered that the Germans were using *Bacillus anthracis* (anthrax) and *Burkholderia mallei* (the bacterium that produced glanders disease) to infect animals being shipped to the enemies of Germany by certain neutral countries (Wheelis 1998). When the US entered the war in 1917 the American counterpart of the Merck company was "expropriated" — meaning its German ownership was terminated and it was taken over by the US government. In 1919, it was, however, re-acquired by George Merck, and now a hundred and one years later both the US company and its smaller German counterpart still remain largely under the ownership and control of the Merck family. In 1957, George W. Merck died at the age of 63 (Anon 2020d). He towered over others in his generation and from his 6 feet and 5 inches in height he uttered the lofty claim that medicines were created "for people not for profits". Coincidentally, the SARS-CoV-2 pandemic, persisting at least in theory throughout 2020 — according to measures grounded largely in tests

known to produce invalid positives in about 99% of the so-called "cases" (so mild as to be completely asymptomatic) of SARS-CoV-2 (Kirkham and Yeadon 2020; Yeadon 2020; also Lyons-Weiler in this issue) — marks the 63rd anniversary of Merck's passing. The public face on the involvement of the bioweapons industry of the USA was all about vaccines while secretly Merck and collaborators were engaged in work that would have given any sensible person the chills.

"Gain of Function" Research and "Dual Use Research of Concern"

Bioweapons research over the last two decades has variously been referred to as "dual use" and more recently "gain-of function" research. These innocent sounding phrases were preferred over the straight-forward "bioweapons" moniker. Later the words "of concern" would be added keeping a poker face in place while acknowledging that bioweapons research is a serious danger to everyone on the planet. After the 2001 mailout of anthrax spores from a source believed to have originated at Fort Detrick, Maryland (Small, Klusaritz, and Muller 2002; Lindler, Lebeda, and Korch 2004, pp. x, 37) — because as one expert, Dr. Quinlisk, testifying before a Congressional Subcommittee put it, "you can't do smallpox or weaponized anthrax in your garage" (Lindler et al. 2004:36) — early in the 21st century the reality of bioweapons loomed in the public imagination and onto the world stage.

After the mailout of weaponized Anthrax spores, what began as whispers behind closed doors about "dual use research of concern" (DURC) and "gain of function research of concern" (GOFROC) were destined to be shouted from rooftops about the ongoing "pandemic" that seems now quite certainly to have been caused by one of the pathogens under study in a multitude of poorly regulated, well-funded, and notoriously insecure bioweapons laboratories of the world (Madjid et al. 2003; Zapanta and Ghorab 2014; Duprex et al. 2015; Evans, Lipsitch, and Levinson 2015; Silver 2015; N. G. Evans 2018; Bhadelia et al. 2019; Latham and Wilson 2020a, 2020b). In plain English, bioweapons are "potential pandemic pathogens" (PPPs) in development, or in plainer language, they are *half-baked and poorly understood deliberately intensified disease causing agents*. They may be poisons produced by disease agents, the active "pathogens" themselves, or they may be the self-same pathogens deliberately "enhanced" like a sharpened sword or a more powerful bomb enabling greater lethality.

Are Communicable Diseases the Greatest Threat to World Health?

Kankeu et al. (2013) asserted that by 2010 it was no longer infectious (communicable) diseases that were the greatest threat to world health. Rather "non-communicable [non-infectious] diseases (NCDs)" had become "the most important cause of mortality worldwide". Calitz et al. (2015) observed that "chronic non-communicable diseases (NCDs) cause the majority of premature deaths, disability, and healthcare expenditures in the U.S." That being noted, funding for research on the prevention of such conditions, they estimated to account for less than 10% of the annual budget of the National Institutes of Health. They concluded that with "the current burden of disease" there is a "funding misalignment" — too much spending on infectious diseases and too little on the prevention of the more costly NCDs. So, prior to the SARS-CoV-2, what was driving the huge upswing in NCDs? The relevant research suggests straightforwardly that NCDs were and are mainly being caused by toxic exposures coming to the unsuspecting public mostly through prescription drugs, medical procedures, and through the most protected industry of all, vaccines.

Now the SARS-CoV-2 pandemic has removed all doubt that the horrendously expensive DURC and GOF research agendas were fraught with mortal danger. Money would have been better spent studying ways to prevent toxic exposures and to strengthen natural human immune defenses. Instead, the vast community of medical researchers, trusting in and joining with the cumbersome, ill-informed, and inefficient government bureaucracy invested billions (and now trillions with the SARS-CoV-2) of dollars in research aiming to transform one or many "potential pandemic pathogens" (PPPs) into bioweapons. The result? Either a real pandemic or an illusion so complete that it has had the impact of a genuine pandemic devastating world economies and resulting in the greatest transfer of wealth from lower and middle classes to rich global technocrats in the history of the world (see the Child Heath Defense paper in this issue).

The intrinsic flaw in the DURC/GOFROC agenda is that the bureaucrats who approved it knew from the start that they did not have the capacity to manage the sort of monsters they were hell bent on creating. The irony of their efforts to understand bioweapons that might be produced by some wicked enemy is that the peace-loving public in the USA was duped into believing the absurd proposition that a monster created by the "good guys" would somehow be easier to manage than one created by an evil state or a non-state cabal. Yet that absurd proposition was backed only by fear of threats and empty government promises about "mitigating regulations" that actually never had a chance of being enforced to prevent a manufactured pandemic.

Intensifying Pathogens

The ongoing DURC research sponsored by the United States government (though not necessarily conducted in the USA), was loosely described in a wordy policy statement in 2012 as "research that involves one or more of the agents or toxins . . . which pose the greatest risk of deliberate misuse with most significant potential for mass casualties or devastating effects to the economy, critical infrastructure, or public confidence, and produces, aims to produce, or is reasonably anticipated to produce one or more of the [following] effects" (EPA 2012):

> a) Enhances the harmful consequences of the agent or toxin;
>
> b) Disrupts immunity or the effectiveness of an immunization against the agent or toxin without clinical or agricultural justification;
>
> c) Confers to the agent or toxin resistance to clinically or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitates their ability to evade detection methodologies;
>
> d) Increases the stability, transmissibility, or the ability to disseminate the agent or toxin;
>
> e) Alters the host range or tropism of the agent or toxin;
>
> f) Enhances the susceptibility of a host population to the agent or toxin; or
>
> g) Generates or reconstitutes an eradicated or extinct agent. . . .

Focusing on the Most Dangerous Pathogens

Disease causing agents listed in that 2012 EPA document included the following:

> Avian influenza virus (highly pathogenic) [bird flu];
>
> *Bacillus anthracis* [Anthrax];

Botulinum neurotoxin [a neurotoxic poison produced by *Clostridium botulinum* and related bacteria];

Burkholderia mallei [a bacterium causing lesions in mucosal membranes, knowns as "glanders disease", which is fatal to 95% of animals infected, and up to 50% of the humans even if treated with antibiotics, believed to have been used as a bioweapon by the Germans in WWI and WWII, and the Russians in the Sovitet-Afghan War 1982-1884];

Burkholderia pseudomallei [an infectious bacterium believed to be the biological precursor of Burkhoderia mallei and which causes melliodosis fatal to about 10% of persons treated for it and 40% for those not treated]; Ebola virus [a virus of "unknown" origins causing "hemorrhagic fever" — bleeding from the body orifices or skin, followed by death in about 25% to 90% of cases];

Foot-and-mouth disease virus [causes blisters in the mouth and feet of cattle and animals with a cloven foot];

Francisella tularensis [causes tularemia also known as "black plague"];

Marburg virus [caused hemorrhagic fever believed to originate in African fruit bat];

Reconstructed 1918 Influenza Virus [the alleged source of the Spanish flu, later asserted to be the H1N1 influenza A virus];

Rinderpest virus [causes cattle plague in animals with even number of toes, fatal to nearly 100%];

Toxin-producing strains of *Clostridium botulinum* [can cause sudden paralysis of vital organs];

Variola major virus [a smallpox virus];

Variola minor virus [another smallpox virus];

Yersinia pestis [causes the diseases known loosely as "the plague" — if it infects the lungs, then it is called "pneumonic plague"; if the blood, then, "septicemic", and if the lymph nodes, "bubonic"] . . . (EPA 2012)

Creating Unenforceable "Mitigating Measures"

So, how did the government propose to protect its people from the "enhanced" pathogens created by its own bioweapons research program? According to that same Federal document published by the US Environmental Protection Agency in 2012, "risk mitigation measures" might include the following laundry list of barely intelligible and certainly unenforceable government gobbledygook distributing responsibility across unnamed "Federal departments and agencies" along with similarly unknown and unnamed "other departments and agencies" for the following empty assurances:

(i) . . . . modifying the design or conduct of the research, . . . applying specific or enhanced biosecurity or biosafety measures, evaluating existing evidence of medical countermeasures (MCM) efficacy, or conducting experiments to determine MCM efficacy against agents or toxins resulting from DURC, and where effective MCM exist, including that information in publications, . . . referring the institution to available DURC educational tools such as http://oba.od.nih.gov/biosecurity/biosecurity.html [an html document, which is, as of November 11, 2020, no longer available from the EPA at the URL supplied] . . . regularly reviewing, at the institutional level, emerging research findings for additional DURC. . . . requesting that institutions notify funding departments or agencies if additional DURC is identified, and propose modifications to the risk mitigation plan, as needed . . . determining the venue and mode of communication (addressing content, timing, and possibly the extent of distribution of the information) to communicate the research responsibly . . . reviewing annual progress reports from Principal Investigators to determine if DURC results have been generated, and if so, flagging them for institutional attention and applying potential mitigation measures as described above, as necessary. . . . if the risks posed by the research cannot be adequately mitigated with the measures above, Federal departments and agencies will determine whether it is appropriate to . . . request voluntary redaction of the research publications or communications . . . classify the research: . . . In accordance with National Security Decision Directive/NSDD-189, departments and agencies will make classification determinations . . . . Actions taken to restrict the publication of technology may have implications under export control laws and regulations (e.g., 15 CFR parts 730-774 and 22 CFR parts 120-130) . . . . the scope of their

> classification authorities and appropriate classification guidelines or may consult with other departments and agencies to make these determinations.
>
> (ii) Departments and agencies may consider whether to refer classified research to another department or agency for funding. (EPA 2012)

Benevolence v. Harm

In 2014 there was an update on the EPA bioweapons policy of 2012. The later formulation opened with a defense followed by a definition of "dual use research":

> Despite its value and benefits [which are hoped for future outcomes], certain types of research conducted for legitimate purposes can be utilized for both benevolent and harmful purposes [the latter being real outcomes of accidents or deliberate releases as in the Anthrax case]. Such research is called "dual use research."

The "benevolent" part is never really spelled out. Apparently it was to consist only of blocking "harmful purposes" intrinsic to research aiming to increase the power of manipulated pathogens to do harm. Driven by *the fear of possible harm* the US Department of Health and Human Services promoted and continues to promote the very research that has the power to turn the feared possibilities into *genuine realities*.

Paraphrasing the Protective Game Plan

The argument works like this: to prevent the horrible potential damage of a Frankensteinian virus that might be created by some known or unknown unfriendly evil power, the USA should create monsters of our own in order to discover their inner workings so we will be able to defend ourselves against them. The bureaucrats spelled out their plan:

> Dual use research of concern [DURC] is a subset of dual use research defined as: "life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied [note that there is no friendly application of such knowledge] to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security" [quoted verbatim from the 2012 document]. The United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern articulates the practices and procedures required to ensure that dual use research of concern is identified at the institutional level and risk mitigation measures are implemented as necessary. (US Department of Health and Human Services 2014)

Thus, realizing that it is dangerous to create monsters that we do not yet know how to defeat, they claimed that it is necessary to take such dire risks, threatening the whole world population, in order to protect ourselves from the monsters that someone else *might be* trying to create. Following the initial defense and the self-sustaining definition of dangerous "dual use research" the government document of 2014 invoked the fear of weaponized pathogens to justify research to produce such "potential pandemic pathogens" (PPPs) in order to learn how, after we have created them, to defend against them. Also, the creators of the doctrine underlying DURC expressed the confidence that the governmental or private agencies engaging in DURC would figure out how to mitigate the dangers of doing the research on the fly, so to speak. It is a little like protecting yourself from falling off the face of a cliff by climbing higher and higher in the hope that you will be able to prevent yourself from falling by constantly increasing the risk of a deadly fall right up until the point when you fall from the cliff. Or, such a program of research could be compared to starting a potential

conflagration in a city or forest in the hope that you will be able to learn how to extinguish the fire once it is fully on the verge of getting completely out of control.

Concentrating GOF research on Airborne PPPs

By 2014, the government's new policy was re-focused on the rapidly reproducing viruses constituting "enhanced" pathogens — ones with sufficient lethality to possibly cause a world-wide pandemic. They began to direct most of their attention to pathogens that could be transmitted in the air. This brought into focus the influenza viruses along with the corona viruses SARS, MERS, and so on because of their facility to spread rapidly from one person to another in the human population (Armesto et al. 2011; Evans 2013). With such particularly infectious viruses explicitly in mind, not only did the US Department of Health and Human Services construct a new policy statement in 2014, but, in view of the obvious dangers associated with that shifting focus, the Obama White House officially proposed a "pause" on "new funding" of "gain-of-function" studies aiming specifically to increase the lethality of such viruses for human beings while at the same time it authorized on-going efforts already underway to continue in order to protect the public (US Department of Health and Human Services 2014). Let's think this through: they ordered a halt because of the dangers, but, oh wait a minute, they ordered the continuation of any projects that were aiming to mitigate the known dangers the ongoing work might lead to. Indeed. Does that make any sense? The wisdom of our government was to suppose that risks were worth taking only if they were severe enough to actually threaten the security of the whole nation. Here, in their own words, are the crucial parts of that policy statement coming straight from the Obama administration:

> In light of recent concerns regarding biosafety and biosecurity [note the euphemistic nature of these terms when what is really at stake is the potential of an accidental release and the likelihood of an intentional one], effective immediately, the U.S. Government (USG) will pause new USG funding for gain-of-function research on influenza, MERS or SARS viruses. . . such that the virus would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. (The White House 2014)

But they qualified the alleged "pause" in funding by allowing the only kind of "exception" that would conceivably justify any such "gain-of-function" research in footnote 1 saying effectively that whatever ongoing projects might be judged necessary to protect the public from the threat of such pathogens should be allowed to continue without regard for the alleged pause in funding:

> An exception from the research pause may be obtained if the head of the USG funding agency determines that the research is urgently necessary to protect the public health or national security. (The White House 2014)

So, what justifies the continuation of the dangerous research? The very fact that it is dangerous was invoked to justify going forward with it irrespective of the pause.

Another Committee Promising Mitigation of Deadly Threats

By 2015, within the National Institutes of Health, under the umbrella of the ubiquitous US Department of Health and Human Services, to deal with the growing likelihood that one or more PPPs might be released, whether intentionally or by accident, the government created another committee, the National Science Advisory Board for Biosecurity (NSABB; Stanley 2015). Their charge according to the 2014 policy statement was

> to draft . . . recommendations for gain-of-function research that will be reviewed by the broader life sciences community. The NSABB will serve as the official federal advisory body for providing advice on oversight of

> this area of dual use research, in keeping with federal rules and regulations. As a second step, coincident with NSABB recommendations, the National Research Council (NRC) of the National Academies then will be asked to convene a scientific conference focused on the issues associated with gain-of-function research and will include the review and discussion of the NSABB draft recommendations. This NRC conference will provide a mechanism both to engage the life sciences community as well as solicit feedback on optimal approaches to ensure effective federal oversight of gain-of-function research. The life sciences community will be encouraged to provide input through both the NRC and NSABB deliberative processes. The NSABB, informed by NRC feedback, will deliver recommendations to the Secretary of Health and Human Services, the Director of the National Institutes of Health, and the heads of all federal entities that conduct, support, or have an interest in life sciences research (including the Assistants to the President for Homeland Security and Counterterrorism and for Science and Technology). The final NSABB recommendations and the outcomes of the NRC conference will inform the development and adoption of a new U.S. Government policy governing the funding and conduct of gain-of-function research. Upon adoption of a federal gain-of-function policy, the U.S. Government will declare the end of the research funding pause. (US Department of Health and Human Services 2014)

Protests and Promises

Apparently, the assurances coming from the NSABB did not make independent researchers like Evans, Lipsitch, and Levinson (2015) feel sufficiently safe. They were particularly concerned about aerosol PPPs that might spin off from DURC and GOF research. They proposed

> an ethical framework for evaluating biosafety risks of gain-of-function (GOF) experiments that create novel strains of influenza expected to be virulent and transmissible in humans, so-called potential pandemic pathogens (PPPs). Such research raises ethical concerns because of the risk that accidental release from a laboratory could lead to extensive or even global spread of a virulent pathogen. (Evans et al. 2015)

On May 6, 2016 the NSABB Working Group, a select panel of experts, concluded with a summary of seven "findings":

> Finding 1: There are many types of GOF studies and not all of them have the same level of risks. Only a small subset of GOF research — GOF research of concern (GOFROC) — entail risks that are potentially significant enough to warrant additional oversight. [Evidently, the expert panelists concluded that they were competent to say in advance which infectious pathogens could safely be made more lethal than ever before while other lethal pathogens would be made unsafe by increasing their lethality. In effect, as Rampton and Stauber (2001) put it in their tongue-in-cheek title, the government's message to the public was, *Trust Us: We're Experts.*]
>
> Finding 2: The U.S. government has several policies in place for identifying and managing risks associated with life sciences research. There are several points throughout the research life cycle where, if the policies are implemented effectively, risks can be managed and oversight of GOF research of concern could be implemented. [So, the panel of experts here again play the *Trust Us: We're Experts* card. They claim their expertise will protect the trusting public because they can discern between really dangerous PPPs and safe PPPs.]
>
> Finding 3. Oversight policies vary in scope and applicability, and do not cover all potential GOFROC, therefore, current oversight is not sufficient for all GOFROC. [Uh oh. Finding 3 suggests the experts cannot be blamed if things go haywire. They issued their own "Get Out of Jail Free" card. It can be played in this game of government monopoly just in case the *Trust Us: We're Experts* card fails to convince.]
>
> Finding 4. An adaptive policy approach is a desirable way to ensure that oversight and risk mitigation measures remain commensurate with the risks associated with the research and the benefits of the research are being fully realized. [By maintaining a certain plasticity, they will be able to bend the policy to accommodate any eventuality. It's a convenient policy for that reason. This is the "One Size Fits All" card that can be played even if the PPP gets way out of control.]

> Finding **5.** There are life sciences research studies, including possibly some GOF research of concern, that should not be conducted because the potential risks associated with the study are not justified by the potential benefits. Decisions about whether specific GOFROC should be permitted will entail an assessment of the potential risks and anticipated benefits associated with the individual experiment in question. The scientific merit of a study is a central consideration during the review of proposed studies but other considerations, including legal, ethical, public health, and societal values are also important and need to be taken into account. [This is the recipe finding: if a certain mix does not work, the panel of experts proposes to add other ingredients on the basis of their expertise until everything is fine. This is the "The Best Exotic Marigold Hotel" rule: if everything is not perfect the recipe is just not finished yet.]
>
> Finding 6. Managing risks associated with GOF research of concern, like all life sciences research, requires both Federal-level and institutional oversight, awareness and compliance, and a commitment by all stakeholders to safety and security. [This one is the "We Feel Good About This So Everything Will Be Fine" rule. They took a vote and the group agreed so it must be right and true and safe and good.]
>
> Finding 7. Funding and conducting GOF research of concern involves many issues that are international in nature. [This finding is the "Other Nations May Be Harmed: So Let Them Beware" caveat.] (National Science Advisory Board for Biosecurity 2016)

Then on December 19, 2017, the Department of Health and Human Services (DHHS) issued its *Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens* and the funding pause (as noted by Evans 2018) was officially ended. The requirements for on-going funded research were that it had to be "scientifically sound", to involve "a credible source" of a PPP, to justify itself by a risk benefits analysis, also to show that there is no way to get the benefits with less risk, that the PI and institution can handle any breaches of security or other problems that might occur, that the researchers promise to communicate their results, that Federal oversight is assured, and that the whole project is ethically justifiable (see Office of Science and Technology Policy 2017, and Evans 2018). The upshot was that all the world should feel quite safe. The experts of the NSABB are on the job and have provided safeguards.

Rushing in Where Angels Fear to Tread

By 2019, the phrase "gain-of-function" research seemed to have swallowed up the former DURC and GOFROC categories because, logically speaking, contrary to Casadevall and Imperiale (2014) as well as Imperiale and Casadevall (2020), *there is no way to do any experimental GOF (genetic engineering of PPPs) research without introducing the danger of turning a "potential pandemic pathogen" into an uncontrollable actual pandemic catastrophe*. The proponents of such research — including Casadevall and colleagues as well as the amorphous US Department of Health and Human Services — nevertheless, have insisted as a matter of policy that the inherent risks of experimental GOF research are compensated by the assertion that hypothetically worse things can somehow be avoided by boldly creating real and actual "enhanced" pathogens in order to avoid the threat of hypothetical developments that might occur:

> Gain-of-function (GOF) studies, or research that improves the ability of a pathogen to cause disease, *help define the fundamental nature of human-pathogen interactions* [my italics to show that the government is talking about assessing something of which researchers are presently ignorant], thereby enabling assessment of the pandemic potential [a hypothetical risk] of emerging infectious agents [ones feared and not fully understood], informing public health and preparedness [future hypothetical] efforts, and furthering medical countermeasure development [non-existent ones, against entities to be created by the researchers doing GOF].

"Biosafety" and "Biosecurity": Read, "Dangerous" and "Insecure" Research

Now, having offered the best argument they could muster for deliberately creating PPPs that might kill millions of people who have no way of knowing what is about to hit them, the government in its wisdom — tempering public fear by "getting out ahead of it" with wise-sounding journalistic language — "comes clean" on the evil it is about to unleash with a subtle bald-faced lie sneaking in with a parade of known facts:

> Gain-of-function studies may entail biosafety and biosecurity risks [what!!!! they certainly do entail such risks by definition and by the historical incidents that have already occurred]; therefore, the [very real] risks and [the wish-list of hypothetical] benefits of gain-of function research must be evaluated, both in the context of recent U.S. [real] biosafety incidents [ones that have already occurred] and to keep pace with new technological developments [that enable a host of new and dangerous GOF/genetic experiments with PPPs], in order to determine which types of studies should go forward and under what conditions. (US Department of Health and Human Services 2019)

By such cleverly composed phrasing, possibly confusing its authors along with the rest of the CDC and government pundits, the potential victims of GOF research are supposed to be assured that the government itself can protect them. By its own declaration it is the sole line of defense against its own dangerous creations. The government must authorize and fund GOF research to effectively weaponize PPPs in order to assess the unknown risks of harm that are certain to follow — all this, in order that the ginned up fear of potential harm may protect the public from the real harm that GOF researchers are being authorized and funded to create — all this for the greater good of the public.

Following the Line of GOF Research to SARS-CoV-2

According to Casadevall and Imperiale (2014), focusing on influenza viruses primarily spread through the air and impacting the respiratory systems — but also taking into consideration the coronaviruses, especially, SARS — boldly assert without any evidence whatever that GOF research with such PPPs is "of utmost importance to societal well-being" (p. 1). They also claim that there has been "a vigorous debate over so-called 'gain-of-function' (GOF) experiments involving pathogens with pandemic potential . . . about the value, safety, ethics, and validity of this type of research" (p. 1). Actually any such debate had scarcely begun to get underway.

Casadevall and Imperiale (2014) harked back to the 1975 conference at Asilomar in California where Paul Berg and others met to consider the potential dangers of genetically engineered monsters made possible the discovery of how to use recombinant DNA to modify and combine genomic components of diverse organisms (Berg et al. 1975; Berg 2008; Yi 2015). Casadevall and Imperiale proposed in 2014 that there should be another such conference to "finding a way to allow GOF research to go forward with minimal risk and maximal benefit" (p. 4). They suggested a "need to lower the level of rhetoric" in order to avoid "the potential to hinder future research and leave society more vulnerable" (p. 4). But it is not the power of the non-existent "debate" to do harm, but of real pandemic pathogens created by microbiologists in the 21st century. Nor can debate protect us from the ongoing SARS-CoV-2 "pandemic" (real or imagined).

GOF Researchers Transform Feared Fictions into Dangerous Realities

GOF research begins with real pathogens with a history of actually causing morbidity (infection or harm) and mortality (death) in human populations, and, possibly, in other species that humans depend on such as farm animals and food crops. The tortured rationale for enhancing, actually, weaponizing, dangerous pathogens such as *Anthracis bacillus*, *Burkholderia mallei*, *Yersinia pestis,* and so on — or the more easily delivered influenza and corona viruses that are in focus in the most recent GOF experiments — is to better understand their inner workings. The strangeness of maximizing the threat of lethal pathogens so those threats can be minimized is hardly removed by noting that the "epistemological value" of such "experiments" is that "they directly imply causality" (Casadevall and Imperiale 2014:2). That is to say, if a newly created GOF pathogen from chickens, bats, or monkeys leads to a pandemic causing wide-spread morbidity and mortality in humans, intelligent people will at least be able to infer that the researchers caused the new disease.

So, anyone not steeped in GOF research might ask how the risk-benefits analysis works for that kind of research. From an actuarial perspective, or using elementary algebra, the general objective of preventing harm from pathogens is to maximize the benefits of a medicine or procedure while minimizing the risks of deploying it. In a perfect world, risks would be reduced to all the way to zero, and benefits would be raised to the level of the greatest possible multitude of multitudes merging at continuity, along the lines of C. S. Peirce (Peirce 1898; Putnam and Peirce 1992; Zalamea 2003). The ratio of risk to benefit would be incalculably great favoring the positive side of the leger. But, of course, we do not live in a perfect world, so what is the effect of changing the ratio of risk to benefits by GOF research? Casadevall and Imperiale (2014) describe that ratio as a "conumdrum" (p. 2). They claim that the risks and benefits of GOF research are "quantitative" but say there are "problems in calculating the numerator [risks] and denominator [benefits]" (p. 3) and that proponents in the hypothetical "debate" tend to magnify the "benefits" in a "risk-benefit assessment" while the opponents focus on "risks" (p. 4).

However, the hypothetical "vigorous debate" about GOF research is irrelevant. It is not taking place while the world-wide SARS-CoV-2 crisis is already underway. With respect to quantification of risks and benefits there is also a huge difference in the calculation of the numerator (risks) that are known to be real — experimental GOF modifications that simultaneously increase (1) transmissibility, (2) host range (from bats to humans, say), and (3) virulence — produce real increases in the numerator of any risk-benefits ratio. By contrast, the denominator is based only on hypothetical benefits, ones that only follow if the GOF research actually reduces the numerator. We are talking about a real strange algebraic construction here.

Whereas the real risks are actualized deliberately by the experimenters engaging in the GOF research — to enable the all important cause-effect inferencing — the future "benefits" of such research are entirely hypothetical, unknown, and incalculable. The hypothetical motive for such research that (Casadevall and Imperiale 2014) lift to a great height is to increase, supposedly, our preparedness to avoid and/or deal with a world-wide pandemic. The difficulty from the "risk-benefits" analysis they are asking us to bet our lives and the the future of the world on, is that it is grounded in non-existent promised future winnings in the form of remedies for any real pandemic that is virtually certain to be caused by GOF researchers. If we think through the actual reality associated with the GOF game plan over time, the longer it persists, the greater is the likelihood approaching certainty at a limit,

that it will actually produce a real pandemic. The logical reality is that the numerator keeps getting bigger irrespective of whatever the denominator is construed to be. Suppose the denominator represents health, wealth, and well-being for all the billions of people on earth, but GOF research continues to increase the risk factor (the numerator) until a genuine pandemic occurs. There is no logic by which the denominator consisting of hypothetical benefits described as "the greater good" can compensate for the certainty that GOF research continues over time to increase the likelihood of an accidental or intentional release of a PPP that can become a real pandemic. The risks-benefit analysis by any reasonable interpretation suggests that GOF research should be shut down in the USA and throughout the world. Existing PPPs should be annihilated, not cultured in poorly regulated laboratories.

Reasonable Probability Estimates: The Known v. Unknown

The funding of ongoing GOF research is like hiring arsonists in a huge city (the whole of civilization) to start fires in order that the fire department (the governments of the world, fractionated as they are) can learn more about how to prevent the whole of civilization or a large part of it from being incinerated. As pointed out by Edwin Thompson Jaynes (1957a, 1957b, 1963, 1965), in his proofs and explanation of "the maximum entropy principle", whenever a "probability distribution" must be estimated on "the basis of partial knowledge . . . the maximum-entropy estimate . . . [that is] the least biased estimate possible on the given information . . . is maximally noncommittal with regard to missing information" (1957a:620). The upshot of the Jaynes' proofs is that the known risks in GOF research so vastly outweigh the hypothetical unrealistically promised benefits, the analysis can only come down on the side of the opponents of such research. Its hypothetical benefits, like the hopes of a compulsive gambler, can only lead toward, never away from, the much feared catastrophe the deranged gambler keeps betting against. In GOF research the maximum entropy principle applies with a vengeance.

The approach of the advocates of GOF research is something like hiring professional fire fighters (some one or more of whom may be arsonists) provided with optimal incendiaries and explosives (known deadly pathogens), to start controlled fires here and there (in GOF laboratories) threatening a large city (the whole human population) in the hopes that doing so will enable fire fighters (virologists, medical professionals, vaccine manufacturers) to protect the city (the world's human population) from the fire or explosion (pandemic) that is certain to reduce large parts of the city to ashes. The law of maximum entropy assures us that such an approach can only trend toward the feared disaster that the GOF research is supposedly aiming to prevent.

Facts on the Real Side of GOF Research (Actual Risks)

Bearing in mind the maximum entropy principle of the mathematician and physicist, Jaynes, it does not require advanced math to see that GOF researchers begin their experiments like an arsonist bent on starting hotter and less containable fires that are likely to maximize damage. They begin their work with lethal pathogens that they know have led to epidemics in the past and that, with the sort of experimental manipulations the researchers are able to come up with, have the potential to lead to a world-wide epidemic, a pandemic like the SARS-CoV-2 crisis. So how is that working out for the proponents of GOF research?

In Search of an Adequate Theory of Causation

It is difficult to fix any particular point for the beginnings of GOF research, but some dates for the discovery of key pathogens are known. For instance, the discovery of *Anthracis Bacillus* is known to have occurred at least by 1877. What is disputed is who got to it first, and just when it was determined, if it was ever actually proved that the bacterium isolated from diseased animals or humans, was the sole cause of the disease. It seems that Heinrich Hermann Robert Koch [born 1843- died 1910], who cultured and injected the pathogen into animals that promptly developed the disease, and Louis Pasteur, who is credited with developing a vaccine for Anthrax, both laid claim to the discovery that *Anthracis Bacillus* causes Anthrax disease (Carter 1988). That particular controversy would also call attention to Koch's postulates about experimentally demonstrating pathogenic causation as now being practiced in GOF research. Likewise, the intimacy of the relation between the theory underlying vaccines and the research with pathogens involved in their development was clarified in the dispute between Koch and Pasteur.

Isolation and Inoculation

In their efforts to experimentally determine the cause of Anthrax disease, both Pasteur and Koch used the strategy of isolating the suspected "germ", purifying it in successive cultures, and then exposing healthy animals to it in order to see if they could be infected by it. This was not a new methodology, but it was Pasteur who doggedly pursued it, thinking aloud in various publications (see the notes in Carter, 1988), that he would be able to produce a "weakened" (attenuated) variant of the pathogen, one that would not have the power to return to virulence, that could be used to prevent the disease in healthy animals deliberately exposed to it (see Carter, 1988, and his references especially, in footnotes 49-52 on p. 51). It was in following out such a line of research that Pasteur proposed the generalization of Jenner's use of *Vaccinia virus* (the cowpox virus) to inoculate humans against *Variola virus* (the smallpox virus), to propose the term "vaccine" (Pasteur 1881b) and to suggest that, in theory, it ought to be possible to find a preventative vaccine for every known pathogen (Pasteur 1880a).

The approach of "isolation and inoculation" actually employed by Pasteur and Koch, as well as certain of their predecessors, as Carter (1985:354) points out, can show that a particular entity is a *sufficient* cause without being powerful enough to prove that it is a *necessary* cause:

> For our purposes, a phenomenon C is sufficient for a phenomenon E if the occurrence of C ensures the occurrence of E. A phenomenon C is necessary for a phenomenon E if the nonoccurrence of C ensures the nonoccurrence of E. It is obvious, but frequently overlooked, that if one wants to bring about some state of affairs, or to explain something that has happened, one seeks a *sufficient* cause, since by bringing that cause to bear one can be certain that the desired effect will follow. On the other hand, if one wants to prevent or to eliminate some state of affairs, or to explain why something did not happen, one seeks a *necessary* cause, since by preventing that cause one can prevent the undesired effect.

As Koch noted during the course of his polemics against the older Pasteur, and as Pasteur had patiently noted early in his generous praise of the younger man's efforts to "prove" that *Anthracis bacillus* is the sufficient and necessary cause of Anthrax disease, sufficiency had been shown adequately, but to prove the rod-like bacterium did not contain on its surface, or in its powers of generation, some other virus or toxin capable of causing the disease would require, in principle, an infinite number of experiments.

For that reason, it is logically quite impossible — that is to say, it is a mathematically provable impossibility — for any number of experiments to rule out all possible causes other than the one singled out for study. Pasteur acknowledged that *Anthracis bacillus* appeared to be the sole cause of the symptoms of what came to be known as Anthrax disease, but there was no way, he argued, to be sure that there was not some other agent on the surface of, or contained within the bacterium, or in some other way associated with it, that was the real causal agent. General proofs reaching all possible cases can sometimes be attained by abstract mathematical or exact logical reasoning, but they can never be attained by ever so many experiments, any more than we could prove that there is no gold on Mars by transporting ever so many handfuls of dirt from Mars back to the earth and finding no gold in any of them. By contrast, one valid experiment, finding a tiny bit of Martian gold, is sufficient to refute the general negative that there is no gold on Mars, just as a single experiment with vaccinated and unvaccinated animals is powerful enough, in principle, to rule out the general propositions (hypotheses) that the vaccine is always harmless (safe), or that it is universally beneficial (effective). Experiments can rule out false general propositions.

However, the empirical proof of a completely general proposition, for instance, that only *Anthracis bacillus* can produce Anthrax disease, would require the experimental examination of all possible agents that might cause it. Such an experimental program cannot be carried out. It could never be completed. This fact was noted by Pasteur early in the exchanges between himself and Koch, and was only later used as an oblique argument against Pasteur, by Koch in which Koch inadvertently refuted his own former claims of having proved empirically (an impossibility) that *Anthracis bacillus* is the only possible cause of Anthrax disease. The fact is that the conclusion might be correct, as virtually all the world now supposes to be the case, but the theory of proof on which it was based, was fatally flawed. Sad to say, that flaw seems to have been incorporated in current GOF and vaccine research and development. However, before connecting the dots all the way to the present SARS-CoV-2 epidemic — it is necessary to take note of Pasteur's notion of "attenuation" and its relevance to current vaccine theory and practice.

The Critical Element of "Attenuation"

Pasteur was the first vaccinologist to explore the possibility that a pathogen could be artificially manipulated in a way that would weaken its harmful effects. He introduced the term "attenuation" in its current use (Moulin 1992; Pasteur 1881a, 1881b) meaning essentially the opposite of "gain-of-function". Whereas GOF researchers, by contrast, are generally seeking to make pathogens more harmful, Pasteur aimed to make them less so in order to use "attenuated" pathogens safely to inoculate animals (or humans) either to prevent their being infected by the disease associated with that pathogen, or to weaken the impact of the disease by strengthening the immune response of the inoculated animal (or person) to the pathogen. Pasteur generalized the idea of weakening a pathogen by suggesting that Jenner's inoculation of humans with cowpox could be thought of as presenting them with an "attenuated" version of the *Variola virus*, the one that causes smallpox. He made this idea explicit in his paper about chicken cholera:

> I infer that vaccine [here speaking specifically of the *Vaccinia vir*us used against *Variola*] rarely acts as a complete preventative [for smallpox]. There are cases cited of vaccinated persons who have had the *Variola*, and there are even cases of persons who have had it, afterwards, as much as three times. (L. Pasteur 1881:55)

Gradation of Effects

Pasteur observed on the basis of his cholera experiments with chickens, that although just one inoculation with the attenuated cholera virus could not prevent the disease in all instances, it always had, in his view, an ameliorative impact: it lessened the effect of the disease, or prevented it entirely. He suggested that this was so for up to three inoculations of the experimental animals he studied. It is noteworthy, however, that he was never aiming to artificially intensify the virulence of the pathogens he was studying, but to render them less virulent experimentally in order to defeat them in their most virulent natural form. He was also concerned to discover whether the pathogens under study could return to their former virulence after being attenuated. If it occurred to him to ask whether *Anthracis bacillus*, cholera, rabies, or whatever pathogen he happened to be studying could be deliberately made more virulent, transmissible, or caused to jump from chickens, rodents, or canines, say, to humans, it was never his own purpose. Pasteur was, it seems, always aiming to prevent or lessen the impact of infectious disease, not to cause them. However, with respect to causation, he was more cautious than Koch who claimed to have ascertained based on a few experiments the sufficient and necessary — the only possible — cause of the Anthrax disease in the whole universe of possible causes.

Pasteur never made such a radical claim. He himself had experimented with bacterial pathogens that prior to his time were so small and difficult to detect that their discovery was denied by many even after their existence was no longer in doubt. As historical evidence of this fact, the work of Ignaz Semmelweis (1861) showing that invisible pathogens from cadavers were unintentionally being transferred by doctors to the epithelial tissues of living patients while they were assisting women in delivering babies, was rejected by mainstream doctors typified by Carl Edvard Marius Levy (while he was head of the leading maternity institution of Europe) for about another 20 years (Anon 2015) until the "germ theory" of disease could no longer be denied because of the work, mainly of Pasteur (Pasteur 1864, 1880a, 1881a). But, Pasteur himself refused to suppose that a bacterium sufficient to cause a disease such as Anthrax was necessarily *the only possible cause of it*. Apparently he kept in mind the fact that something much smaller than a bacterium — some pathogenic element, a toxin or another pathogenic organism accompanying the bacterium, attached to it, or inside it — might be causing the disease. In the case of Anthrax, it seems that Koch's claim that it was the only cause of the disease might have been correct, but it certainly would not have been correct in the case of rabies.

The Special Case of Rabies

Pasteur's empirical disproofs of the popular theory of "spontaneous generation" (1864) also demonstrated that microbes too small to be seen by the naked eye could cause disease. He put it this way in one of his now famous Sorbonne lectures of 1864:

> The air in this room is replete with dust motes, with those tiny nothings which ought not always to be despised, for they sometimes carry sickness or death, in the form of typhus, cholera, yellow fever, and many other kinds of flux (Pasteur, 1864:12).

Thus, having demonstrated the existence of certain microbes that had long gone undetected, Pasteur was cautious not to over-generalize his findings with *Anthracis bacillus* in relation to the symptoms of the disease it was evidently sufficient to cause. Perhaps, as the younger Koch insisted, that bacterium

was the sole cause of Anthrax, but leaping to that conclusion on the basis of a few experiments was still a severe error of logic, an over-generalization that would be false in the case of many diseases that involve viruses that are now known to interact with an organism's immune defenses in a great variety of ways, some of them involving deadly deceptions. Pasteur's work with what was known as *hydrophobia* or rabies was described by Plotkin (2014). He said, "Pasteur and his colleagues . . . most clearly formulated the idea of attenuation and demonstrated its utility, first with *Pasteurella multocida*, the cause of a diarrheal disease [cholera] in chickens [Pasteur 1880b], then anthrax in sheep [Pasteur, Chamberland, and Roux 1881] and most sensationally rabies virus in animals and humans [Pasteur 1885]" (Plotkin 2014:12283-12287). Pasteur inferred that the pathogen he was dealing with was much smaller than a bacterium and he consistently used the term "virus" to describe it in spite of the fact that the first virus, the tobacco mosaic virus, would not be found for several years (Iwanowski 1892) nor would any virus become visible before the advent of the electron microscope in the 1930s. However, Pasteur correctly inferred the existence of viruses, and in 1886, he and Chamberland, one of Pasteur's laboratory assistants developed and patented (Hansen 2016) a porcelain filter that could strain out bacteria leaving viruses and their reproducing particles, virions, behind. It was that filter which would enable Iwanowski to detect the tobacco mosaic virus six years later.

Leading up to the development of that filter, Pasteur's most "sensational" inoculations with an attenuated pathogen involved the yet to be discovered rabies virus with which he began his experiments in 1882. His work would anticipate the differentiation of injections with an attenuated pathogen as contrasted with injections containing antibodies that pathogen harvested from the blood or tissues of a host that was formerly infected by it. His method of inoculation in his rabies experiments combined both types of inoculation. He not only found that pathogens in general can be rendered less virulent by merely exposing them to oxygen or heat, but he also inferred that tissue harvested from an infected animal could be passed through a series of laboratory animals to produce a further attenuation of the pathogen by what would come to be known by the term "passaging" (Anon 2020f). He found that by harvesting rabies from the marrow of a rabid dog, then injecting it into the brain of a healthy laboratory rabbit, would lead to the rabbit developing rabies within about 15 days. Then, he would similarly harvest the infection from that rabbit and inject it in another healthy one. After repeating this cycle through 20 to 25 successive rabbits, he reached what he believed to be the purest attainable form of the pathogen. If it were injected, it would produce rabies in a healthy rabbit within about seven days. Having thus isolated and purified the rabies virus as much as he believed possible, he found that he could attenuate it more and more by exposing it to dry air for longer and longer periods. It was with 13 graded levels of decreasingly attenuated virus that he was able to inoculate the nine year old boy, Joseph Meister, bitten by a rabid dog two and a half days earlier, over a ten day period of treatments, thus saving him from the horrible death of rabies. What worked in immunizing dogs against rabies also worked for humans.

On the Edge of Life?

Pasteur's research with the pathogens that were eventually judged to be the respective causes of Anthrax, cholera, and rabies, led him to speculate that cowpox is like an attenuated variant of smallpox (L. Pasteur 1881). A couple of years earlier, one of Pasteur's co-workers inadvertently allowed a culture of *Vibrio cholerae* to age for a month before injecting chickens with it. He reportedly

(VBI Vaccines, Inc. 2016) went on vacation and failed to inject the experimental chickens until he returned. But, when he did so, the chickens only became slightly ill and later recovered. Pasteur wondered if the aged bacteria, exposed to the air, oxygen in particular, had been weakened, "attenuated", over time. With that in mind he injected the same chickens, now recovered, with full strength laboratory cultured *Vibrio cholerae*. When they did not become ill, he inferred that the inoculation with "attenuated" bacteria, led to the strengthening of the immune defenses of the chickens. With that discovery, in 1879, the field of immunology in medicine was born.

Later on, with the discovery of the unbelievably intense biosignaling functions of nuclei acids and proteins interacting across time, the similarities of *Vaccinia* and *Variola* viruses could be examined in detail (Aguado, Selmes, and Smith 1992; Silverman et al. 2008). It would also be discovered that viruses, much smaller than a bacterium but vastly larger than the nucleic acid strings from which they are constructed, are, as Rybicki put it, "at the edge of life" (1990:182). They are peculiarly small complex molecular entities that depend on their power to invade the essential signaling systems of living hosts in order for the viruses themselves to propagate and thus to survive. In the cells of human beings, the central biosignaling systems attacked by pathogenic viruses are known to fall ultimately under the supervision of nuclear DNA deeply protected within barrier after barrier clear down inside the nucleolus of each nucleated cell's intelligence system of nucleic acids (Oller and Shaw 2019). While some of the RNA viruses can replicate in protoplasm, the cancer-causing viruses, according to current research, in keeping with the "depth hypothesis" Shaw and I proposed in our 2019 paper, must penetrate the barriers protecting the nucleoli of infected organisms and deceive the host's systems of replication into regarding the virus itself as worthy of multiplication.

As noted by Rybicki, viruses are necessarily "intracellular parasites" — that is to say, in order to survive they must not only be associated with a living host, but to reproduce their own genomes, whether consisting of either DNA or RNA — they must commandeer "host cell machinery to synthesize specialized self-assembled particles called virions, whose function is to contain the genome [of the virus] and transport it from cell to cell" (Rybicki 1990:182). Though some viruses, like bacteria (Dietert 2014; Min and Rhee 2015; Rao and Gershon 2015; Shamriz et al. 2016), may be "pathogenic", many are not harmful (Robinson and Pfeiffer 2014; Voelkner 2019), and like the notorious *E. coli* bacterium which is essential to a healthy large intestine in humans, many viruses are not just useful but may even be essential to optimize rather than diminish the health and well-being of the host (Piast 2019).

So Where Is the Center of Life?

Thus, comes the question, if viruses are at the "edge of life", where is the center? Biologists in general, virologists included, are unable to offer a definitive answer, though speculations abound. For example, Piast (2019) hypothesizes a continuum moving from Rybicki's "edge" deeper into the systems of complex organisms. Other ideas are offered by theoreticians like Barbieri (2014, 2019, along with Vega 2018). They end up arguing for a mechanical explanation of life and others have urged quantum complexities in an effort to make sense of the fractal like patterns within patterns and loops within loops that seem to connect things in ways that defy linear thinking (Rajagopal et al. 1999; Salari et al. 2011; Ho 2011, 2012; Li, Walker, and Michaelides 2011; Maleeh 2015; Rogers 2016; Montagnier et al. 2017; Hatano and Ordonez 2019). These last several theories seem to deny any edge or boundary separating living from non-living matter (Krylov 2017). However, one thing

that seems to be agreed upon is that dynamic interpretations of meanings expressed in biosignaling, alias biosemiotic, systems manifested in genomes, proteins, organelles, cells, tissues, and whole organ systems nonetheless remain essential to life and entail an orderliness that seems to reach out and touch, if not embrace, the whole cosmos. If it is supposed that there is a continuum from inert matter merging with viruses at a limit of minimal organization, what would we find at the opposite end of such a continuum?

The Highest Known Level of Symbolic Organization

In the biosphere it is plain to see that there is no form of organized representation that rises above the complexity of human discourse as manifested by the human language capacity. It is that capacity which enables us to probe the mysteries of our own lives and the universe in which we find ourselves (Chomsky 2011; Berwick and Chomsky 2017a, 2017b). Approaching the problem of life from that highest perspective — a "linguistic" or "discursive" perspective — we can define a kind of "gold standard" of the immensely complex systems by which living organisms, from microbes to human beings, wax and wane with respect to the much desired well-being that we refer to generically as "life". The human language capacity led Berwick and Chomsky to pose a deceptively simple question: *Why Only Us?* Why is the language capacity with its amazing complexities enabling us to probe the mysteries of life limited to human beings? Likewise, how are the complexities of that highly abstract system of systems somehow embedded in our genome?

At the center of the well-formed representations upon which viable living systems depend are the unique logical systems known as true narrative representations (TNRs). Such well-formed dynamic systems have three essential components each of which represents and virtually contains the whole: TNRs have the sort of relation to each other that each of the parts invariably represents the whole. It was this fact, evidently, like the persons of the Trinity in Christian theology that led C. S. Peirce to his various conceptions of what he called firstness, secondness, and thirdness (Peirce 1908; Oller 1984; Oller and Collins 2000; Robinson 2010; Slater 2013). It was Peirce, also, who showed more clearly than any other mathematician why Euclid's fifth "common notion" that the whole must be greater than the part is false because, as in TNRs, the part may be equal to the whole. In well-formed TNRs we always find three parts: (1) at the most abstract level, there is a string of symbols manifested in some material way (like the base-pairs of DNA, or the amino acids of a protein, the words of a true story, and so forth); (2) in the middle connecting the other two components of the TNR there are indexical lines in a tensional equilibrium connecting the abstract string of symbols to the concrete complex of facts referred to by that string; and (3) there must be a complex arrangement of real material facts that are faithfully represented by the manifested string of abstract symbols with which those particular facts are connected through the indexes that link them to the abstract symbols of the TNR. Among the unique logical properties that are only found in TNRs, and in no less well-formed representations are the power to determine the facts they represent, to be well connected to the facts they represent, and to be generalizable to all similar facts exactly to the extent of their similarity with the facts of the TNR at hand.

Ordinary Truth: An Abstract, Spiritual Foundation

The edge of life may be a boundary of great uncertainty, but it has been demonstrated with algebraic certainty (Peirce 1897; Tarski 1941, 1949; Oller 2014, 2020) that at the pinnacle of successful

communications of any kind — and, therefore, of the life, health, and well-being of living organisms in general — we find valid TNRs connecting manifest (real) sequences of abstract symbols with and through concrete complexes of material facts in the real world. The logicomathematical proofs of Peirce and others show that all fictions, errors, lies, and even nonsense strings depend for whatever semblance of meaning they may have on the extent of their resemblance to known TNRs. That is to say, all of the less interpretable sequences of symbols that may be constructed in any language, or in any language-like system whatsoever, must be (are mathematically proved to be) parasitic. Another way of summing up the argument is to say that to the less well-formed representations (fictions, errors, lies, and nonsense of varying degrees) depend for whatever meaning they may acquire on their resemblance to well-formed TNRs. From such a standard, it is possible to refine the meaning of Pasteur's "attenuation" in terms of the degree of departure of the derived form from its starting point.

Thus, it follows that the center of living systems is not to be found in the parasitic entities at the edges, nor in the many boundaries of the containers of containers that define living organisms as systems of systems (Oller and Shaw 2019). On the contrary, it seems that the center of organization of any any living thing can only be found in the enormously complex but well balanced TNR that is dynamically adjusted on the fly as that organism maintains the validity of its biosignaling systems over time. We can say that a coherent biosignaling system of systems must reside at the center of every healthy living organism, or we can turn the proposition the other way around and say that health and well-being are defined by a coherent system of biosignaling systems. The empirical demonstration of the existence of such a living system of systems consisting of TNRs at their basis is the fact that disruptions of those systems universally trend toward disorders, diseases, and the inevitable catastrophic failure known as death — an outcome, sad to say, which is guaranteed by the cumulative effect of disruptions of the biosignaling systems of every living thing (Oller 2010; Gryder, Nelson, and Shepard 2013; Oller 2014b). Life, therefore, dependent as it must be on TNRs, as I have argued (Oller 2010) is the logical antithesis of entropy. Or, putting the case in the opposite form, the antithesis of life, the kind of organization found in TNRs, is the sort of attenuation, decay, degeneration, and so forth, that leads ultimately to the complete dissolution of organization which can be thought of as death.

Amplifying the Concept of "Attenuation"

With the just stated logicomathematical basis in mind a more explicit articulation of what is meant by Pasteur's "attenuation" can be offered along with a simple articulation of experimental ways to assess and measure the degree of attenuation achieved in specific instances: *the attenuation of a known disease causing agent can be judged (measured) in principle (theoretically) by the reduction in its resemblance to its own formerly virulent genome (its former self), and in practice (experimentally) by the extent of reduction in virulence (after attenuation) with respect to organisms known to be susceptible of infection by that pathogen.*

The reasoning underlying this amplification of the concept of attenuation, as first clearly articulated by Pasteur (Pasteur 1881a, 1881b), is grounded in proofs developed in 2014 showing that any given TNR of whatever complexity it may possess, all else being held equal, can be successively "attenuated" (Peirce would have used the logical term "degenerated"; Peirce 1877) to produce one or many (1) fictions, by reducing one or more of the material elements of the starting TNR to turn it into a less well-formed representation where some part or parts of the material facts represented, are

not real, and must be imagined; (2) errors, by accidentally replacing some fictional element with a material or abstract element making that part of the representation false; and (3) lies, by deliberately (as in human discourse) or accidentally (as in the hypothetical progress of evolution) polishing up the false parts of an error so as to make it better resemble a TNR in order that it might be mistaken for one. We can take a further step of degenerating the surface form of any meaningful string of symbols by scrambling them or otherwise damaging them so as to reduce them bit by bit toward randomness.

One of the virtues of the logicomathematical proofs in which the theory just articulated is grounded, is the fact that the transitivity of the progression still holds if the starting point, say the genome of a bacterium (such as *Anthracis bacillus*, *Vibrio cholerae*, or whatever) or any virus (say, rabies, cholera, or smallpox), is construed as an "error" or as a deliberate destructive deception (a "lie") to begin with. According to the Nobel Prize winning research of David Baltimore (Huang and Baltimore 1970; Baltimore 1975), the replication of viruses by commandeering the replication systems of their hosts involves a lot of mistakes, errors where bits and pieces of the original virus end up in the cytoplasm of the host. The whole history of viruses, according to Baltimore and mainstream theoreticians, is a progression that theoretically sorts through a multitude of errors, making functional sense of some of them. Bearing in mind that an average-sized bacterium can contain hundreds of average-sized viruses (Oller 2020:94), it is little wonder that disease causing viruses were more difficult to discover than pathogenic bacteria, and it is also unsurprising that some viruses are much more likely to be transmitted through the air in multitudinous ways. Their much smaller size also enables viruses in general to multiply faster than the much larger bacteria that commonly contain and transport them (Guerin and Hill 2020). Whereas the Baltimore method of classifying viruses according to their means of replicating or transforming themselves by combining their genomic identity with some other virus, seemed to be the industry standard for a while, recent work with "structure-based analysis" superimposing viral capsid proteins one on another suggests a simplification from as many as seven or even 15 ranks (International Committee on Taxonomy of Viruses Executive Committee 2020) down to as few as four distinct classes according to Ravantti, Martinez-Castillo, and Abrescia (2020). The authors of the latter study, however, acknowledge "the difficulty of establishing structural 'self' traits for enveloped viruses" notably including the "coronaviruses" and especially SARS-CoV-2.

Regardless, no matter the complexity of the starting composite of "self traits" that might be associated with a given viral pathogen, the mathematical proof showing that all meaningful strings of signs in any language or language-like system whatever, must derive their meaning from TNRs also proves conclusively that the details of any fiction, error, lie, or even chaos of any degree of complexity can be represented in TNRs, but the reverse does not follow. Jaynes (1963) showed that his principle of "maximum entropy" in irreversible processes such as the kind of recombinant experimentation GOF researchers engage in on a regular basis, mathematically guarantees the transitivity of Pasteur's concept of attenuation, or Peirce's logical degeneration, even if applied to the corrupt and degenerate form of an error or a deliberate lie as a starting point. Baltimore's research with corrupted composite of "self traits", as seen in the multitudinous fragments of a virus that are about as apt to be replicated as the original virus, show the meaning of "attenuation" in the case of a recombinant viral pathogen. The pragmatic force of the progression from any given TNR to derived fictions, errors, or lies must also hold for the progression from any selected pathogen to attenuated

variations of it. The theoretical shape (say the genome) of a given pathogen (bacterium or virus) and the infective powers of such an entity are just as subject to the transitivity of attenuation (degeneration) as are any of the other categories of representations that can be derived from TNRs.

GOF Research Is a Game Changer

Following the line of Baltimore's thought about viral replication and its progression across time, it is not entirely irrational to suppose that the accidents of biochemical history can result in fragments of DNA, RNA, and proteins that may quite by chance, over fairly long periods of time, sort themselves into an array of infective pathogens consisting of viruses or even prions (Diener, McKinley, and Prusiner 1982; Prusiner et al. 1982, 1983; Scheckel and Aguzzi 2018). However, when intelligent researchers introduce deliberate experimental manipulations aiming to exploit suspected or known weaknesses of mammalian or human immune defenses against known PPPs in order to cause them to gain in virulence, transmissibility, or to leap across barriers from one species to another increasing the range of hosts infected, inoculation of potential hosts with such beefed up PPPs introduces a far greater likelihood that some one of these "enhanced" pathogens will produce a real pandemic.

As even the proponents of GOF research are quick to admit (Casadevall and Imperiale 2014; Imperiale and Casadevall 2020), there are two classes of uncertainty: on the one hand there is the risk of an inadvertent release of a real PPP similar, for instance, to the SARS-CoV-2 virus of the SARS-CoV-2, and, on the other hand, there is the virtual certainty that nefarious powers aiming to develop offensive bioweapons will be at pains to gain control of the products of GOF research. Meantime, decades of research with influenza vaccines have not produced any notable success in developing effective vaccines to prevent influenza or the common cold. Because of the demonstrated instability of viruses themselves (Huang and Baltimore 1970, et. seq.), and of the vaccines manufactured to emulate and thus help immune systems to defeat them (Kumru et al. 2014), developing stable forms of intrinsically unstable viruses to be delivered in some kind of "attenuated" (less potent) form in a vaccine is a risky enough proposition all by itself.

Is the Reduction in Virulence Adequate in Influenza Vaccines?

Very often, as Eaton et al. (2018) demonstrated (inadvertently, see my discussion of their results; Oller 2020:285–86), the instability factor combined with adjuvants such as aluminum hydroxide (Santiago et al. 2015), evidently sets up anti-viral vaccines such as the monovalent H1N1 influenza vaccine and the trivalent influenza vaccine (TIV) to bring about instabilities in the recipient. For the pregnant women studied by Eaton et al. (2018), either of the vaccines, H1N1 or TIV, on the average, were associated with developmental irregularities ranging from "preterm birth" to "congenital anomalies" and "still birth" (death of the baby) in 71.19 and 67.93 cases per 1,000 administrations, respectively (Oller 2020:285). With such vaccines, the objective of research and development is to achieve sufficient stability to lessen the risk of infection and harm from the pathogen. It is, in the case of influenza vaccines, doubtful whether the the risks to unborn babies and their mothers are lessened or increased by the vaccines.

Unfortunately, Eaton et al. did not compare data for healthy pregnant women receiving neither of the vaccines against the results for those who did get vaccinated. The fact that such a comparison is the obvious basis for making the judgment call as to whether or not a vaccine is safe or effective is

plain in Pasteur's experiments with animals in developing vaccines for Anthrax, cholera, and rabies. He systematically compared vaccinated cases against unvaccinated. Setting aside the fact that current vaccine research almost universally compares one vaccine against another — as Eaton et al. did with H1N1 compared against TIV — and avoids any comparison of vaccinated against unvaccinated persons (E. P. I. C. Magazine 2017; Habakus, Holland, and Rosenberg 2011; Olmsted, Blaxill, and Kirby 2011; Miller and Blaylock 2017) on the ground that it would be unethical to permit, much less encourage, anyone not to be vaccinated, it is notable that the FDA sees no problem in administering dangerous "challenges" (US Food and Drug Administration 2019:5–6) in the form of untested vaccines to human volunteers. If human beings are judged to have enough sense to take a voluntary risk that might inform researchers about the impact of an inadequately tested vaccine, why is the reverse scenario, volunteering to reject vaccination, judged to be unethical?

What If the Aim Is to Increase the Virulence of the Pathogen?

Setting aside the earlier question pertaining to the government's efforts to promote the creation of prophylactic procedures (especially, vaccines) to lessen the threat of pandemic disease from airborne viral pathogens, what about the risks of research aiming to increase the likelihood that some dangerous pathogen can be turned into a real pandemic disease? Proponents may deny that the goal of GOF research is to increase the risks euphemistically referred to as "biosafety" and "biosecurity" (Casadevall and Imperiale 2014:2), but the definition of GOF research ensures that outcome. There is, on the one hand, no guarantee that anything good (any benefit) will come of GOF research, but it is a lead pipe cinch that GOF research increases the risks of producing something very bad — namely something exactly like the SARS-CoV-2. The bio-risk euphemized as "biosafety" is the intensification, weaponization, of dangerous pathogens that is necessary to qualify research as the GOF kind, and the bio-risk dressed up as "biosecurity" is that conducting and publishing GOF research is an open invitation to evil-doers to figure out some way to gain access to one or more weaponized pathogens, or to learn how to create them on their own hook. More importantly, if we have learned nothing else from the recent SARS-CoV-2, government protections for the public are totally inadequate in both categories.

Laboratory Accidents

Documented incidents of accidental and deliberate releases of weaponized pathogens (N. G. Evans et al. 2015; Silver 2015; N. G. Evans 2018) from level 3 and 4 laboratories is where this whole public discussion began to capture public interest. Now, with the SARS-CoV-2, the whole world is interested in the largely unenforceable regulations in place for the most advanced GOF research laboratories in the USA and the world (Centers for Disease Control and Prevention National Institutes of Health 2020). The fact is that levels 3 and 4 laboratories (Jahrling et al. 2009; Risi et al. 2010; Günther et al. 2011) have not achieved the safety and security record that should be demanded by the public if GOF research is to be permitted anywhere on the globe. A malingering question that seems likely to be answered definitively as the greatest lapse of biosafety in world history is whether the virus credited with the causation of the SARS-CoV-2, attributed to SARS-CoV-2, was owed to an accidental release or a deliberate release of a manipulated (laboratory intensified) variant of SARS-CoV (Zhan et al. 2020).

Digging up and Reviving the 1918 Influenza Virus

The CDC (Centers for Disease Control and Prevention 2019e) and related resources (Scull 2020) identify four modern and well-documented "pandemics" preceding the one we are calling SARS-CoV-2. All of them were attributed to airborne influenza viruses — H1N1 (the "Spanish flu if 1918), H2N2 (the "Asian flu" of 1957), H3N2 (an unnamed 1968 epidemic), and another H1N1 (epidemic of 2009). All of these and other airborne viruses, in recent years, have been the focus of genetic engineering in GOF research laboratories. Curiously, the first and probably the most deadly epidemic in modern history was the 1918 influenza epidemic attributed to H1N1. It is known to have killed about 17.4 million persons based on records examined by Spreeuwenberg, Kroneman, and Paget (2018) although the Centers for Disease Control and Prevention (2019a) commonly multiply that number up to five times suggesting that the H1N1 virus may have killed as many as 40 to 100 million (Taubenberger, Reid, and Fanning 2000; Hagemann 2020).

Reconstructing the 1918 Virus to Develop Measures Against Future Pandemics?

The H1N1 virus believed to have been the primary cause of the 1918 epidemic (though most of the deaths were caused by secondary bacterial infection, according to Taubenberger et al. 2000), was literally dug up by Johan Hultin in 1997 (see Jordan, Tumpey, and Jester 2019). The virus was extracted in fragments from the lungs of a victim buried in November of 1918 beneath the Alaskan permafrost (Taubenberger et al. 1997). In the year 2000, GOF researchers at the Armed Forces Institute of Pathology in Washington, DC stressed the importance of receptor binding between the proteins of the host and the H1N1 virus (Taubenberger et al. 2000:242). By 2005 the putative deadliest influenza virus ever known, H1N1 of 1918, was fully reassembled by genetic engineering thanks to funding from the National Institutes of Health and the Armed Forces Institute of Pathology (Taubenberger et al. 2005:893). The public justification for this re-assembly was "to protect public health and to develop measures effective against future influenza pandemics" (Taubenberger et al. 2005:80). It did not take long for the next so-called "pandemic" to come along, and it just happened to be named the H1N1 flu of 2009 (Jordan et al. 2019).

Was it merely a coincidence that the "pandemic" proclaimed in 2009 by the CDC occurred just a few years after the reconstruction of the 1918 virus? Was there any connection with the H1N1 virus manufactured by the CDC and FDA using "reverse genetics" to create a "candidate vaccine" that planned in advance to "be sent out to manufacturers" so they could begin to produce "pilot lots of vaccine" at a cost of "about $1 billion for clinical studies of vaccine pilot laws and for commercial scale production of potential ingredients for a pre-pandemic influenza stockpile" (CDC Newsroom 2009)? Was there just an amazing series of lucky coincidences for the manufacturers of vaccines, or did the research involved in the reconstruction of the 1918 H1N1 virus have anything to do with the H1N1 "pandemic" of 2009? Latham, with a PhD in virology and a post-doc in genetics at the University of Wisconsin, Madison, and Wilson with a doctorate in molecular biology and genetics from Indiana University, surmised that

> the most coherent explanation for the H1N1 variant "swine flu" pandemic of 2009/10 that resulted in a death toll estimated by some as high as 200,000 (Duggal et al., 2016; Simonsen et al. 2013), is that a vaccine was improperly inactivated by its maker (Gibbs et al., 2009). If so, H1N1 emerged from a lab not once but twice.

Skipping over the lesser "pandemics" of H2N2 in 1957 (Asian flu beginning in Singapore, Centers for Disease Control and Prevention 2019b) and H3N2 in 1968 (bird flu beginning in the US, Centers for Disease Control and Prevention 2019c), the very return to the H1N1 nomenclature for the 2009 pandemic by the Centers for Disease Control and Prevention (2019d) is interesting. The series of events bringing about a billion dollars to vaccine manufacturers in 2009 is even more telling in view of the fact that GOF scientists had been seeking to intensify the H1N1 reconstruction at least from about 2004 (Stevens et al. 2004; Sun et al. 2010), along with H5N1 (Evans 2013; Fouchier et al. 2013; Tian and Zheng 2015), H7N9 (Fouchier et al. 2013; Tian and Zheng 2015), as well as corona viruses (Casadevall and Imperiale 2014; Imperiale and Casadevall 2020).

The Ubiquitous "Spike" Protein

Critical systems focused on by GOF researchers in PPP viruses of interest are those involved in the penetration of the host cell "mediated by a spike protein present in the virus envelope . . . In the case of influenza virus, the viral spike protein hemagglutinin (HA) mediates both receptor binding and membrane fusion" (Sun et al. 2010). By 2012 GOF researchers engineered an avian virus H5N1 to leap across from birds and infect mammals (Herfst et al. 2012; Imai et al. 2012). In August of 2013, a group of 22 scientists based in the Netherlands, the USA, Hong Kong, and the UK, wrote a letter to the editor of *Science* (Fouchier et al. 2013) concerning an avian influenza H7N9 infecting people in China. They claimed that the virus had accounted for 43 deaths in 130 cases of human infections. On that basis they argued in their letter that

> The A(H7N9) virus hemagglutinin protein has several motifs that are characteristic of of mammalian-adapted and human influenza viruses, including mutations that confer human-type receptor-binding and enhanced virus replication in mammals. The pandemic risk rises exponentially should these viruses acquire the ability to transmit readily among humans. . . . [Because] classical epidemiological tracking does not give public-health authorities the time they need to mount an effective response to mitigate the effects of a pandemic virus. To provide information that can assist surveillance activities — thus enabling appropriate public-health preparations to be initiated before a pandemic — experiments that may result in GOF are critical. . . . (Fouchier et al. 2013:612).

The authors proposed GOF research to "determine whether genetic changes [engineered by GOF researchers] that confer altered virulence [greater infectivity], host range [jumping from chickens, to ferrets, or, from ferrets, mice, or bats to humans] or transmissibility also change antigenicity [the power of the virus to resist or defeat the host's defenses]" (Fouchier et al. 2013:612). They spelled out their intention to use GOF research specifically to explore the "hemagglutinin cleavage site, that would enable circulating A(H7N9) viruses to become more pathogenic" (Fouchier et al. 2013:612). Focus on that kind of cleavage site had been associated with pathogenicity and the power of the virus to bind to host a receptor was also done with H7N1 (Sutton et al. 2014). Meantime work was also progressing to develop PPPs (bioweapons) from SARS and other lethal airborne corona viruses (Fouchier et al. 2013; Evans et al. 2015; Board on Life Sciences et al. 2016; Fears and ter Meulen 2016; Frank et al. 2016; National Science Advisory Board for Biosecurity 2016; Selgelid 2016; N. G. Evans 2018; Spieler et al. 2020). Perhaps the most disturbing aspect of that research was the hardly concealed collaboration between militarists in the Chinese Communist Party and GOF research proponents, notably the influential Anthony Faucci, insisting that the NIH and its international partners were all working together to prevent, not to produce, the weaponization of the PPPs under experimental investigation by GOF scientists (Breggin and Breggin 2020).

Is the Source of the SARS-CoV-2 Virus Discoverable?

The critical question addressed in this paper is whether the virus identified as the source of the COVID-19 epidemic, the SARS-CoV-2 virus, was (1) a product of nature, like a little green apple that grows in a tree, or (2) was it a man-made variation on something natural, like an apple pie cooked up in a bakery. Is SARS-CoV-2 an ordinary natural virus that just happened to make the leap to human beings, or was it a virus assisted to make the leap to humans through genetic engineering in one or more bioweapons laboratories. Attention has focused on "key interactions between SARS-CoV spike protein and its host receptor angiotensin-converting enzyme 2 (ACE2), which regulate both the cross-species and human-to-human transmissions of SARS-CoV" (Wan et al. 2020:e00127-20). The focus on that spike protein in GOF research and in vaccine development to try to counter-act the impact of SARS-CoV-2 in the COVID-19 epidemic, as Sørensen, Susrud, and Dalgleish 2020) warn, unless is etiology is taken into account, could cause more harm than good by "including the risk of antibody-dependent enhancement" whereby the virus attaches itself to inefficient or defective antibodies in a way that increases its power to invade healthy cells (Sørensen et al. 2020). To stress two points: the ongoing frantic vaccine research in response to COVID-19 shows the inevitable relation between the costly manufacture and distribution of vaccines as being motivated and facilitated by the GOF research aiming to create PPPs in the first place. If SARS-CoV-2 is a manufactured bioweapon, as many have suspected and as some are aiming to demonstrate empirically, it is a huge experimental proof of concept of the historical connection between modern bioweapons research and vaccine development.

Natural or Manufactured?

The public discussions coming from GOF research advocates suggested several possible intermediate animal species that might have facilitated the infection of the first human thus initiating the incubation and proliferation of SARS-CoV-2 leading to the COVID-19 epidemic. In defense of GOF research, and consistent with the virtually homogeneous mainstream publications on the "proximal origin" of SARS-CoV-2, Andersen et al. (2020), published in March 2020 (cited 652 times in the Web of Science database, and 1946 times according to Google Scholar, by December 1, 2020), concluded:

> Although the evidence shows that SARSCoV-2 is not a purposefully manipulated virus, it is currently impossible to prove or disprove the other [natural animal origin] theories (p. 452).

However, there is a logical problem with that claim: it asserts an empirical proof of a completely generally proposition — namely, that no demonstrable connection between SARS-CoV-2 and any intentional bioweapons research will ever be found. Further it is a self-refuting proposition: it asserts that no conclusive trail from a "previously used backbone virus" (p. 450) could "prove or disprove" (p. 452) what they claim to have already proved — that SARS-CoV-2 cannot possibly have been humanly constructed from some prior animal virus.

Their claim is an overgeneralization on both accounts and it is a self-refuting claim with respect to what they say is impossible to either prove or disprove. On the one hand, the 2020 argument of Andersen et al. it is like climbing several apple trees in search of apple pie, finding none, and claiming therefore to have proved that no apple pie exists. No number of failed searches for evidence that the genome of SARS-CoV-2 was a GOF construction can prove that it was not such a

construction. To pursue the analogy, finding an apple pie growing spontaneously in an apple tree would go a long way toward disproving the theory that apple pies do not grow on trees, whereas finding an apple pie in the oven at the bakery — say, at Wuhan laboratory aiming to convert corona viruses into PPPs — would pretty much demolish the natural origins theory that apple pies do not involve any participation from human bakers. Whereas any number of failed searches can never prove that what we may be looking for does not exist, just one successful search can show the opposite.

Cutting to the Chase

With the foregoing in mind, skipping over the hundreds of publications accepting the claim that SARS-CoV-2 could not possibly be a manufactured result of GOF researchers, a great deal of effort has ensued trying to show that SARS-CoV-2 must have originated from the horseshoe bat (Zhou et al. 2020), with a possible stop over in a snake, a civet, or a pangolin (Piplani et al. 2020). Attention was famously directed away from the Wuhan bioweapons laboratories to an outdoor meat market in Wuhan near the epicenter of the "outbreak" of COVID-19 where SARS-CoV-2 might have made its leap to humans. It was speculated that the first human infections might have occurred when buyers and sellers exchanged the meat of just the right SARS-CoV infected reservoir. However, as Latham and Wilson (2020) point out, citing the authoritative *Lancet* article by Huang et al. (2020), the very first case and 13 others among the earliest 41 cases that were infected had no contact with the Wuhan meat market. The fact that Wuhan is the epicenter of bioweapons research with coronaviruses harvested mainly from bats — combined with the fact that bat meat was not for sale at the market — led some researchers to suggest that SARS-CoV-2 may have been an engineered product of the bioweapons research with bat viruses going on in the Chinese Communist Party's military research in one of the Wuhan laboratories (Zhan et al. 2020).

Definitive Research?

While it may not be possible to rule out all of the conceivable ways that SARS-CoV-2 might have been created in a bioweapons laboratory from some prior corona virus, it may be feasible by making some invidious comparisons between proposed parent viruses and the gaps they would have to cross to complete the transformation from their starting genome to the known genome of SARS-CoV-2. Every researcher concerned with the etiology of SARS-CoV-2 has been considering routes by which some particular corona virus from a bat, especially the *Rhinolophus affinis* bat, according to Andersen et al. (2020), the source of RaTG13 which they claimed to be "~96% identical overall to SARS-CoV-2" (p. 450). That particular corona virus, with a genomic sequence "first submitted to *GendBank* on January 27th, 2020" (Yan et al. 2020a:3), however, has an interesting history going back to 2013. It was called "RaTG13" where the "Ra-" portion was taken from the *Rhinolophus affinis* bat, the "-TG-" from the location where it was discovered near "Tongguan" in the Yunnan Province extracted from one or more of three miners who died with COVID-19 like symptoms in 2013, thus completing the designation with the number "-13" commemorating the year of the supposed discovery of the RaTG13 virus (Swarajya Staff 2020). Strangely, as Yan points out, the discovery of the corona virus in question was not reported for seven years by China's famous "bat-woman" Zhengli Shi and her team at the Wuhan Institute of Virology (Hu et al. 2020) and despite its being credited with the deaths of half of the Mojiang miners infected by it in 2012 was not sequenced until

2018 (Cohen 2020; Yan et al. 2020a:5). Meanwhile, it was, along with other coronaviruses the subject of intensive GOF research for the development of PPPs at the Wuhan Institute of Virology (Daszak 2014-2019; Menachery et al. 2015; Breggin and Breggin 2020; Guterl 2020; Lin 2020). Moreover, certain US universities, notably the Galveston National Lab, University of Texas Medical Branch and Department of Epidemiology, University of North Carolina at Chapel Hill, teamed up with Zhengli Shi and her team at the Wuhan Institute of Virology to help them in their GOF/bioweapons research with PPPs, focusing specifically on coronaviruses.

To come to the bottom line, Yan et al. (2020) have produced persuasive evidence, perhaps sufficient for a legally probative case (though not a strict logical proof), that the Mojiang Mine theory proposed by Latham and Wilson (2020a) is grounded in a fictional viral genome, specifically the recently "sequenced" RaTG13 that Yan et al. believe was invented by Zhengli Shi on her laptop and then submitted to *GenBank* on January 27, 2020. Moreover, the corona viruses supposedly extracted from Malayan pangolins, and from bats, ones unnaturally similar in excessively improbable ways to RaTG13, are also very likely to be either laboratory creations, or fakes created to direct attention away from the growing conviction, plausible if not definitively demonstrated, that SARS-CoV-2 is a humanly manufactured bioweapon that either was deliberately or accidentally released from the Wuhan Institute of Virology. After that occurrence, which Yan et al. assert was deliberate, the plot thickens in a way that suggests very plainly that the Chinese Communist Party and the militarists at the Institute, headed up from January 2020 by China's bioweapon's expert Major General Chen Wei of the People's Liberation Army (Thomson 2020), decided to cut their own internal losses while performing an unrestricted biological warfare experiment of the rest of the world: they systematically restricted travel to and from Wuhan within China (covered up the epidemic occurring there and all of the research on the SARS-CoV-2 causative agent), while encouraging as much international traffic as possible to the rest of the world (Yan et al. 2020a:26–28).

Summary

Bioweapons research and development in the free world has been linked closely to vaccine research dating back at least to the creation of the the War Research Service in the United States in 1942. Prior to that time, it is true that vaccine research enjoyed the reputation of being "for the greater good" — with risks that seemed worth taking on the theory that worse things could be avoided. In the latter part of the 19th century, Louis Pasteur became an international celebrity of great renown for his work in demonstrating that some deadly pathogens could be killed with heat, and that ones as lethal as Anthrax, cholera, and rabies could be weakened, "attenuated", by exposing them to oxygen or heat. On the basis of the supposition that cowpox (*Vaccinia*) is regarded by the body as a weaker version of smallpox (*Variola*) — on account of the supposed resemblance of one pathogen to the other — Pasteur inferred that animals and humans inoculated with weakened versions of any pathogen could become immune to them. As Christopher A. Shaw has suggested (personal communication), by such logic, we could argue that the purpose of a vaccine is to trick the human immune defenses into treating the attenuated pathogen as if it were the real thing. In this way, vaccinologists are inadvertently producing an experimental proof of concept of TNR-theory with every inoculation: for the deception to work at all, as the logical theory requires, the attenuated (substitute) pathogen, must resemble the real thing. The fact that the resemblance can never be perfect except in the case of the natural pathogen representing itself, can be hypothesized to account

for the relatively shorter lived resistance engendered by vaccines as contrasted with naturally occurring pathogens.

Pasteur also did something that is not required in the current climate of frantic, catch-up vaccine development running behind GOF research: he systematically compared vaccinated against unvaccinated animals to experimentally assess the efficacy and safety of the vaccine he was developing. The inoculation of Joseph Meister after he was bitten by a rabid dog was Pasteur's most sensational success though it may have worked in part by not only exposing the child to successively more virulent forms of the virus but also exposing him to antibodies effective against rabies coming from the formerly infected laboratory animals. That question aside, immunoglobulin capable of binding and possibly destroying a pathogen, is almost certain to be safer than deliberate exposure to the pathogen itself. Also, immunoglobulins in general would, according to current research (Akazawa-Ogawa, Nagai, and Hagihara 2018), retain their integrity under the drying out protocol for attenuation used by Pasteur.

All that being said, with respect to GOF research, it seems that Pasteur's careful reasoning and his ethical concern for the lives of animals and human beings, have fallen by the wayside as vaccine developers frantically chase after the PPPs being cranked out and released, whether by accident or on purpose, from bioweapons research laboratories. Does it really make sense to maximize the virulence, transmissibility, and host range of the most dangerous pathogens in the biosphere in the hope that doing so will enable the well-intentioned researchers of the world to outsmart the evil ones and also to outsmart themselves by figuring out how to contain the monsters they are helping to create?

Competing Interests

The author declares no competing interests.

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Balance of Risk in COVID-19 Reveals the Extreme Cost of False Positives

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ABSTRACT

COVID-19 public health responses, including lockdowns and diagnostic testing strategies, have had consequences. Economic costs (see the CHD paper in this issue) could reach $16 trillion dollars, 90% of the US annual GDP. While harm to small businesses, unemployment, worsening poverty, death from cancer, increased suicides, social isolation, and restriction of freedom all increase the perceived need for drastic responses from the top, flawed measures are costly. A *diagnostic assay*[2] of tests for COVID-19 depends for its validity on its *sensitivity* and *specificity* assessed in terms of the true positive rate (TPR), false positive rate (FPR), true negative rate (TNR), and false negative rate (FNR) of the assays. In this pandemic, Real Time — Polymerase Chain Reaction (RT-PCR) testing has been relied on for drastic top-down responses (as in shutting down the economy of whole nations or the entire world). Here I focus on false positive results where RT-PCR testing suggests many infections by SARS-CoV-2 where there are none. I show by mathematical modeling how reporting positive results of RT-PCR testing, ones known to be false in a measurable percentage of instances, is at least 40 times more impactful (in a detrimental way) than increasing or decreasing the number of tests conducted. To balance the risks of errors in diagnosis, false positive results must be minimized by validating nucleotide sequences and estimates of *viremia* to avoid flagging individuals as contagious when they are not.

Keywords: *balance of risk, diagnostic assay, economic costs, real time - polymerase chain reaction (RT-PCR) testing, viremia*

Introduction

The consideration of the outcomes of tests for use in diagnosis of COVID-19 have included concern over false positives (Kirkham and Yeadon, 2020; Yeadon, 2020), and no fully academic

[2]**Author's Note:** A short **Glossary** is provided as an **Appendix**. Items listed there appear in the text in *italic font.*

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treatment has addressed the attendant consequences of false positive test results. The cost of the false positive depends entirely on the policies put in place to respond to positive tests, which range from a patient becoming aware, in private of their own test status (in-home, private testing) to shutting down schools, businesses, and public spaces (e.g., grocery stores and malls). Unnecessary disruptions can lead to job loss, and permanent shuttering of businesses. On an individual patient basis, false positives can lead to useless and harmful quarantining, wasteful contact tracing, and patient harm due to failure to provide an accurate diagnosis. If the patient is hospitalized due to the results of the test, hospital-acquired infections of SARS-CoV-2 and other pathogens is a real and unnecessary risk if the test result is false. For hospitals, wastage of COVID-19-related resources can result from false positives. For society, inaccurate published rates of "cases" can lead to unwarranted levels of panic, fear, anxiety, and social stress.

Whilst it is now recognized that when prevalence is low, false positive COVID-19 diagnoses may be high, the problem is not generally expressed as "when prevalence is low, the number of false positives can be vastly greater than the number of true positives"(but see Skittrall et al., 2020), as long as a test has a non-zero FPR. No consideration to any quantified cost of the false positives has been conducted; this would require the derivation of a utility function that captures consequent and indirect risks, and no system of outcomes surveillance is in place capable of capturing that information for modeling.

No generally accepted cost/benefit analysis has been applied to testing strategies in COVID-19 in the US. The initial fumbling of testing led to an urgency to get testing "up and running", with too little rational consideration regarding implementation. Little to no consideration has been given to the question of when and how symptom-based testing (i.e., testing those who have symptoms) might ethically be switched to arbitrary testing, random sampling, or screening. The haphazard program is co-occurring with the testing of contacts of confirmed cases.

With any imperfect test with non-zero false positives, false positive test results vastly outnumber true positives when prevalence is low (Skittrall et al., 2020), and, to date, prevalence of SARS-CoV-2 infections are always low. One of the few investigations into false positive rates suggested consequent validation of the RT-PCR test result using serology weeks after the initial test result (Basile et al., 2020). The current per-week average prevalence of COVID-19 "confirmed" cases is 4.5% (CDCa), a low prevalence at any given time. Basile et al. (2020) reported a false positive rate of RT-PCR testing of 11%; Lee (2020) reported 30% of reference sets mislabeled as "COVID-19 positive") and 20% mislabeled as "COVID-19 negative". The potential consequences to societal responses are immense and must be re-addressed.

A few approaches have been devised to minimize the false positive rate but are not in widespread use. The most employed attempt is repeated RT-PCR testing. Repeated PCR with the same kit will not guarantee zero FP, especially if the patient being tested has genetic sequence that matches the primer sequences for the kit used, or if the kit used is prone to false positives. Restricting testing only to those with high prior probability of a positive result (e.g., known exposure to confirmed cases) has also been proposed as a way to prioritize patients for testing (Skittrall, 2020), and this strategy would under the scenario where cost of the false positive is much greater than cost of the false negative (CFP>>CFN) be superior to indiscriminate (random) testing and population screening. However, this does not change the intrinsic false positive rate of the tests themselves.

Among the approaches proposed, the only approach that would drive FPR to zero is the use of Sanger sequencing to validate the PCR product pool, is in fact SARS-CoV-2, and not the product of other off-target non-specific amplification (Lee, 2020).

Distortions and Misinterpretations on Testing

"Too Sensitive" – One perspective misrepresents COVID-19 false positive diagnoses as a result of RT-PCR tests being "too sensitive", with the idea that it could detect the virus if someone walked through the room with the sample within a sealed test tube. In other words, the test is too good if there is contamination. It's at best a poor choice of words to claim that the assay is "too sensitive"; the fabricated scenario itself it patently false. CLIA-certified laboratories use clean rooms and have built-in safeguards preventing among-sample contamination. While contamination can occur, the likelihood is low, and laboratories that produce false positive results due to cross-sample contamination should lose their certification. We should reserve the term "sensitive" for use in the context of performance evaluation measures.

The term "case" should not be loosely used. "Case" implies symptoms and "diagnosis". *"Test Positive = 'case'"* –, and test-only results as "cases" is commonplace and is incorrect. The medical diagnosis, COVID-19, has a set of symptoms, and is in part diagnosed with radiologic assays. COVID-19, not the presence of SARS-CoV-2, is the illness, i.e., a "case". Substitution of a positive result for the detection of the virus for a clinical diagnosis makes "COVID-19" clinically inexact. Examples of how a positive test result – a test-positive true detection of the SARS-CoV-2 virus sampled from a patient – can still be a diagnostic false positive includes (a) a person recovering from a SARS-CoV-2 infection with lingering viral remnants and (b) recent, non-transmissible infection in a person who is already immune and who will not experience sufficiently high viremia to cause transmission.

Unfortunately, and remarkably, CDC's final COVID-19 guidelines made a radical departure from the historic norm, in that COVID-19 diagnosis use the same code, "U07.1, COVID-19" for both symptomatic and asymptomatic persons with a positive COVID-19 RT-PCR test (CDCb)(5). As we will see, this will dramatically amplify not only the number of "cases" but also visit upon society a massive cost of continuous stream of false positive test results.

"Test, test, test" and *"test everyone"*. Once containment had failed, some called for mass testing under the assumption that more testing – or any testing at all – is necessary for a rational public health response to COVID-19 (e.g., Linnarsson et al., 2020)(6). In the United States, the protocols in place to contain (via early, accurate testing) and control (via testing followed by contact tracing) were both made intractable due to flaws in CDC's test kit (Hinton, 2020). FDA initially offered only emergency use authorization (EUA) to CDC, withholding the same for other RT-PCR test makers. When it became apparent that CDC's test was flawed, FDA finally allowed EUA of tests made by other providers (FDA, 2020).

FDA's EUAs only required empirical evidence of sensitivity and did not require any data in support of assertions of test specificity. In lieu of data on specificity derived using human samples, FDA allowed test manufacturers to estimate specificity based on the computational comparison of their primer sets to the host organism (*Homo sapiens*) based only on a computational comparison of the nucleotide sequences of the primer set for each test to the human genome using the Basic Local

Alignment Search Tool (BLAST) sequence matching algorithm. Due to lax standards on empirical estimation of sensitivity, FDA then requested data from PCR test suppliers on sensitivity, but not specificity, in contrast to their EUA requirements for antigen and serology testing (FDA, 2020b). Data on pathogen specificity was later supplied by some test makers proposing pooled testing.

This situation stands in stark contrast to the approach used by scientists in Germany in January 2020, who used sputum samples from healthy individuals spiked with synthetic oligonucleotides matching SARS-CoV-2 virus (Corman et al., 2020) to determine the sensitivity of their assay (100%), and matched sets of sputum samples that had not been spiked to determine the specificity of their assay (100%). They also used sputum samples of individuals with non-SARS-CoV-2 respiratory pathogen illness to estimate their test pathogen specificity (100%, Corman et al., 2020).

As we will see, the absence of a requirement of empirical estimates of false positive rates for EUA may prove to have cost society far more than the benefit of the resulting ad-hoc, irrational indiscriminate testing program.

"Flatten the Curve"

The overall strategy to "Flatten the Curve" was a derivation on the initial effort to "protect the medical community" while they prepared for a "surge" in cases of COVID-19. While the number of test-positive "cases" certainly did increase, few hospitals reported ICU demand beyond capacity. This is in part due to the shut-down of non-essential medical care visits. Emergency care resulting from medical errors and hospital-acquired infections dropped. In-person care for those struggling with mental conditions plummeted.

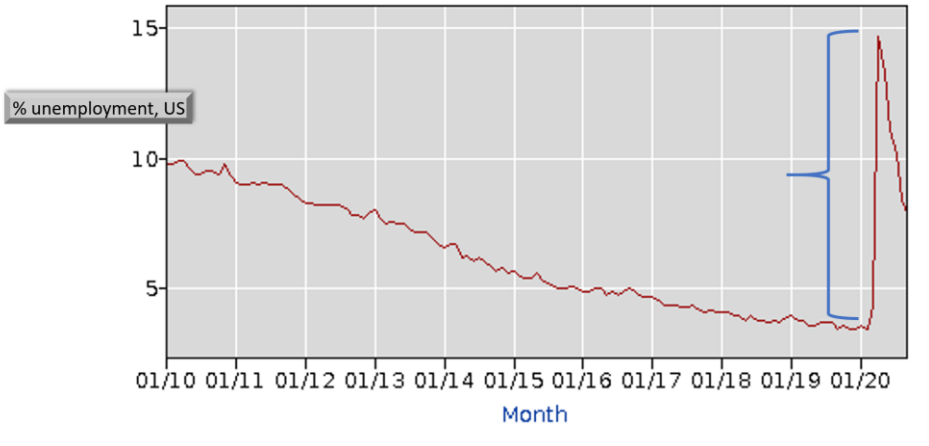

Figure 1. US Unemployment 1/10-present. The massive rise is usually attributed to "COVID-19" but is actually due to the unnecessary and damaging effects of societal responses mediated through mass false positive rates of diagnoses of "cases" of COVID-19. Source: US Bureau of Labor Statistics, 10/20

Weeks after the medical community came to be aware that they could handle the number of confirmed cases of COVID-19 requiring hospitalization, the social contract to protect the medical

community morphed into "Flatten the Curve" – including extensions of policies of social distancing, closure of businesses, and masking. In Pennsylvania, Governor Tom Wolf classified businesses as "essential" and "non-essential". After clamor from some, certain businesses were re-categorized as "essential", demonstrating that the Governor's decisions and actions have been arbitrary.

In the meantime, messages from voices like Bill Gates and Anthony Fauci warned that there may not be a return to normalcy, i.e., re-opening businesses, return to work, etc. until a vaccine was approved by the US FDA. Importantly with no definitive timeframe available, these reactive policies had a devastating effect on the unemployment rate in the US, which had declined steadily for ten years prior to 2020 only to shoot up from 2.5% to just under 15% (US Bureau of Labor Statistics) between 2019 and 2020 (Figure 1).

"All COVID-19 Cases Must Be Detected"

The sentiment that deaths from COVID-19 are somehow more tragic than other deaths seems to have taken hold to the point where the presumption of concern over other deaths – including deaths of despair due to unbalanced public health policy responses – was only able to take hold nine months following the beginning of the outbreak in the US – and then only by part of the medical and scientific community (Signees, 2020). Comparisons of death rates between COVID-19 and influenza are made impossible due to loose accounting and exchanges of default diagnoses for people dying from respiratory viruses of any kind without a molecular test, a practice started by CDC in 2014.

Deaths due to cancers undiagnosed due to the suspension of non-essential medical care, deaths due to delayed "elective", but life-saving surgeries, can be combined with deaths of despair due to unemployment and social isolation. The consideration of deaths from COVID-19 as more important than deaths from suicides due to economic despair has no rational basis.

"Diagnostic Substitution of Respiratory Viruses is 'Erring on the Side of Caution' "

In 2014, CDC changed the manner with which it counted – and reported – deaths due to influenza. Prior to 2014, CDC reported deaths from confirmed cases of influenza viral infection (i.e., "influenza") separately from pneumonia. Following 2014, they began combining influenza and pneumonia deaths into "influenza & pneumonia", and then also combined "influenza & pneumonia" (aka "P&I") with deaths from RSV, SV, and coronaviruses into a catch-all category they referred to as "Influenza Disease". Prior to 2014, about 11% of cases of P&I were deaths that involved confirmed influenza viral infections (Lyons-Weiler, 2020).

At the tail end of 2019/2020 flu season, the reporting of "Influenza Disease" in 2020 clearly had to exclude COVID-19 – and any reports of COVID-19-like respiratory illnesses not confirmed by RT-PCR. Coming into the 2020/2021 flu season, influenza-related infections and deaths have decreased dramatically – a shift sometimes attributed to widespread masking and social distancing – and yet COVID-19 "cases" continued simultaneously to increase. It is reasonable to suspect diagnostic substitution of "influenza disease" for "COVID-19" 'cases' as the northern hemisphere enters the influenza season. The default that all respiratory cases without molecular testing defaults to COVID-19 is harmful to society's ability to mount a rational and appropriate response.

Social Pressure

In the US, enforcement of public health policies, however well- or ill-founded, falls largely to the Governors of each state as empowered by their state constitution and amendments thereto from legislation. The policy makers seem to suppose that "the tools of social pressure are appropriate in response to an outbreak/epidemic/pandemic". The media plays a large role in the public's perception of their rights and responsibilities in matters of public health. Appeals to self-sacrifice for the "greater good" do not work for all individuals, especially to members of the public who are suspicious of clustered profit incentives, and of government/industry collaborations which are seen as serving interests other than the public "good".

Top-down control, one-sided public health strategists made weakly supported assumptions. When combined with a clear — and in some cases overtly stated — bias against antiviral treatments (CNBC, 2020)(10), and with the use of disparaging name-calling (e.g., "Anti-maskers" and "Anti-vaxxers"), the polarizing effects of the politicization of deeply intimate personal and private matters of choice become worse than ineffectual — they can damage public health by ignoring or externalizing unintended consequences. The positions held by public health servants can become juxtaposed as antithetical to an informed public's positions on matters of medical and public health. Industry profits priorities lead to what many in the public and professional sphere now see as a cycle of abuse and betrayal of trust.

Tests for SARS-CoV-2 have a bad track record in the US, beginning with CDC's failure to adopt a validated test available from Germany (Corman et al., 2020)(11), available in mid-January. By January 16, a total of 141 other countries had adopted that test. While computational predictions provided to FDA led to the expectation of zero false positives, field experience has shown that SARS-CoV-2 RT-PCR testing indeed has a significant false positive rate that can no longer be ignored. Formal empirical field estimates range from 30% (Lee, 2020) to 11% (Basile et al., 2020). Use of test cycle counts that bias the result toward positive in a manner that does not quantify the viral load can be expected to lead to positive test results in people who do not necessarily pose a risk of contagion. They, too, count as false positive "diagnoses". The real-world performance evaluation characteristics of diagnostics (SN, SP, Accuracy, PPV, NPV) will be a function of the design of the test. The benefits and costs of their use depend also on our strategies, rational or not, and the attendant costs of both false positive and false negative diagnoses of COVID-19.

Balance of Risk

I assert that the most productive representation of COVID-19 testing risks is a Balance of Risks between cost of false positives (CFP) and cost of false negatives (CFN). This reality has counterintuitive and important consequences for national testing strategies. As medical care improves for COVID-19 and shifts primarily to outpatient protocols, the cost of the false negatives has been dramatically reduced. As issues around COVID-19 public health policy become increasingly politicized, the perceived need to control the public's perception that the greatest risk to them is COVID-19, leads to public health strategies that maximize the cost of the false positives. I introduce this analysis under various scenarios reflecting the relative size of CFN and CFP. These various application-of-testing scenarios all have distinct outcomes of the attendant costs of false positives to society. In this analysis, I review each scenario from the perspective of a public health

official seeking information on when, and how, to incorporate testing into a public health response to an outbreak similar to COVID-19.

None of the considerations above have represented evidence-based attempts to derive a public health policy founded on a Balance of Risk scenario. In a Balance of Risk scenario, all information, regardless of whether it supports a specific conclusion or not, is seen as highly valuable, and it is imperative to use all information to derive optimized decisions on policies. Balance of risk is used by US Federal Reserve banking theorists to balance the opposing risks of inflation and risks of recession. Since costs to economic health exist on both sides of the equation, due consideration of costs by changing interest rates in favor of inflation or recession is seen as counterbalancing.

In public health no rational approach described as a Balance of Risk has been formulated in which costs associated with specific public health and medical options are seen as counter-balancing forces, leading to an optimization by which harm from both sides of the equation can be simultaneously minimized. Just like the Federal Reserve can adjust inflation rates to attempt to balance the opposing dangers of both inflation and recession to maximize overall economic health, a similar approach could be envisaged in which the costs of false positives might be weighed against the costs of the false negatives, if not in a manner designed to impact public health policy, certainly in a manner by which such policies might be more realistically interpreted by health care professionals and the public.

Parameters

The modeling of scenarios requires input parameters of N, population size, CFN (always 1.0, a stabilizing parameter), CFP (relative to CFN, so CFP = 1.1 is 10% higher CFP relative to CFN), prevalence, test sensitivity (SN=0.99), test specificity (SP=0.89), and %T, the percentage of the population tested over the time period of interest. In the US, the average weekly number of tests has been 581,631. Testing "rates" (per capita) therefore depend on the timeframe and should be expressed as such (581,631/328M or 0.177% of the population tested per week, 4*581,631/328M or 0.709% of the population tested per month, 52*581,631/328M, or 9.22% of the population tested per year). The percentage of the population tested, %T, is thus varied from low (5%) to high (95%). The output terms of CFP and CFN can be thought of (inexactly) as the sum of individuals impacted negatively by all possible negative impacts represented as the input levels of CFN and CFP. The scenarios below therefore reflect the costs over any period, given a specific prevalence of active transmissible infections, chosen from over the entire range of possible prevalence. The analyses below assume the population size of the US (328M); across the entire outbreak, the prevalence across all states has averaged 4.5% (source: Our World in Data). I used the FPR estimate of 11% for SP = 0.89 (Basile et al., 2020); the spreadsheet for these analyses will be made available as supplementary material for parameter value exploration.

Outcomes

Cost of the False Positive = CFP, Cost of False Negative = CFN, Total Cost = CFP+CFN; Cross-Over Prevalence = COP = incidence (% infected) during an outbreak when CFN > CFP. MaxTotalCost% is the Total Cost at the prevalence where the Total Cost is maximized; when

MaxTotalCost% = 100%, more testing is warranted once the population achieves the COP (before then, the CFP may be prohibitive). When MaxTotalCost% = 1%, no testing is warranted because the cost of the false positive vastly exceeds the cost of the false negatives and every test endangers society more than an additional false negative. In the Scenarios below, a is the constant of proportionality of the CFP relative to the CFN; i.e., when a = 0.1, CFP = 0.1(CFN).

Scenarios

The goal of the analysis is to characterize the responses of costs of each type, and total costs, to variation in input parameters that we can control, such as %T, and, via our responses to positive test results, CFP. In each of the following scenarios, testing of a given percentage of population is modeled over a range of prevalence. In practice, the spatiotemporal clustering (or lack thereof) of testing in juxtaposition to risk of being infected or being infectious varies with testing strategy, which therefore might have different exact relative and total values, such as symptom-based testing, random limited testing (sampling), and screening. Thus, relative input values of CFN and CFP are assumed to be independent. Importantly, the modeling is not dynamic, i.e., it does not include consideration of spread of the virus throughout the population, nor the effects of transmissions from FNs or the untested to those not infected. It is a demonstration of principle of a decision-making tool that could be used on daily basis for best-available Balance of Risk. Other models can be used to provide inputs on exact types of costs via utility function.

Scenario 1 – CFP << CFN

When CFP << CFN (e.g., CFP = 0.1CFN), the maximum cost exists at highest prevalence until near-universal testing is achieved (Fig 2A). Under these conditions, CFN makes up most of the of the total cost (Fig 2B), with a cross-over prevalence (COP), depending on testing level, ranging from COP=0.01 (5% testing) to 0.36 (99% testing; (Fig 2C). The Max Cost Prevalence (location on the curve) when the total cost (CFN+CFP) is highest is at 100%. The Total Cost Prevalence when CFP << CFN varies with testing (arbitrary units of cost) and is minimized at 99% testing.

In this setting, testing is warranted until somewhere between 95-100% testing, at which point the optimization function flips and less testing becomes less costly. It is important to note that this analysis considers real costs, not perceived costs, including indirect costs and costs externalized to the medical testing industry. Thus, for relevance to current events, the CFP must be much lower than the CFN in reality, not via argumentation or rationalization.

Scenario 2 – CFP < CFN

When CFP << CFN (e.g., CFP = 0.9CFN), the maximum total cost is found at highest prevalence until between 75% and 90% testing, at which point the optimization function flips and less testing becomes the optimal decision.

Scenario 3 – CFP = CFN

When CFP = CFN (e.g., CFP = 1.0CFN), the maximum total cost is found at highest prevalence until between 75% and 90% testing, at which point the optimization function flips and less testing becomes the optimal decision, a repeat of Scenario 2.

Scenario 4 – CFP > CFN

When CFP > CFN (e.g., CFP = 1.1CFN), the maximum total cost is found at highest prevalence until between 75% and 90% testing, at which point the optimization function flips and less testing becomes the optimal decision, a repeat of Scenarios 2 and 3.

Scenario 5 – CFP >> CFN

When CFP >> CFN (e.g., CFP = 1.9CFN), the maximum total cost is found at highest prevalence until between 75% and 90% testing, at which point the optimization function flips and less testing becomes the optimal decision, a repeat of Scenarios 2-4.

Scenario 6 – CFP >>> CFN

When CFP >> CFN (e.g., CFP = 3CFN), the maximum total cost is found at highest prevalence until between 50% and 75%, at which point the optimization function flips and less testing becomes the optimal decision.

Table 1. Output of Modeled Scenarios Among Various Testing Levels

5% Testing Scenario		a	Max Cost prevalence	Crossover prevalence*	Total Cost Prevalence 0.045	RelMaxTotalCost**
1	CFP << CFN	0.1	100%	0.01	15934240	0.135728
2	CFP < CFN	0.9	100%	0.1	43643680	0.371756
3	CFP = CFN	1	100%	0.11	47107360	0.40126
4	CFP > CFN	1.1	100%	0.12	50571040	0.430764
5	CFP >> CFN	1.9	100%	0.12	77631040	0.66126
6	CFP >>> CFN	3	100%	0.26	117398580	1
10% Testing			Max	Crossover	Total Cost	
Scenario		a	Cost prevalence	prevalence	Prevalence 0.045	RelMaxTotalCost
1	CFP << CFN	0.1	100%	0.01	15284800	0.131011
2	CFP < CFN	0.9	100%	0.1	44309520	0.379792
3	CFP = CFN	1	100%	0.11	46457920	0.398206
4	CFP > CFN	1.1	100%	0.12	49921600	0.427895
5	CFP >> CFN	1.9	100%	0.19	77631040	0.665402
6	CFP >>> CFN	3	100%	0.27	116667960	1
50% Testing			Max	Crossover	Total Cost	
Scenario		a	Cost prevalence	prevalence	Prevalence 0.045	RelMaxTotalCost
1	CFP << CFN	0.1	100%	0.05	10899440	0.092841
2	CFP < CFN	0.9	100%	0.17	38464560	0.327641
3	CFP = CFN	1	100%	0.18	41910200	0.356991
4	CFP > CFN	1.1	100%	0.2	45355840	0.386341

5	CFP >> CFN	1.9	100%	0.3	72920960	0.62114
6	CFP >>> CFN	3	100%	0.4	110823000	1
75% Testing			Max	Crossover	Total Cost	
Scenario		a	Cost prevalence	prevalence	Prevalence 0.045	RelMaxTotalCost
1	CFP << CFN	0.1	100%	0.05	7246340	0.067615
2	CFP < CFN	0.9	100%	0.17	34811460	0.324825
3	CFP = CFN	1	100%	0.28	41910200	0.391063
4	CFP > CFN	1.1	100%	0.32	41702740	0.389127
5	CFP >> CFN	1.9	100%	0.45	69267860	0.646337
6	CFP >>> CFN	3	1%	0.57	107169900	1
95% Testing			Max	Crossover	Total Cost	
Scenario		a	Cost prevalence	prevalence	Prevalence 0.045	RelMaxTotalCost
1	CFP << CFN	0.1	100%	0.16	4323860	0.041477
2	CFP < CFN	0.9	1%	0.63	31888980	0.305897
3	CFP = CFN	1	1%	0.65	35334620	0.33895
4	CFP > CFN	1.1	1%	0.68	38780260	0.372002
5	CFP >> CFN	1.9	1%	0.78	66345380	0.636422
6	CFP >>> CFN	3	1%	0.85	104247420	1
99% Testing			Max	Crossover	Total Cost	
Scenario		a	Cost prevalence	prevalence	Prevalence 0.045	RelMaxTotalCost
1	CFP << CFN	0.1	1%	0.36	3739364	0.036072
2	CFP < CFN	0.9	1%	0.84	31304484	0.301983
3	CFP = CFN	1	1%	0.85	34750124	0.335222
4	CFP > CFN	1.1	1%	0.86	38195764	0.368461
5	CFP >> CFN	1.9	1%	0.86	65760884	0.634372
6	CFP >>> CFN	3	1%	0.95	103662924	1

*Cross-over prevalence is the switch point at which more testing become the rational decision. At lower prevalence, testing, especially indiscriminate testing, becomes more costly than less testing. RelMaxCost is the relative scale of the cost of a given level of testing compared to the worst-case scenario modeled in this study.

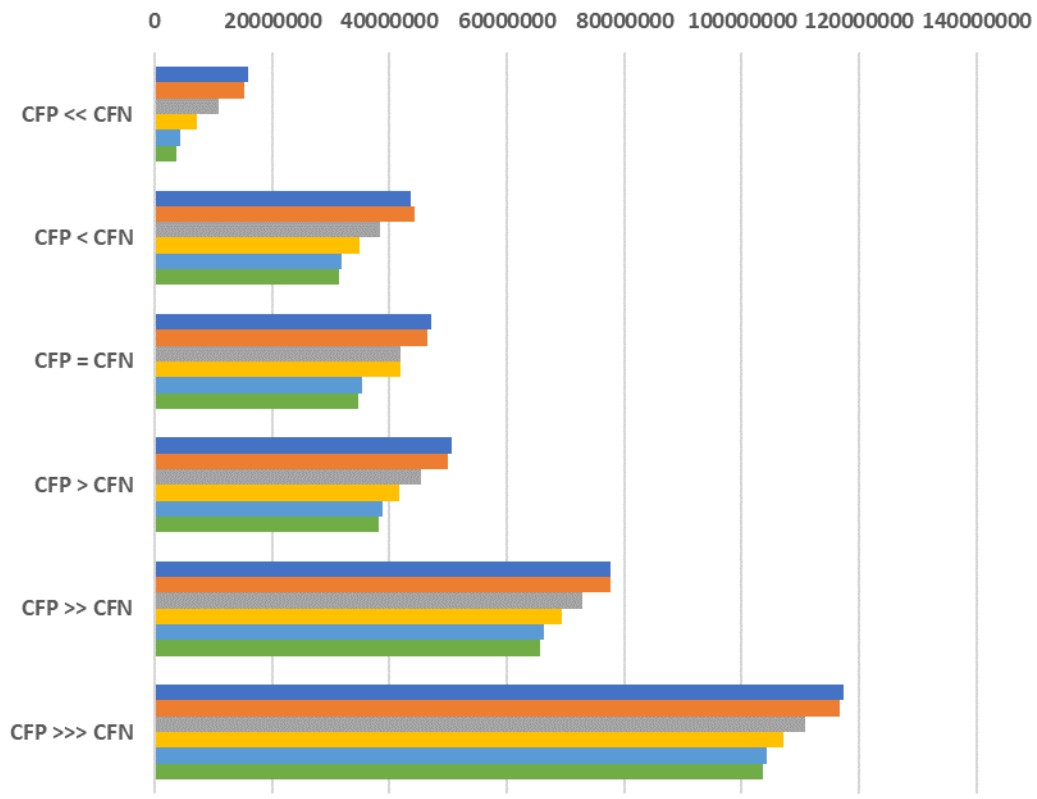

Figure 2. Total Costs Under Six Scenarios Across Testing Levels. Cost units are arbitrary and represent in "real" terms the number of people affected by costs considering both CFP and CFN.

Discussion

These results demonstrate the feasibility of modeling cost functions in Balance of Risk scenarios to optimize decisions of public health responses to outbreaks and epidemics. The ratio of the variance among scenarios relative to the variance among testing levels is >44. These results, summarized as a total cost figure in Fig 2, show that society's response to handling positive test results, via the cost of the false positive, has > 44-fold greater impact on variation of total cost of outbreaks and epidemics relative to increasing or decreasing testing overall, without exceptions among scenarios. The Cost of the False Positive reflects the sum impact of our decision on whether we demand 100% Specificity, or whether we spend the energy and resources to perfect our understanding of the impact of cycle number thresholds on the resulting transmission dynamics of those diagnosed via a given cycle number. Most importantly, we must derive — immediately — a reason-based approach to minimize CFP, reducing as much as possible CFP/CFN, while also working to reduce CFN. The problem, therefore, is indeed and inherently a Balance of Risk problem. Modeling the process of bringing testing online may have some utility in informing whether specific test kits and approaches are acceptable, as well as allowing the consideration of strategic layouts of testing to minimize total costs. Lockdowns are an unhelpful extreme in which CFP becomes far greater than CFN without any rational justification.

As medical care improves toward primarily outpatient care for COVID-19, and policies fail to relax – or become more stringent (i.e., unwarranted lockdowns based on high reported "cases") the nightmare scenario for CFP >>> CFN becomes a more likely reality. The media should report statistics on COVID-19 confirmed and presumed cases, and treat the data stream more like those related to economics, focused on measures such as the number deaths per cases, the change in the percent of tests that are positive over time. Reporting total number of "cases" and "largest number of cases to date" can be misleading and harmful due to public acquiescence to massively costly responses such as lockdowns. All possible efforts are necessary to reduce the FPR of every PCR kit in use to zero, even if that includes the more expensive "complex" sequencing of PCR products, so be it. Society can no longer afford a half-hearted or half-baked attempt at diagnostics in COVID-19.

Limitations

This demonstration of principle does not map to any specific real-world situation or country; instead, it provides a proof of principle and reveals features of the cost functions in a Balance of Risk setting which could, in principle, be conducted with ever-increasing granularity. The most important feature is the finding that the amount of overall testing has lower impact than how we configure our approach to responding to positive test results.

Conclusions

To date, public health responses have included oversimplification of public messages, and bleed-over from misguided attempts using inhumane and immoral tactics to control perception and social behavior, all designed to reduce "vaccination hesitancy," — and all without consideration of the attendant negative consequences of such programs to some families and to society as a whole. Any cost to society stemming from errant policy is blamed on "the pandemic", not on the malformed policy or politicization of public health policy positions. Social pressures, once in place, are difficult to reverse. The unquestioned idea that more testing is always better must come under new review unless FPR = 0, CFP = 0, or CFP <<< CFN. Given the massive impact of top-down control of public health perception on society, serious consideration must be given to the question of whether the powerful tools of social pressure are in any way appropriate in the arena of public health at the expense of allowing society to attend to and address, overtly, consequential costs of one-sided policies.

In the "Fog of Outbreak", the fear factor has driven people and policies to the naïve position that (1) any death due to COVID-19 is more important than any deaths due to other factors, (2) therefore, all COVID-19 cases must be detected. This is a clearly suboptimal strategy — and it is worth giving due consideration to scenarios in which an adaptively flexible strategy might be adopted. One thing is clear: false positives are non-zero, and their cost cannot be externalized: they impact everyone. Harvard economists Cutler and Summers project economic losses attributable to COVID-19 to be $16 Trillion dollars, or 90% of the US GDP. Change must be made to public health perception so we can minimize the cost of the false positives as well as the cost of the false negatives. COVID-19 has provided an extremely valuable but expensive lesson that perception-control based public health is a failed paradigm — it is ours to learn from if we have the tenacity. We must decentralize public health, reduce its "authority", and restructure it to be as non-political

and non-corporatized as possible. A follow-up essay will describe a far superior arrangement of public health infrastructure for the United States and for any country concerned with the impact of centralized authoritarian-based public health and medical care.

The importance and value of educating public health officials, the medical community and the public of these issues and factors should not be understated.

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Appendix - Glossary of Terms

cross-over prevalence - incidence (% infected) during an outbreak where the cost of the false negative becomes greater than the cost of the false positive (CFN > CFP)

diagnostic assay – a medical procedure used to aid in the diagnoses of disease or medical injury.

sensitivity (of an assay) – the probability that a diagnostic assay will lead to an accurate diagnosis of "disease" when a person does, indeed, have the disease state or condition for which the assay is designed to detect.

specificity (of an assay) – the probability that a diagnostic assay will accurate not lead to a diagnosis of "disease" when a person does, in fact, not have the disease state or condition for which the assay is designed to detect.

viremia – viral count or concentration in a person.

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Excitotoxicity (Immunoexcitotoxicity) as a Critical Component of the Cytokine Storm Reaction in Pulmonary Viral Infections, Including SARS-Cov-2

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ABSTRACT

A hyperimmune state secondary to dysregulation of the immune system during lower pulmonary viral infections, sepsis and in some cases non-infectious disorders, is now considered to be the principle event leading to clinical deterioration and eventual death in these patients. While most studies have attributed the pathological damage to the lung to be primarily due to high levels of cytokines and chemokines along with massive infiltration of principally neutrophils and macrophages, there is compelling evidence that overactivation of glutamate receptors is also playing a significant, if not critical role in this process. Functional glutamate receptors, along with two important glutamate transport systems, have now been described in epithelial and endothelial cells in the pulmonary airways as well as all involved immune cells. Experimental studies using cytokine models have shown considerable protection against pathological damage to pulmonary tissues by reducing the activation of these glutamate receptors.

Keywords: *activation of glutamate receptors, chemokine storm, cytokine models, cytokine storm, dysregulated hyperimmune response, excitotoxic amino acid transport, excitotoxicity, glutamate transport, hyperimmune response, ibotenate, inflammation, immunoexcitotoxicity reaction, infiltration of immune cells, N-Methyl- D-aspartate, NMDA*

Introduction

The concept of a "cytokine storm", in most cases a dysregulated hyperimmune response to an infectious organism, was first described in a 1993 article as related to the graft-vs-host disease (Ferrara et al. 1993). Since then, most cases have been in reference to viral infections such as cytomegalovirus, EB-virus, influenza viruses, SARS, MERS, H1N1, H5N1 and the new SARS CoV-2 virus (Yurn & Wong, 2005).

While the extensive lung tissue damage is most often attributed solely to the pro-inflammatory reaction and its association with high concentrations of reactive oxygen and nitrogen species, and lipid peroxidation products, newer evidence suggest that a second arm of the damage may arise from overstimulation of glutamate receptors found both on lung tissues and immune cells. It may be that this excitotoxic reaction is the primary mode of damage to these tissues. This remains to be demonstrated.

That pro-inflammatory cytokines, by themselves, may not be sufficient to cause the pathological damage that we see in cases of cytokine storm is suggested by the observation that no level of TNF-alpha elevation can cause tissue damage in the CNS, rather the damage appears to be from the excitotoxic arm of an immunoexcitotoxicity reaction (Blaylock & Maroon 2011; Blaylock, 2013). While activation of pro-inflammatory cytokines and chemokines is an early event in the cytokine storm reaction, animal studies have shown that knock out models or inhibition of major cytokines, such as IL-6, TNF-alpha and CCL2, did not offer significant protection against the cytokine storm reaction (Salomon, Hoffmann & Webster., 2007; Paquette et al. 2012)

As regards this aberrant hyperimmune state, we know that there exists an extensive variability in innate immune responses among even healthy humans, which includes hyper-responders and under-responders (Tisoncik et al. 2012). An intense immune induced inflammatory response as seen with the cytokine storm phenomenon can cause severe damage to lung tissue of a widespread nature (Peris et al. 2004).

Genomic studies of the 1918 influenza virus, demonstrated a sustained hyperimmune reaction with dramatic upregulation of cytokine/chemokine genes controlling IL-6, IL-8, CCL2 and CCL5 in the lungs of infected animal models (Kash et al. 2006). A similar microarray analysis of lung tissue from H1N1 infected animals demonstrated prolonged expression of genes controlling CCL2, CXCL9 and CLCL10 (Baskin et al. 2009).

Attempts to discover why only certain individual appear to be susceptible to these hyperimmune reactions has been only partially successful. Critical to innate immune reactions are the toll-like receptors (TLRs), which can vary in their reactivity based on genetic influences. For example, Wurfel et al. in examining a large population of septic patients, found that those with a single nucleotide polymorphism (SNP) as a marker for a hyperfunctioning variant of the TLR1, experienced increased organ damage and morbidity following a Gram-positive bacterial infection (Wurfel et al. 2008). It has also been shown that variants in TLR4 reactivity, the principle receptor for lipopolysaccharide (LPS), can predispose an individual to sepsis reactions when exposed to bacterial endotoxins (Michael et al. 2003).

One would intuitively expect an intense hyperimmune reaction to increase killing of the initiating micro-organisms, yet the opposite appears to be true (Neilli et al. 2012). Despite a robust cytokine response, viral titers are not reduced. Failure to eliminate the invading organism further stimulates the hyperimmune reaction.

Pathological Findings in the Cytokine Storm Reaction

In patients with serious lower lung infections, such as with various influenza viruses, SARs-CoV, MERS and newly engineered SARS-CoV-2 virus, we see high viral loads in the lower lungs, which rapidly initiate local immune cell activation in the distal airways and alveoli as well as a triggering of massive migration of immune cells, principally neutrophils and macrophages, to these same areas of the lungs. (Peiris et al. 2004; de Jong et al. 2006; Kash et al. 2006; Baskin et al. ,2009). While high viral loads initially may initiate a cytokine storm, some studies have found no relation between the viral load and the intensity of the cytokine response (Liu Q, Zhou & Yang, 2016).

While neutrophils and macrophages play the major role in lung pathology in severe viral infections of the lungs, $CD4^+$ and $CD8^+$ T-cells are the principle cells involved in viral clearance. La Gruta et al. 2007; Clark 2017). Massive influx of these immune cells, especially macrophages, are thought to play a critical role in the pathology of these viral infections, such as apoptosis of airway epithelium and the cellular structure of the alveoli, pulmonary edema, thickening of alveolar walls, microhemorrhages, thrombosis in smaller vessels and hyaline membrane formation. (Nicholls et al. 2003). The primary pathological damage is within the alveoli with diffuse alveolar damage being prominent (DAD). Several cytokines, such as TNF-alpha, enhance monocyte and neutrophil transmigration across the infected endothelium and epithelium (Wijburg OL et al. 1997; Kidney & Proud 2000). Because of a mandate from the CDC, very few autopsy studies have been performed on SARS-CoV-2 fatalities (Xu et al. 2010). From the few that have been done the pathological finding are quite similar to that seen with fatal pathogenic influenza infections.

The key cells involved in the cytokine storm reaction include epithelial cells, endothelial cells and macrophages (Nelli et al. 2012) While all three cell types can produce proinflammatory cytokines, the highest TNF-alpha levels are induced by macrophage activation, some 3 orders of magnitude higher than human epithelial cells (Nelli et al. 2012). As the process advances, the inflammation can spill over into the general circulation, triggering pathological damage in several organs, such as the kidneys and liver (Tisoncik et al. 2012).

The Immunoexcitotoxic Process Explained

I coined the term immunoexcitotoxicity in 2009 in an article concerning the pathophysiology of autism spectrum disorders, but the actual process had been described by others previously (Dzenko et al. 1993; Gelbard et al. 1993; Chao & Hu 1994; Takeuchi et al. 2006; Leonoudakis, Zhao & Beattie 2008; Blaylock RL 2009). Lucas and Newhouse in 1957, before glutamate was known as a neurotransmitter, described destruction of neural retinal cells in animals exposed to monosodium glutamate (Lucas & Newhouse 1957). Twelve years later Olney coined the name excitotoxicity to describe the process (Olney & Sharpe 1969). Subsequent studies established glutamate as the major neurotransmitter in the CNS and described several subtype glutamate receptors in the central nervous system. Recently, researchers discovered similar functional glutamate receptors on a number of peripheral tissues and cell types, including the GI tract, pancreas, kidneys, liver, megakaryocytes, endothelial cells, male lower urogenital tract and testes and a number of immune cells (Erdo 1991; Skerry & Genever 2001).

Yawata et al. demonstrated that both LPS and TNF-alpha stimulated macrophages could induce robust neurotoxicity, which was completely blocked by the N -Methyl- D -aspartate (NMDA) receptor antagonist MK-801 (Yawata et al. 2008). Others have also shown a critical link between inflammation and excitotoxicity (Shijie et al. 2009). Morimoto et al. found that co-injection of LPS plus the NMDA agonist ibotenate (ibotenic acid, a neurotoxin from *Amanita muscaria* mushrooms and an analogue of glutamate), led to significant neuronal damage, but blocking the excitotoxicity arm of the reaction prevented any tissue damage despite substantial inflammatory microglial activation (Morimoto, Murasugi & Oda 2002). Further, if the ibotenate was given one day after the LPS, severe tissue damage was elicited. If this is also true in inflamed lung tissues, it may be that all or most of the tissue damage is secondary to excitotoxicity rather than damage by pro-inflammatory

cytokines. This could result in a need for a change or at least an addition in treatment direction. Further demonstration of this immunoexcitotoxic effect is in the demonstration that adding subtoxic concentrations of LPS to subtoxic concentration of glutamate (released by rotenone) become fully toxic when combined (Gao 2003).

The effect of inflammation on excitotoxicity can be explained to some degree by molecular mechanisms. For example, it is known that TNF-alpha and less so IL-1ß, increase insertion of NMDA and AMPA receptors (GluR2 lacking) onto the cell surface (Bernardino et al. 2005; Leonoudakis, Zhao & Beattie 2008). Another way inflammatory cytokines, such as TNF-alpha, can enhance excitotoxicity is by inhibiting glutamate transporters (EAATs), which elevates extracellular glutamate levels (Zou & Crews 2005). TNF alpha and IL-1ß also stimulate glutamate production by macrophages and microglia by upregulating the activity of the cellular glutaminase enzyme, responsible for the conversion of glutamine to glutamate (Ye et al. 2013). The two processes acting in concert, inhibition of glutamate uptake and increase glutamate production, can dramatically elevate extracellular glutamate to toxic levels. This not only stimulates high levels of reactive oxygen and nitrogen species and lipid peroxidation products, but also acts as a stimulus for migration of macrophages and neutrophils from the blood (Gupta & Chattopadhyay 2009; Gupta, Palchaudhuri & Chattopadhyay 2013).

Inflammation is known to raise glutamate levels in affected tissues and because neutrophils and macrophages also release glutamate when stimulated, it can act as an autocrine/paracrine loop to further increase invasion of these immune cells into the injured lung (Lawand, McNearney & Westlund 2000). This interaction between inflammatory mediators, extracellular glutamate levels and glutamate receptors is intimately involved in such a way that it constitutes a common immunoexcitotoxic pathological mechanism for a number of disorders. It appears that inflammation rarely if ever occurs without the involvement of excitotoxicity.

Glutamate Receptors in the Lungs: Pathophysiological Considerations

Said et al. first described functional glutamate receptors in the lungs using a high concentration of NMDA in a perfusate of isolated, ventilated rat lungs (Said, Berisha & Pakbaz 1996). In a follow-up study, they found that an inhibitor of NMDA receptors greatly attenuated oxidant lung injury caused by paraquat or xanthine oxidase (Said et al. 2000). In addition, Said made a link between activation of NMDA receptors in the lungs and airway hyperresponsiveness in bronchial asthma (Said 1999).

In the Dickman et al. rat lung study, they found that NMDAR1 mRNA and protein were moderately expressed in all regions of the lung tissue and airways. NMDAR2D was predominately expressed in the peripheral gas-exchange regions of the lungs and NMDAR2D and 2C were expressed in medium-sized and larger airways. He proposed that all of these receptors were within non-neural tissues, as no neurons are present beyond the conducting airways (Van Genechten et al. 2003). In the Dickman et al. study they found no evidence of NMDAR2A or 2B in any lung compartment or trachea (Dickman et al. 2004).

Robertson et al. using autoradiography with radio-labeled MK-801, demonstrated binding sites in the rat peripheral lung, which included alveolar walls as well as bronchial epithelium and bronchial smooth muscle (Robertson et al. 1997). In addition, one observes selective expression of NMDA

receptor subtype 2D in alveolar macrophages, a major immune cell involved in viral and bacterial lung inflammation (Dickman et al. 2004). The differential localization of NMDAR2D suggest that it is most closely connected to excitotoxic lung injury, especially excitotoxic-induced pulmonary edema. This includes both airway hyperresponsiveness and airway and alveolar inflammation.

Said et al. demonstrated that NMDA receptor subtypes involved in lung injury were co-localized with vasoactive intestinal peptide (VIP) and neuronal nitric oxide synthase (nNOS), and that excitotoxic lung injury was mediated by excessive generation of nitric oxide and markedly attenuated by VIP (Said, Berisha & Pakbaz, 1996).

Also, of interest, Dickman et al. found that infusing the lung with NMDA caused a marked upregulation of NMDAR-2D receptor expression, thereby increasing lung sensitivity to excitotoxic injury (Dickman et al. 2004). They suggested that these glutamate receptor subtypes may act as a positive feedback mechanism, which would allow an amplified and perpetuated excitotoxic lung injury.

Collard et al. demonstrated that injured neutrophils release glutamate into the interstitial spaces in high concentrations, which can then markedly increase local tissue injury by further stimulating immune cell infiltration and by excitotoxicity (Collard et al. 2002). Macrophages, one of the more abundant infiltrating immune cells in cytokine storm reactions, also releases high levels of glutamate on stimulation (Piani et al. 1991). With a massive infiltration of neutrophils and macrophages into the injured areas of the lung, one can appreciate the tremendous inflammatory-excitotoxic enhancing effect of further glutamate release from these immune cells.

De Cunha et al. conducted an in vitro study of the effect of blocking NMDA receptors (using MK-801) using a cecal ligation and perforation model (CLP) of sepsis (da Cunha et al. 2010). In the study, they divided male Wistar rats into four groups: group 1 as sham operated controls, group 2. CLP rats treated with saline given immediately after injury and then 12 hours later. Group 3. CLP plus MK-801 in a dose of 0.3mg/kg given 4 hours after injury and group 4. CLP plus MK-801 in the same dose given 7 hours after injury. In addition, they performed a survival study by dividing the animals into three groups. Group 1 was given 50mg of saline subcutaneously. Group 2 was given MK-801 (0.03mg/kg) subcutaneously bid for two days starting 4 hours after the CLP lesion. Group 3 was given MK-801 (0.30mg/kg) bid for two days starting four hours after the CLP lesion. They recorded the animals' mortality for the next five days.

They observed an increase in NR1 and NR2A receptor subunits within the lungs at 6 hours, but not at 12 or 24 hours. There occurred a statistically significant increase in bronchoalveolar lung fluid (BALF) protein level and LDH activation after the CLP lesion, as normally occurs with such lesions. The MK-801 significantly decreased the BALF volume when the receptor blocker was given at four hours but not when given first at 7 hours. Importantly, they found that the CLP lesion resulted in significantly higher lung oxidative injury in the untreated group than the MK-801 treated group. That is, blocking NMDA receptors significantly reduced lung oxidative injury.

Also, of critical importance, the massive increase in total immune cell count within the BALF of the CLP lesioned animals, was significantly decreased by treatment with MK-801 when given at 4 hours, but not when first given at 7 hours.

Histopathological examination of the lungs of CLP lesioned animals without treatment demonstrated typical alveolar disruption, massive inflammatory cell infiltration, with moderate alveolar exudate. When MK-801 NMDA receptor blocker was given at four hours, they observed only mild inflammatory cell infiltration and no alveolar exudates.

The survival study demonstrated that among the CLP-lesioned animals given the higher dose (0.3mg/kg) of MK-801 there was a significantly improved survival when compared to those given a vehicle. The group given the vehicle had a 20% survival rate as compared to a 30% survival in the group given the lower dose MK-801 (0.03mg/kg), and a 45% survival among the group given the higher dose of MK-801 (0.3mg/kg).

In the same study, they also tested the effect of MK-801 against LPS stimulated release of TNF-alpha from spleen cells. The MK-801 NMDA receptor blocker significantly decreased the TNF response following LPS stimulation. In unstimulated spleen cells, neither NMDA, MK-801 or NMDA plus MK-801 had any effect on TNF-alpha release, suggesting that only in primed immune cells are the NMDA receptors active. TNF-alpha, along with IL-1, have been shown to play a major role in the cytokine storm reaction (Tisncik JR et al. 2012).

They concluded from these results that NMDA receptors are upregulated in the lungs during sepsis and that this effect is time dependent, with a reduction in response of the inflammatory cells by MK-801 occurring at 4 hours but not at 7 hours following sepsis onset. In essence, the combined effect of early NMDA receptor activation and increased insertion of NMDA receptor subunits may explain the increased survival observed by reducing the role played by these glutamate receptors in sepsis-induced lung injury. As with excitotoxic injury in the CNS, nitric oxide upregulation plays a major role in the pathogenesis of septic-induced lung injury. Glutamate and NMDA both stimulate the production of nitric oxide via upregulation of iNOS in rat alveolar macrophages. (Shang et al. 2010) Glutamate alone is known to provoke acute lung injury (Shen et al. 2007).

Macrophages, both derived from the blood and intrinsic alveolar macrophages, are considered to be major immune cell types within the lungs in the cytokine storm reaction. In addition, there is compelling evidence that alveolar macrophages are the major source of monocyte chemoattractants, such as MCP-1 (CCL2; Brieland et al. 1992). In the Dickman et al. study using a CLP lesion, the fact that they observed a significant increase in MCP-1 levels 12 hours after the septic lesion was initiated explains why NMDA receptor blockade with MK-801 had no effect if given at 7 and 12 hours (Dickman et al. 2004). A massive influx of macrophages into the lung lesion worsened the injury as at this stage there is already an overwhelming inflammatory response caused by the release of reactive oxygen and nitrogen species from the earlier glutamate stimulated immune cells.

Acute lung injury by glutamate is dose dependent and directly related to activation of glutamate receptors as shown by the complete protection from lung injury afforded by NMDA blocking agents (AP-5, AP-7 and MK-801; Said, Berisha & Pakbaz 1996). Magnesium, a blocker of NMDA receptors, was also shown to be protective when added to the lung perfusate.

Glutamate Receptors and Immune Cells

Lymphocytes

Several studies demonstrated lymphocyte activity being influenced by glutamate (Droge et al. 1988; Eck, Drings & Droge, 1989). Kostanyan et al. demonstrated that human lymphocytes express quisqualate-sensitive (AMPA) binding on specific sites of the lymphocyte outer membrane (Kostanyan , Merkubva, Navolotskaya & Nurieva, 1997). Others have also shown lymphocyte activation by AMPA receptor stimulation, which is intimately involved in lymphocyte adhesion and chemotaxis (Ganor et al. 2003).

Metabotropic glutamate receptors have also been demonstrated on lymphocytes. Pacheco et al. demonstrated group I and group III metabotropic glutamate receptors on human lymphocytes (R. Pacheco, Ciruela et al. 2004). They also demonstrated that mGluR5 was expressed constitutionally in T-cells whereas mGluR1 was expressed only after a T-cell receptor-CD3 complex was formed. Kostanyan et al. demonstrated that human lymphocytes express quisqualate-sensitive (AMPA) binding on specific sites of the lymphocyte outer membrane (Kostanyan, Merkubva, Navolotskaya & Nurieva, 1997).

Lombardi et al. in a study using healthy young volunteers found that glutamate in a concentration between 0.001 and 1mM could significantly potentiate lymphocyte response but lymphocyte reactivity progressively declined when exposing PHA-activated lymphocytes to higher concentrations of glutamate (3mM and 100mM; Lombardi et al. 2001). This observed suppression of lymphocyte activity was shown not to be due to glutamate injury to lymphocytes, but rather is acting through functional glutamate receptor mechanisms.

One of the characteristics of SARS-CoV-2 infections is a lymphocytopenia, which could be explained by the high levels of glutamate occurring secondary to widespread inflammation (Xu et al. 2020). The Lombardi study found that NMDA, AMPA and kainite (KA) all produced a significant potentiation of calcium response in activated lymphocytes, similar to the glutamate response described by others (Lombardi et, 2001).

A number of diseases can raise glutamate levels sufficiently to impair lymphocyte immune functions, such as AIDS, neoplastic disease, hepatic encephalopathy, intense inflammation, traumatic injury and autoimmune disorders (Aliprandi et al. 2005).

Glutamate (NMDA) stimulated lymphocytes also produce high levels of reactive oxygen and nitrogen species, which is prevented by exposure to the NMDA blocker MK-801 (Tuneva, Bychkova & Boldyrev, 2003). The normal range of blood glutamate in human circulation is between 70 and 100mM but can reach levels considerably higher in these conditions. Stimulation of NMDA receptors on lymphocytes has also been shown to increase the production of proinflammatory cytokines, such as IL-1ß, IL-6 and TNF-alpha (Valdychenskaya et al. 2011). Both free radicals and pro-inflammatory cytokines inhibit glutamate uptake, leading to higher levels of extracellular glutamate, which acts in an autocrine manner to worsen the pathology in the lungs. Blocking NMDA receptors on lymphocytes has been shown to inhibit T helper cell differentiation, thereby reducing the secretion of proinflammatory cytokines (Gao et al. 2011). Several researchers concluded that glutamate should be considered an immunotransmitter (Valdychenskaya et al. 2011).

Neutrophils

Circulating neutrophils during inflammatory states are captured by pulmonary vessel endothelial cells, followed by leukocyte tethering and rolling activation, and subsequent tight adhesion to endothelial cells. Transendothelial diapedesis results in invasion of these immune cells into the alveoli (Ley, Laudanna, Cybulsky & Nourshargh, 2007). Gupta et al. demonstrated that glutamate could stimulate neutrophil migration by acting through class I metabotropic glutamate receptors (Gupta , Palchaudhuri & Chattopadhyay, 2013; Gupta & Chattopadhyay, 2009).

Glutamate alone has been shown to reduce endothelial barrier function, leading to pulmonary edema (Collard et al. 2002; Nassar et al. 2011). As the neutrophils accumulate in massive numbers within the pulmonary tissues, they release high levels of glutamate, further driving neutrophil migration and leakage of fluid through the vascular barriers. Studies using a mouse model for traumatic brain injury have also shown mGluR5 of group I metabotropic receptors play a significant role in neutrophil migration into the site of injury (Yang et al. 2017). In this study, they found that deficiency of mGluR5 inhibits neutrophil infiltration into the injury site as well as inhibiting the release of inflammatory cytokines and chemokines.

The interaction between CD11b/ CD18 on neutrophils, as well as ICAM-1 on endothelial cells, is critical for neutrophil adherence to endothelial cells in the process of transmigration. Li et al. (2015) demonstrated that NMDA increases CD11b on neutrophils.

These studies clearly demonstrate that glutamate receptors, both ionotropic and metabotropic, play a critical role in neutrophil migration, pulmonary edema, release of high concentrations of free radicals, lipid peroxidation products, release of pro-inflammatory cytokines and chemokines, and ultimate destruction of alveoli structures and prevention of gas exchange.

Macrophages

As with the other immune cells thus far discussed, monocytes/macrophages also release high levels of glutamate upon stimulation (Piani D et al. 1991). Macrophages are a heterogenous population of immune cells in which the microenvironment determines the functional immune status, which includes either a classical activated state (M1) or an alternatively activated state (M2; Montovani, Sica & Locati, 2007).

Extracellular glutamate increases macrophage migration by activating class I and 5 mGluRs (Chiocchetti et al. 2006). Stimulation of mGluR5 appears to be mainly immunosuppressive, by reducing nitric oxide production and increasing production and release of IL-10 (Byrnes et al. 2009; Werry et al. 2011). Alveolar macrophages also express functional NMDA receptors, and release glutamate into the alveolar space during infections (Reijerkerk et al. 2010; Shang et al. 2010).

While under physiological conditions macrophages reduce extracellular glutamate levels and are therefore protective, in the face of intense inflammation the opposite can be true. This is based on how macrophages regulate extracellular glutamate levels and the effect of inflammation on this transport.

Human macrophages have two transport system for glutamate, a sodium dependent Excitatory Amino Acid Transport system (EAATs or X_{AG} system), consisting of 5 subtypes and a sodium-

independent glutamate/cystine antiporter system (X_C^-; Rimaniol et al. 2000). It has been shown that EAAT function is developmentally restricted in cultured astrocytes and macrophages (Stanimirovic et al. 1999; Rimaniol et al. 2000). These studies suggest that under inflammatory conditions circulating monocytes/macrophages may rapidly acquire EAAT transporters in a dose dependent manner (Klegeris, Walker & McGeer, 1997). The same was found for alveolar macrophages, in that they possessed no EAATs until stimulated. Under inflammatory conditions circulating macrophages may acquire EAATs by stimulation from TNF-alpha or other inflammatory mediators (Piani et al. 1991; Zerangue, Arriza, Amara & Kavanaugh, 1995).

Elevation of extracellular glutamate levels from macrophages occurs principally by the X_C^- system and not by EAATs (X_{AG}; Rimaniol et al. 2000; Watanabe & Bannais, 1987). Elevation of extracellular glutamate, as would occur during inflammation, inhibits cystine entry into the cell, thereby reducing the production of glutathione, a major cell antioxidant and protectant (Eck & Droge, 1989). EAATs would also be inhibited by elevated levels of reactive oxygen and nitrogen species and inflammatory cytokines, especially TNF-alpha (Trotti, Danbolt & Volterra, 1998; Zou & Crews, 2005). Under inflammatory conditions reverse glutamate transport can occur, dramatically raising extracellular glutamate levels (Grewer et al. 2008; Mandolesi et al. 2015). Not only would this suppression of glutathione synthesis increase damage and death to lung tissues directly, but also large number of macrophages, depleted of their protective glutathione, would release their stores of glutamate into the extracellular space upon cell destruction, further enhancing excitotoxic damage to the lungs. In combination, macrophages contribute to the extensive lung pathology by releasing massive concentrations of inflammatory cytokines, glutamate, reactive oxygen and nitrogen species and lipid peroxidation products into the alveolar fluid (BALF) and along the major airways deep in the lungs. In essence, the cytokine storm appears to be an immunoexcitotoxic storm.

Other Immune Cells Damaged by Glutamate

Functional glutamate receptors have also been demonstrated on thymocytes, dendritic cells (DCs) and natural killer cells (NK cells; Rezzanni et al. 2003; Pacheco et al. 2006; Kuo et al. 2001). Each of these immune cells play critical roles in both a normal response to respiratory viral and bacterial infections and in the pathological cytokine storm reaction. Elevated glutamate levels, acting through glutamate-linked cell signaling, could affect each of the cells in terms of effective immune responses, either resulting in a hyperimmune response or impairing viral and/or bacterial clearance in the lungs. DCs are the most potent of the APCs, in part by direct activation and differentiation of naïve T-lymphocytes (Banchereau & Steinman, 1998).

Pacheco et al. (2006) demonstrated that dendritic cells release glutamate upon stimulation, which was dependent on the X_C^- system. Exposure of DCs to lipopolysaccharide increased their basal glutamate release, and glutamate was shown to modulate cytokine production. For example, in this study after 48 hours following T-cell-DC cell contact, the released glutamate acted via mGluR1 on the T-cells to increase secretion of IL-6 as well as TNF-alpha, IL-2, INF-gamma and IL10. Stimulation of mGluR1 on the T-cells increased TNF-alpha production with a positive feedback upon dendritic cells. Glutamate, when acting through the mGluR5 was shown to inhibit T-cell proliferation, again possibly contributing the lymphopenia seen with the cytokine storm associated with SARS-CoV-2 infections. They also demonstrated that DCs and macrophages both release the same concentration of glutamate upon stimulation.

Controlling Immunoexcitotoxic Reactions in the Cytokine Storm Reaction

Experimental in vivo studies using various models have shown the effectiveness of blocking excitotoxicity in preventing and reducing the pathological damage caused by the cytokine storm. Li et al. used bleomycin to induce acute lung injury and fibrosis in mice, which produced similar lung injury as seen with highly pathogenic influenza and SARS-CoV-2 (Li et al. 2015). Their previous study demonstrated that glutamate alone could cause acute lung injury (Shen et al. 2007).

In their bleomycin study they demonstrated that the drug selectively induced the release of very high concentrations of endogenous glutamate into the lungs, resulting in acute lung injury (Li et al. 2015). They used memantine, a glutamate NMDA receptor blocker in the study. Animals given the memantine demonstrated significantly less histological lung damage, pulmonary permeability and lung wet/dry ratio than the untreated animals. The meantine appeared to work by suppressing neutrophil accumulation and by decreasing IL-1ß and TNF-alpha, while increasing the anti-inflammatory cytokine IL-10. They also demonstrated that activation of the NMDA receptors increased expression of the adhesion molecule CD11b on neutrophils, thus increasing transmigration of neutrophils into the alveolar space from surrounding vessels.

The increase wet/dry weight of the animals' lungs, along with protein leakage into the alveolar spaces, is consistent with the high incidence of pulmonary edema seen with pathogenic lung infections. Glutamate is known to induced pulmonary edema by increasing vascular permeability, which can be inhibited by MK-801 (Nassar et al. 2011).

Glutamate has been shown to mediate lung injury secondary to both hyperoxia and sepsis, suggesting that glutamate receptor activation is a common event with acute lung injury from various causes (Wang et al. 2009; Da Cunha et al. 2010). Studies in which other glutamate receptor inhibitors reduced lung pathology add further evidence of the importance of the excitotoxic arm of immunoexcitotoxicity in infectious lung injury.

Curcumin has been shown to provide powerful protection against the cytokine storm reaction in at least two cytokine storm animal models. In one such model of a pulmonary infection-induced cytokine storm utilizing mice infected with reovirus serotype I, strain Lang (reovirus I/L), researchers were able to reproduce the acute exudative phase, which included hyaline membrane formation as seen in human cases of virally induced cytokine storm. The untreated survivors also developed intra-alveolar and interstitial fibrosis as seen in human cases (Avasarala et al. 2013).

The researchers first established that curcumin had no effect on viral clearance or viral replication. They used three staining methods, haematoxylin and eosin (H&E), Sirus Red and Mason's trichrome to determine histological damage to the lungs, paying particular attention to diffuse alveolar damage (DAD), which is characterized by edema, capillary dilation and hemorrhage with hyaline membrane formation. Mice surviving the acute phase of the disease developed significant pulmonary fibrosis, just as seen in human cases.

The mice treated with the curcumin had significantly less inflammatory cellular infiltrate and significantly reduce fibrosis in the survivors. Untreated animals demonstrated significant accumulation of collagen in the lungs, which was greatly reduced by curcumin. They also found a dramatic decrease in recovered cells from the alveolar fluid in the animals treated with the curcumin,

in particular the number of PMNs (GR1+) and CD4+ cells on day five and CD19+ cells on day 9. On day 14 they observed a significant decrease in PMNs, NK cells, CD8+ T-cells and CD19+ B cells in the animals given curcumin. Curcumin was also found to differentially modulate TNF-ß1, NF_kB and p58 signaling, as well as significantly reducing phosphorylated p65 NF_kB as compared to untreated virally infected animals. Overall, curcumin was shown to significantly reduce inflammation and fibrotic lung damage in animals with a viral-induced cytokine storm reaction. The greatest lung damage in the virus infected animals without treatment occurred on day 14, with high levels of IL-6, IFN-gamma and MCP-1. Infected animals treated with curcumin demonstrated downregulation of all these pro-inflammatory factors.

Curcumin has been shown to effectively suppress NF_kB activation, a transcription factor linked to elevation in IL-1, IL-8, IL-6 and TNF-alpha upon immune cell activation (Singh & Aggarwal, 1995; Literat et al. 2001; Oh et al. 2011). Activation of NF_kB is associated with sepsis-induced acute lung injury (Bohrer et al. 1997; Arnalich et al. 2000). Suppression of TGF-ß by curcumin is important as its elevation has been associated with a poorer prognosis in ARDS (Fahy et al. 2003; Fahey, Robins & Constantinescu, 2007). Curcumin has been shown to suppress fibrosis under a number of conditions, such as that induced by cyclophosphamide, whole-body radiation and bleomycin (Venkatesan & Chandrakasan, 1995).

Later stages of sepsis are often associated with systemic organ damage, especially liver injury. In this study, Venkatesan and Chandrakasan demonstrated elevated liver enzymes at day 14 in the untreated virally infected mice. Treatment with curcumin reduced these liver enzymes back to control levels.

Curcumin is known to suppress the release of numerous cytokines and chemokines including IL-1ß, IL-2, IL-6, IL-8, IL-12, INF-gamma, TNF-alpha, MCP-1 and MIP-1alpha from monocytes and macrophages (Abe, Hashimoto & Horie T, 1999; Gao et al. 2004; Fahey, Robins, Constantinescu, 2007). Curcumin has also been shown to lower IL-6, IL-8 and MCP-1 secretion in cultured monocytes treated with high glucose concentrations as well as lowering blood TNF-alpha, IL-6 and MCP-1 levels in diabetic rats (Jain et al. 2009). Zhou et al. found that curcumin stimulated the production of SOCS proteins (Suppressor of Cytokine Signaling) a factor that fine tunes cytokine networks and helps prevent hyperimmune states, such as the cytokine storm (Kedzierski et al. 2014, Zhou et al. 2016).

While a significant portion of the protective effect of curcumin against lung damage by infections appear to be due to its ability to reduce pro-inflammatory mediators, curcumin also inhibits several glutamate receptor subunits and reduces excitotoxicity. Khalil RM and Khedr found that curcumin could protect against monosodium glutamate neurotoxicity in rats by decreasing NMDA2B and mGluR5 in hippocampal neurons (Khalil & Khedr, 2016). Curcumin was found to lower TNF-alpha levels in the hippocampus elevated by MSG, and may also lower glutamate levels. Lowering of extracellular glutamate levels occurs by several mechanisms, such as increased uptake of glutamate into glial cells and macrophages and by conversion of glutamate to glutamine by upregulation of glutamine synthease and glutamate decarboxylase (Zhou & Danbolt, 2014).

Chen et al. demonstrated an anti-inflammatory effect by dextromethorphan (DXM), an NMDA receptor blocker, using a murine model of collagen-induced arthritis and in humans with rheumatoid arthritis (Chen et al. 2017). IL-17A plays an important role in arthritis by enhancing the production

of TNF-alpha, IFN-gamma and IL17A (Mills, 2008). DXM suppresses IL-17A. Reduction of the inflammation is partially due to a blocking effect by DXM on dendritic cell function, suppression of the TH1 response, the TH17 response, or both. In a previous study, Chen et al. demonstrated dextromethorphan could inhibit activation of dendritic cells and dendritic cell functions (Chen et al. 2013) Future studies will have to determine if suppression of NMDA receptors on dendritic cells is responsible for the immune effects observed in these studies.

Conclusions

Most practicing physicians, as well as academic physicians, consider the cytokine storm as a purely immunological reaction resulting in progressive damage to the deep lung tissues, leading to a high incidence of death, or severe complication in survivors. Growing evidence indicates that an excitotoxic element is also involved and appears to play a major role in the disorder—perhaps a central role. An interaction between immune/inflammatory mediators, principally pro-inflammatory cytokines and chemokines, and glutamate receptors occurs in the cytokine storm reaction—immunoexcitotoxicity—in the same manner that we see in the central nervous system. In multiple sclerosis, for example, progressive destruction of the axons and neurons of the CNS continue to occur long after the immunological reaction has cooled down (Matute C,2001; Gonsette, 2008). We see a similar relationship in certain viral encephalic infections, where there is a progressive neurodegenerative response after the virus has been cleared by the immune system (Espey, Kustova, Sei & Basile, 2002; Hirai et al. 2017).

In the case of the CNS, it has been determined that there are several pathways of interaction between immunity and excitotoxicity. For example, TNF-alpha, and less so IL-1, stimulate glutaminase production of glutamate by microglia and astrocytes, and these same cytokines can stimulate insertion of certain glutamate receptors that can enhance the neurotoxicity of specific glutamate receptors (GluR2 lacking AMPA receptors; Stellwagen, Beattie, Seo & Malenka, 2005; Beattie, Fergursen & Bresnahan, 2010). Similar interactions are seen with monocytes, macrophages and neutrophils.

As the inflammatory process progresses, elevation in glutamate from the presence of activated macrophages and neutrophils within the alveolar spaces, stimulates an increase in immune cell migration to the lungs, especially neutrophils and macrophages, the principle immune cells found with cytokine storm reactions, which further increases glutamate levels in an autocrine and paracrine manner. With activation of the immune cells, we see a production of high levels of reactive oxygen and nitrogen species and lipid peroxidation products, which inhibit glutamate transport proteins (EAATs) and causes a suppression of the glutamate, cystine antiporter (system X_C^-) function by raising extracellular glutamate levels. This makes the macrophages and neutrophils more susceptible to apoptosis and necrosis, which releases their content of glutamate into the alveolar fluid and bronchial secretions. It would also trigger cell death in the epithelial cells of the airways and alveola. Activation of glutamate receptors on the endothelial cells lining the microvessels within the lungs, increase permeability of the vessels, leading to pulmonary edema, something well demonstrated with primary damage cause by glutamate exposure.

Immunoexcitotoxicity operates in both directions, in that excitotoxicity also triggers inflammation, producing a cyclic cascading effect of destruction. While not conclusively demonstrated, compelling

evidence suggest that activation of immune cells with release of pathogenic levels of pro-inflammatory cytokines always triggers excitotoxicity (immunoexcitotoxicity; Gelbard et al. 1993; Herman et al. 2001; Beattie et al. 2002; Bernardino et al. 2005; Floden,2005; Li & Combs, 2005; Zou & Crews, 2005; Takeuchi et al. 2006; Carmen, Rothstein & Kerr, 2009; Han & Whelan, 2010; Olmos & LLado, 2014). Brison et al. found that excitotoxicity played a major role in paralysis in mice following infection with a human strain of coronavirus with a single mutation in its spike protein (Brison, Jacomy, Desforges & Talbotr, 2011). While this discussion is limited to local inflammatory reaction within the lungs, glutamate receptors in the medial septal area of the brain also regulates immune reactions (Podlacha et al. 2015). NMDA injected into the medial septal nuclei in stressed Wistar rats was shown to significantly increase in NK cell cytotoxicity and cause a rise in large granular lymphocytes in the plasma.

Studies have also shown that neurodegeneration secondary to viral infections may not be secondary to directly infected neurons, rather the damage is secondary to accumulation of glutamate in the extracellular space secondary to interference of glutamate uptake, which is powerfully inhibited by inflammatory cytokines (Darman et al. 2004; Nargi-Aizenman et al. 2004).

In most of these studies the source of the excess glutamate was intrinsic, principally from immune cells. Yet, oral ingestion of glutamate can raise glutamate levels to neurotoxic levels and should be considered. Ironically, many parenteral tube feedings contain high levels of glutamate and other excitotoxic amino acids. This could worsen existing excitotoxicity in seriously ill patients and may play a role in the rapid deterioration of moderately ill patients infected with a respiratory virus, including SARS-CoV-2, especially since so many processed foods contain significant levels of glutamate and other excitotoxin additives.

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Vitamin C Mitigating and Rescuing from Synergistic Toxicity: Sodium Fluoride, Silicofluorides, Aluminum Salts, Electromagnetic Pollution, and SARS-CoV-2

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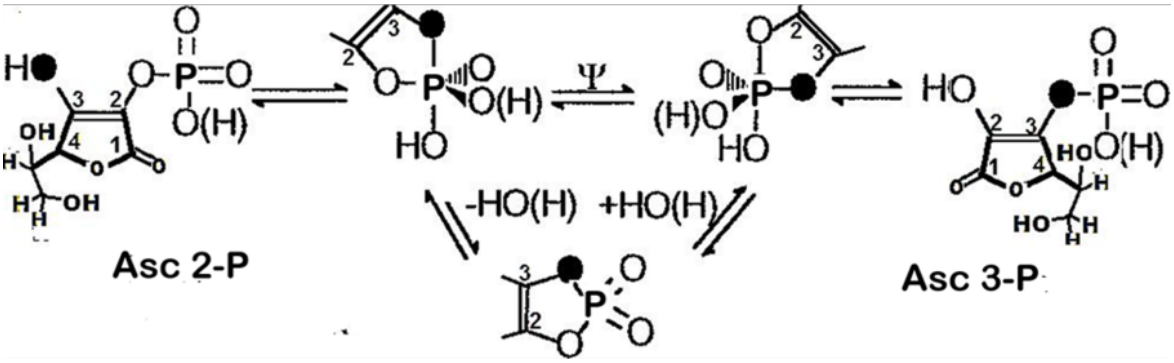
ABSTRACT

A supramolecular paradigm for mitigation and rescue from SARS-COV2 infection is proposed. Similarities between the Sanarelli-Shwartzman phenomenon and biological responses to viral pathogens are considered. Non-enzymatic group transfer catalysis (NGTC) by L-ascorbic acid, the L-ascorbic acid free radical and the 2-O-phosphate substituted L-ascorbic acid derivative are proposed under the ascorbolysis hypothesis to provide a supramolecular basis for mitigating the synergistic toxicity and catalytic mimicry by the environmental toxicants, sodium fluoride, aluminum salts, and silicofluorides in public water supplies. Ascorbolysis is the term we adopt to describe a redox active, hyperconjugated, vinylogous variant of acidolysis. The objective of this paper is to provide a plausible supramolecular basis for mitigation and rescue from well-known environmental toxicity represented by the presence of sodium fluoride, aluminum salts, and silicofluoride species in public water supplies. An overview of the conceptual basis for NGTC by vitamin C during inflammatory states is provided. Controversies concerning the initial oxidation steps and pH-dependent speciation of L-ascorbic acid are addressed. Non-skeletal fluorosis is a serious systemic malady which we propose arises from disruption of hydrogen bond networks and hydrogen bond cooperativity resulting from the marked electronegativity and hydrogen bond accepting ability of fluoride atoms found in NaF and AlF_x species. AlF_x species have been previously shown to arise *in situ* spontaneously from NaF, aluminum salts, and silicofluorides often found in toothpastes and "fluoridated" drinking water. AlF_x species are thought to act as isosteric mimics of biophosphates during group transfers of phosphoryl moieties. We propose that catalytic mimicry by AlF_x species inhibits postulated non-enzymatic kinase-like and RNA polymerase-like function of the AA-2P derivative during inflammatory states. We describe how NGTC by L-ascorbic acid is likely to be disrupted by AlF_x and sodium fluoride of a specific H3-O2 intramolecular hydrogen bond in L-ascorbic acid, the L-ascorbic acid free radical, and their 2-O-substituted derivatives, which are necessary for NGTC in the moderately acidic, mildly oxidative, relatively hydrophobic microenvironment which typify inflammatory states. Suggestions are made to achieve less variation in results of large randomized clinical trials (RCTs) seeking to validate use of high-dose intravenous vitamin C in critical care and cancer settings.

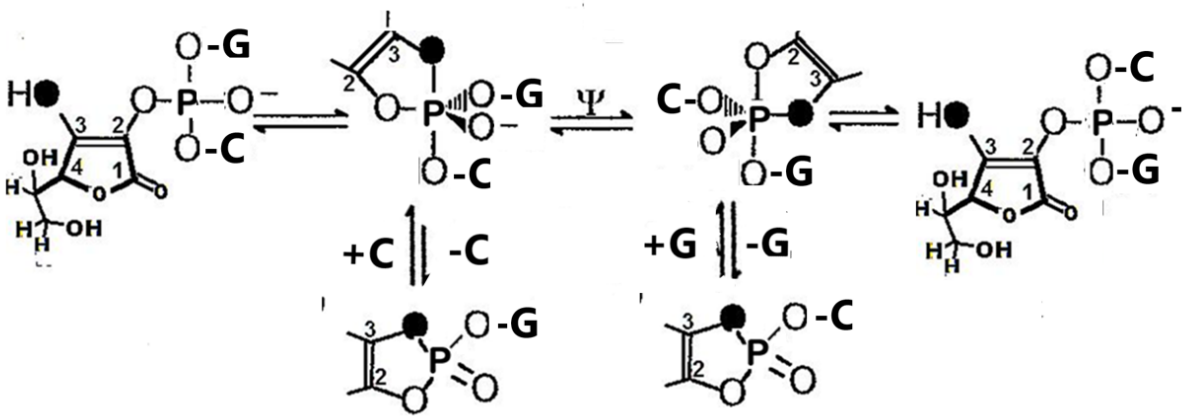
Keywords: *non-enzymatic group transfer catalysis, ascorbolysis, catalytic mimicry, toxic synergy, reproductive biology, electromagnetic pollution, induced intramolecularity, hydrophobic effect, pH-dependent speciation, kinetic solvent effects, intramolecular 1,4 hydrogen atom*

transfer, proton coupled nucleophilic attack, charge reorganization catalysis, oxidative photo-activation, SARS-CcV2, KEAP1 inhibition, NRF2 activation, NFkB-MAPK pathway, MAPK phosphorylation

SUMMARY GRAPHIC



(a)



(b)

Figure 1. A supramolecular strategy for combatting the current persistent global SARS-CoV-2 pandemic is urgently needed. If you look under the hood of "vitamin" C, don't be surprised to find ancient molecular motors. (**a**) Generalized depiction of reversible, auto-catalytic prebiotic "kinase-like" function; (**b**) generalized depiction of RNA editing under the non-enzymatic group transfer catalysis (NGTC)/ascorbolysis/universal non-specific mesenchymal reaction (UNMR) framework (as explained in this article).

Introduction

(i) Inferences based on pattern recognition from seemingly unrelated, tangential fact-patterns

The human central nervous system has an absolute requirement for cholesterol, cholesterol sulfate, sphingosine, sphingosine-1-phosphate, and L-ascorbic acid (Strott 2003; Ceccom et al. 2014; Buehrer 1992; Spiegel 2020). Mammalian reproductive biology is strongly dependent on the presence of L-ascorbic acid, including that of fruit bats (Krutzsch cites; Wang 2011), Guinea pigs, and humans, species which can all become scorbutic — showing the symptoms of scurvy — and will die in the absence of exogenous dietary sources of L-ascorbic acid. Bats are known to be

pollinators of plants, and consume mosquitos as a dietary staple. They can also navigate and fly in total darkness. In 2005, a severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats (Lau 2005) was reported. In the midst of the current, persistent, global SARS-CoV2 pandemic, as we "circle the wagons" on a world-wide scale (Davidson et al. 2015a-c), it is also wise to take a more global perspective on human health and our biosignaling systems inside the body and outside in the environment. An additional, seemingly disparate historical observation, is thought by the authors to have considerable implications for the rational design of a supramolecular strategy for coping with the ongoing and promised future scourges of global pandemics (see Shaw's paper in this issue). Specifically, we call the readers' attention to the many literature citations to research examining the non-enzymatic cleavage of bacteriophage polynucleotides by L-ascorbic acid and the essential trace mineral, copper (Richter 1982; Wong 1974; Chiou 1983, 1984). We will return to these observations in both the Results and the Discussion sections to follow.

(ii) Vitamin C in the supramolecular mitigation and rescue from stress and synergism of environmental toxicants

Colostrum and so-called "mother's milk" is known to be very high in levels of L-ascorbic acid (Przybylska 2007). Heffers that calve in freezing weather must nurse their newborns very soon after birth or the calf will not survive. It has been shown that mice, whose reproductive tissues have been damaged by 30 days of sodium fluoride and aluminum chloride in their feed, can be "rescued" from this damage by L-ascorbic acid (Chinoy et al. 2005a-b). None of these observations are mere serendipity in terms of vitamin C. In the 2015 conference proceedings from Atlanta, GA and London, UK, Davidson presented the hypothesis that vitamin C possessed properties far beyond its prodigious anti-oxidant properties, to account for the growing number of its pleiotropic health effects in humans (Davidson et al. 2015a-c). In 2018, Yu et al. showed that genetic reprogramming of porcine oocytes is dependent on L-ascorbic acid. Bovine oocyte maturation is dependent on L-ascorbic acid (Dalvit et al. 2005). Both male and female germ cell lines evidently depend on L-ascorbic acid for maturation. It has been known for at least 3 decades that L-ascorbic acid protects DNA from oxidative damage in human spermatocytes (Fraga et al. 1991).

(iii) Non-enzymatic group transfer catalysis: the proposed biophysical basis for the supramolecular, biophysically-pleiotropic properties of vitamin C

In this paper we will present an overview of what we believe to be the biophysical basis for numerous reports of pleiotropic behaviors of L-ascorbic acid. We have been strongly influenced by the large body of scientific contributions from Linus Pauling and Hans Selye. Cameron and Pauling anticipated the supramolecular properties of vitamin C in relation to cancer (Cameron & Pauling 1973). Hans Selye in the 50's and 60's made compelling arguments for supramolecular biology using small animal histopathology as the basis for this assertion (Selye 1950, 1966, 1967, 1968). In 2016, Kennedy et al. published a paper titled "Environmental Toxicants and IMR…" which should be a wake-up call for toxicologists worldwide (Kennedy et al. 2016). While Davidson was presenting arguments supporting quantum phase-coherence at all biological signaling levels in 2015 conference proceedings in London, UK (Davidson et al. 2015a), Winey was presenting his discovery of activated water at an international conference on water in Varna, Bulgaria (Winey 2015). The present paper represents a brief summary and initial results from the collaboration between Winey and

Davidson, a collaboration whose focus is on supramolecular biology, in a process they describe as non-enzymatic group transfer catalysis ("NGTC"), an over-arching process which spans all levels of biological signaling organization, and subsumes the supramolecular properties of activated water and L-ascorbic acid.

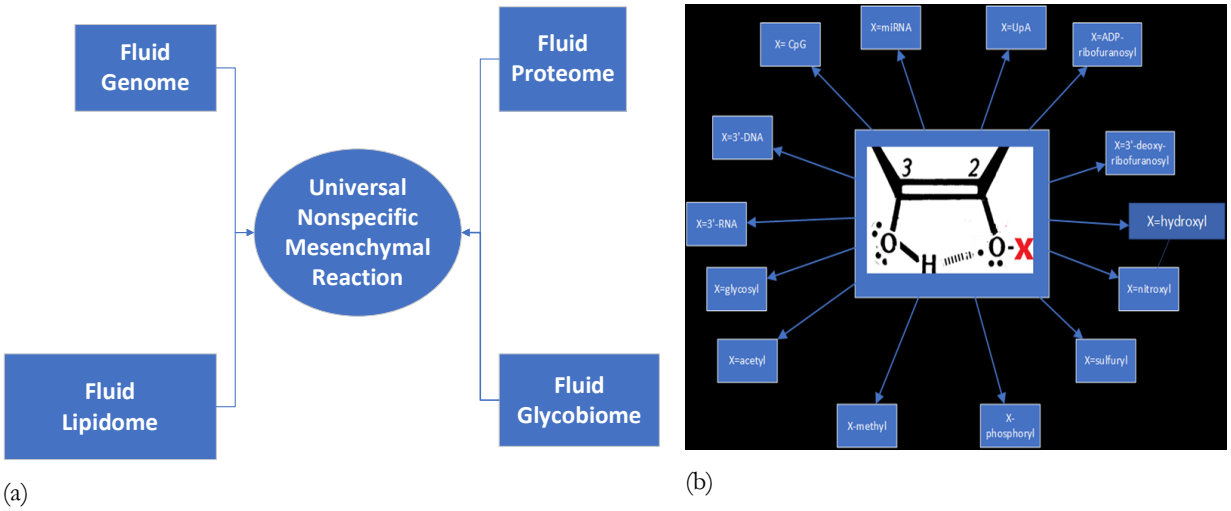


Figure 2. (a) Conceptual depiction of the "universal non-specific mesenchymal reaction" (abbreviated herein as "UNMR") originally described by Hans Selye, and others; (b) conceptual depiction of the "ascorbolysis hypothesis", i.e. the hypothesis that L-ascorbic acid, the L-ascorbic acid free radical, and the 2-O-substituted L-ascorbic acid radical derivatives provide living organisms with non-enzymatic group transfer catalysis (abbreviated herein as "NGTC"). Under this framework, ascorbolysis is a subsystem, i.e. is subsumed by NGTC.

As essential background to this paper, we need to describe the so-called "universal non-specific mesenchymal reaction" (UNMR), originally described by Selye, Hauss, and others (Selye 1950, 1968; Hauss 1962, 1969). Also essential is the "ascorbolysis" hypothesis, initially introduced in 2015, though it has been substantively modified since then. An introduction to the UNMR and ascorbolysis hypotheses are available in the Winey and Davidson conference presentations from 2015, available in the public domain at ResearchGate and YouTube as cited in our reference list. Briefly stated, the UNMR refers to the different causes of accelerated metabolism in connective tissues and in all organs studied (Hauss *et al.* 1962). Selye (1966) described a local or general intravascular coagulation that occurs in response to certain toxins or systemic stress. Figure 3 is a recent depiction of ascorbolysis, wherein the chemical steps and radical chain reactions catalyzed will be presented in the Results and Discussion sections.

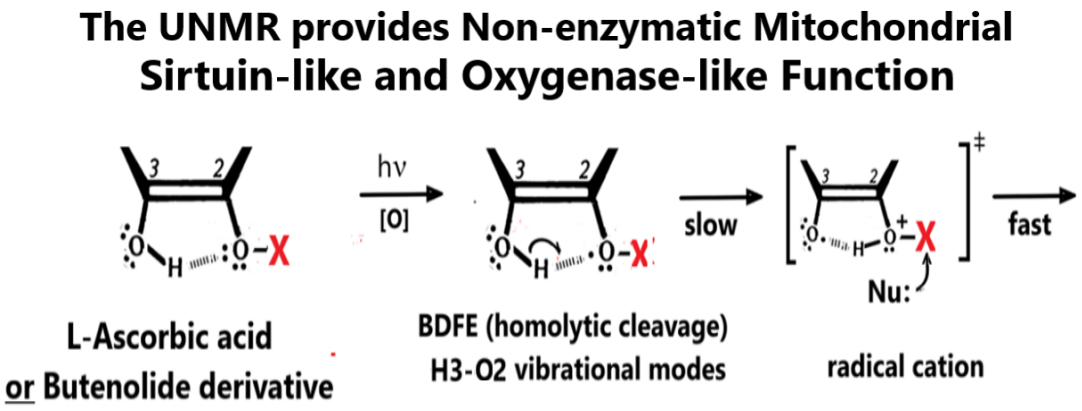
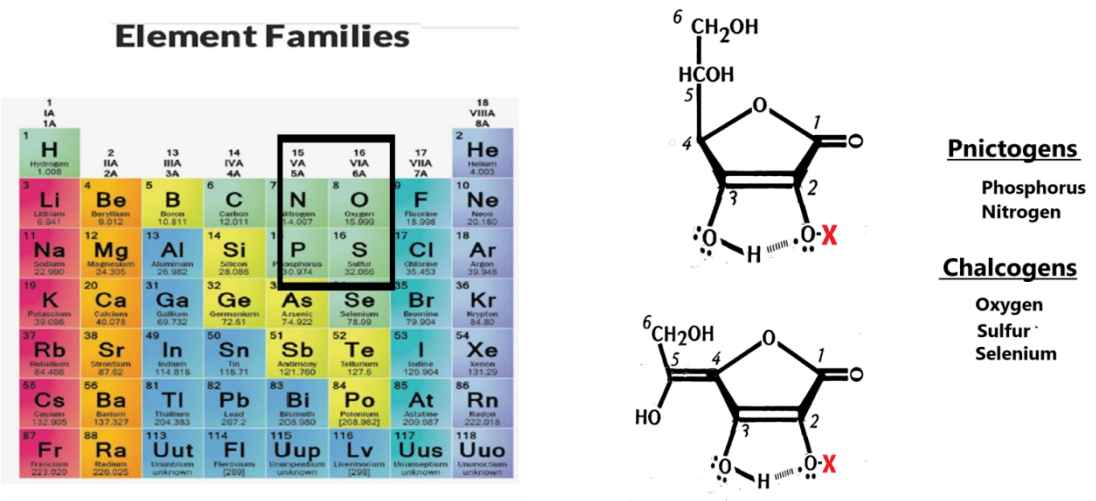


Figure 3. Proposed scheme by which photo-oxidatively super-activated derivatives of L-ascorbic acid are thought to provide reversible non-enzymatic trans-acetylation function and non-enzymatic hydroxylation function throughout the entirety of chemical evolution, within a moderately acidic, mildly oxidative, relatively hydrophobic aqueous microenvironment. Importantly, reversible, non-enzymatic kinase-like, methyl-transferase-like, sulfuryl transferase-like, acetyl transferase-like, hydroxylase-like, glycosyl transferase-like, and nitrosyl-nitroxyl-transferase-like function are examples of pnictogen- and chalcogen-based functional groups whose transfers are contemplated by the NGTC and ascorbolysis hypotheses. Ascorbolysis is postulated to provide the biophysical basis for the regio-, stereo-, and chemio-specificity of reversible post-translational modifications (PTMs) of proteins, including PTMs of genetic transcription factors, e.g. reversible PTMs of the NRF2-KEAP1 pathway (Mukhopadhyay 2015; Suzuki 2015; Song 2017).



(**a**) (**b**)

Figure 4. Relationship of chalcogen- and pnictogen-based functional groups to the periodic table of elements: (a) group 15 elements (denoted pnictogens) and group 16 elements (denoted chalcogens); (b) the chiral redox active hyperconjugated L-ascorbic acid free radical and its early planar (achiral) oxidation products (butenolides) are both postulated to non-enzymatically catalyze biological group transfers of chalcogen- and pnictogen-based functional groups, in quantum phase-coherent manner within activated "spin water" during inflammatory states, within moderately acidic, mildly oxidative, relatively hydrophobic aqueous microenvironments.

(iv) Proposal for mitigation and rescue from environmental toxicants by means of NGTC, ascorbolysis, and the UNMR

It has long been known that fluorides impair collagen structure and function (Gupta 2013; Lee 2018; McGarvey 1996). Collagen structure and PTMs of collagen proteins form the vast majority of the "mesenchyme" throughout our bodies for our entire lifetime. PTMs of cytoskeletal proteins are thought to be dynamical and reversible, demonstrating both mechanical and conductive properties (Mittal and Saluja 2015). The tensile properties of both fibrillar and globular proteins play a structural role in many tissues throughout our bodies. From an architectural perspective, Buckminster Fuller coined the term "tensegrity" to describe such structural properties (Ingber 2003; Bywater 2017). In the folding of milk proteins, the "molten globular state" is thought to be an intermediate (Qi 2001). Hydrogen bonding networks are thought to provide for much of the tensile strength and structural determinants during protein folding (Bywater 2017) in proteins such as collagen, actin, and milk proteins, including prions and amyloid proteins. Misfolded proteins are distinct from unfolded proteins.

Vitamin C has long been known to play an essential role in the synthesis, modelling, *and remodelling* the structure of various collagen biopolymers (Robertson 1953; Murad 1981; Franceschi 1994; Park 2010; Robertson 2014; Gomez Ruiz 2018) as well as playing a role in the regulation of collagen gene expression (Chojkier et al. 1989). A very provocative observation was made by Kumano et al. in 1998, when they reported that the 2-O-alpha-D-glucopyranosyl derivative of L-ascorbic acid has an "enhancing effect" on collagen synthesis (Kumano 1998). When these facts are considered in combination, our proposed mechanisms for "rescue" of various fluoride-intoxicated tissues, becomes much easier to appreciate. One need not postulate the necessity of innumerable intermediate enzymatic steps in the chain of causation under the NGTC/ascorbolysis framework.

(v) Ascorbolysis endows vitamin C with a supramolecular means of "stimulating" intracellular antioxidant activity, cytoprotective activity, and anti-ageing activity

In 2016, Katsuyama et al. reported that a novel derivative of L-ascorbic acid demonstrated not only antioxidant effects and direct ROS radical scavenging activity, but also stimulated intracellular antioxidants (Katsuyama 2016). They said it

> … up-regulates the expression of mRNAs encoding peroxisome proliferator activated receptor-γ (PPAR-γ) and nuclear factor E2-related factor 2 (Nrf2), which in turn up-regulate the levels of mRNAs encoding γ-glutamyl cysteine synthase (γ-GCS), heme oxygenase-1 (HO-1) and NAD(P)H quinone oxidoreductase-1 (NQO1).

We will present in the Results and Discussion sections, our proposal for how ascorbolysis endows vitamin C with supramolecular characteristics that enable it to stimulate intracellular antioxidants at all biological signalling levels, in a quantum phase-coherent manner, including but not limited to regulating the reversible expression of genes, e.g. antioxidant genes whose expression is stimulated or inhibited by the interaction of transcription factors, e.g. NRF2 and KEAP1. The "ascorbyl phosphate" derivative of L-ascorbic acid has been identified intracellularly. We propose, herein, that the 2-O-phosphate-L-ascorbic acid radical acts as a non-enzymatic kinase in the reversible PTMs of proteins such as KEAP1 (Abed et al. 2015) and MAPK of the NFkB-MAPK pathway (Eguchi 2003).

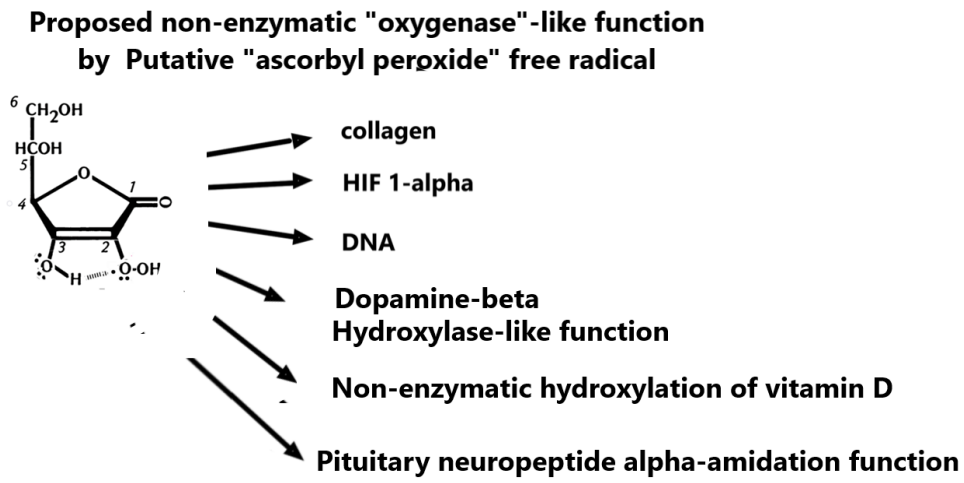
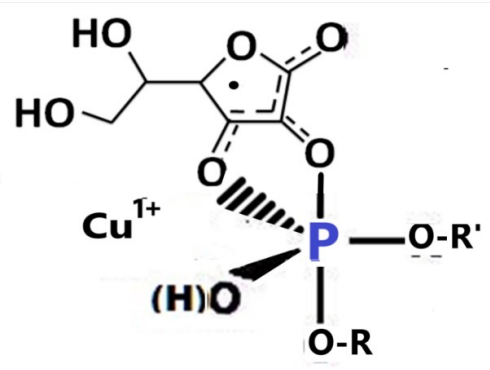
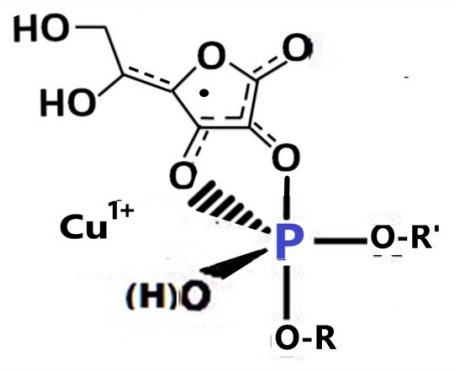


Figure 5. Postulated role of ascorbyl peroxide free radical in hydroxylation of collagen, HIF-1-alpha, vitamin D (Sergeev 1990), DNA, dopamine-beta hydroxylase (Weinshilboum 1978), and alpha-amidation of pituitary neuropeptides (Simpson 2015). Scheme depicts postulated reversible non-enzymatic "oxygenase" and "dioxygenase" functions of putative "ascorbyl peroxide" free radical in inflammatory states, such as that induced by fluoride and aluminum environmental neurotoxicants. L-ascorbic acid, the L-ascorbic acid free radical, and their 2-O-substituted derivatives may provide a chemical biological means of reversal and rescue from fluoride- and aluminum-based neurotoxicity, reproductive toxicity, immune toxicity, and the multi-faceted toxicity associated with viral pathogens, such as for example, Dengue, Ebola, and SARS-CoV-2. Fluoride-related mitochondrial dysfunction and oxidative stress can be mitigated by L-ascorbic acid (Chinoy et al. 2005a, 2005b) wherein its function as a "cofactor" for mitochondrial oxygenases and dioxygenases is likely to actually represent NGTC via ascorbolysis. See Figures 3, 6(e), and 23. Under the current embodiment of the NGTC/ascorbolysis/UNMR hypotheses, all "kinases", including protein kinases, generally, are likely to be rendered superfluous during inflammatory states, wherein the pH does not match the pH optimum of the kinase or the stability of the endogenous phosphorylation factor, typically ATP. ATP is well known to be highly labile to hydrolysis in the acidic pH range (Stecher 1968).



(**a**)



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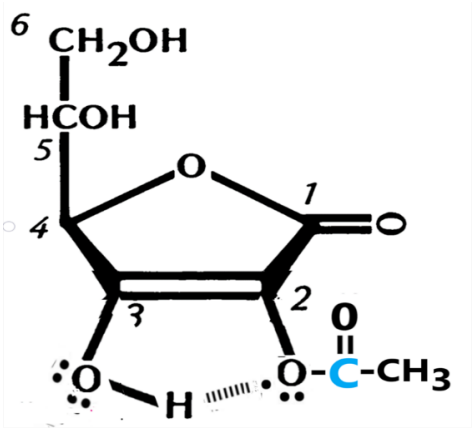

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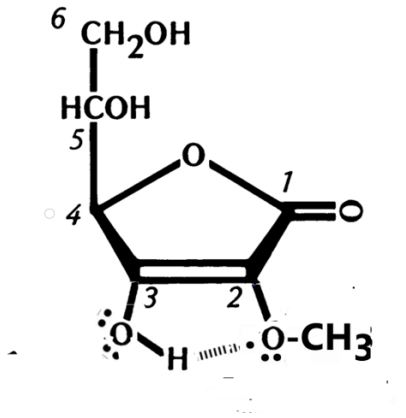

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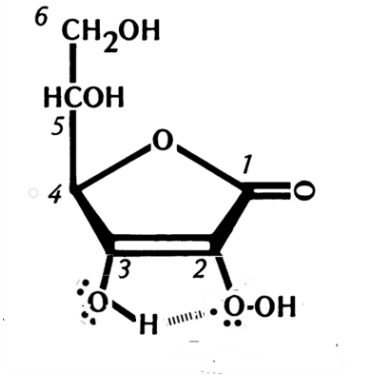

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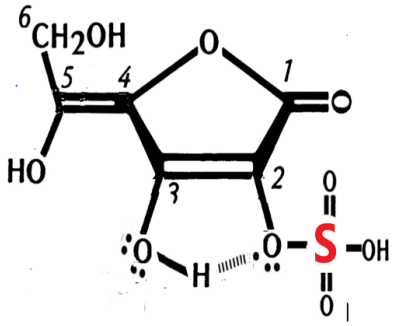


(f)

Figure 6. Putative prebiotic photo-oxidatively super-activated "molecular motor" catalysts/reactants for radical chain reactions: (a) putative primordial ascorbyl phosphate "kinase-like" reactive transient; (b) putative "pro-chiral" butenolide early oxidation product of "ascorbyl phosphate"; (c) putative primordial "sirtuin" (non-enzymatic trans-acetylase; (d) putative primordial methylation "factor" (reactive transient); (e) putative primordial hydroxylation factor (dioxygenase-like reactive transient); and (f) putative primordial "sulfotransferase". In the acidic pH range, ca. pH 4-6, (a)-(f) would be "free radicals" (uncharged) and butenolide derivatives would be "pro-chiral" reactive transients. In a moderately acidic, mildly oxidative, relatively hydrophobic micro-environment, (c)-(f) are postulated to be intramolecularly hydrogen bonded, i.e. they would all demonstrate "induced intramolecularity" and increased "effective molarity" at the H3-O2 hydrogen bond, the path postulated to be taken for "intra 1,4 HAT" (hydrogen atom transfer) (see both our Results and Discussion sections to follow, for explanation). Within so-called activated "spin water", homo-chiral "bias" or "filtering" of (a)-(f) is postulated to occur. Generally, chiral induced spin selectivity (CISS) is a central tenet to the NGTC/ascorbolysis/UNMR framework. CISS is today a very active field, as is the field of nano-biology, generally (Naaman 2015, 2019, 2020). In total, the processes are proposed to comply with the Second Law of thermodynamics and Jeremy England's dissipative-adaptation theory of biological complexity (J. England 2015). Inflammatory states are postulated to favor the anabolic direction to the reversible reactions proposed under the NGTC/ascorbolysis/UNMR framework.

Before embarking on an overview of our work, we posit that the increasing US infant mortality rate (IMR) represents a reality (Kennedy et al. 2016) that should concern us all, including non-US countries, especially in the midst of a global pandemic. Both man-made chemical and electromagnetic toxicants are rapidly increasing in numbers and quantity, in parallel with rising IMR. Here we focus on the known effects of certain environmental toxicants and micro-trauma from radiant energy: fluoride, aluminium, and EM radiation. Scorbutism, especially the sub-clinical variety

of scurvy (Booth 1972), is rarely diagnosed, yet readily treatable. Certain mammalian species have lost their ability to synthesize their own L-ascorbic acid. While the explanation for the loss of this capacity is uncertain, we suggest that the greater complexity of the central nervous systems in these species, calls for a greater need in the "input function" provided by environmental sunlight, for trapping and transduction, by interfacial water, and in a non-adiabatic environment, leads to greater complexity in the form of homo-chirality, anisotropy, and quantum phase-coherence on all scales of time and space. Fractals based upon "the fractal dimension" will one day, we firmly believe, be shown to be the rule, not the exception due to the quantum phase-coherence of living organisms, including humans (Davidson et al. 2015a). What price, if any, might be paid for this increase in complexity? Dissipation of heat is the price which might be paid, under Jeremy England's dissipative adaptation theory (2015). What price, if any, might be paid for ever increasing amounts of environmental toxicants, including fluoride, aluminum, and EM pollution? Extinction of the species is a distinct possibility, for which many examples exist in nature, over time (Liu et al. 2012). Computer modeling of populations for risk of extinction should arguably include the concept of toxic synergy discussed in the Kennedy et al. 2016 review article.

To manage the scope of the requisite global internal and external perspective of this paper, we direct attention to the seminal earlier work by Chinoy, et al. (2005a; 2005b), and the review articles by Barbier et al. (2010) and Kennedy et al. (2016), to provide essential background. With that in mind, to make our arguments fully intelligible, we must briefly describe the relevant findings from those works, before moving on to our own Results and Discussion sections. We will conclude this paper with the assertion that in the future AI techniques are almost certain to be employed to reverse engineer, with clinical translational potential, the "initial common pathway" to life on Earth. We suppose that time is running short on maintaining our own genomic resilience, stability, and the long term survival of our species as discussed recently by Robert F. Kennedy, Jr. and Zach Bush: (see *'Truth' with RFK, Jr. and Dr. Zach Bush* at https://vimeo.com/490903719). Their discussion is entirely consistent, incidentally, with the thesis one of us, along with Stephanie Seneff, put forward some years ago concerning the critical role of inflammation in disorders, diseases, and the catastrophic systems failure that we call death (Davidson and Seneff 2012). We can liken the status quo to being at sea in a rudder-less ship with icebergs on the horizon — witness the alarming rise in IMR in the US, and in other so-called "developed" nations (Kennedy et al. 2016), along with exponential increases in a vast and growing list of chronic non-communicable diseases (Calitz et al. 2015), not to mention pandemics of infectious pathogens such as SARS-CoV-2.

Chinoy's studies of fluoride toxicology in a mice model of human disease is prescient (Chinoy et al. 2005a; 2005b). The review article by Barbier (2010) links fluoride toxicology to that of aluminum toxicology. The Kennedy et al. review article (2016) describes how NaF and the silicofluorides in public water supplies are likely to impair biological signalling by G-proteins. We will describe in the Results and Discussion sections, how according to the NGTC hypothesis, vitamin C and activated water may serve as a means of reversing and rescuing living species, including ourselves, from aluminum and fluoride toxicity. The ever increasing presence of EM pollution, e.g. from the advent of 5G technology globally, remains an evolutionary "wild card" for which there are many uncertainties. In any case, the long term safety of ramped up EM exposure has not been established. Because EM fields from sunlight, e.g. environmental torsion fields, play a central role in NGTC, ascorbolysis, and the UNMR, and given that manufactured environmental EM pollution is on the rise, an irreversible state might soon be reached which is unsustainable, in terms of inflammation, disease, and deaths.

Chinoy's Work Summarized

Male mice were orally fed sodium fluoride 10 mg/kg body weight) and $AlCl_3$, 200 mg/kg body weight for 30 days. Alterations in structure of the testis with formation of giant cells and decreased protein levels were observed. Alterations in steroidogenesis, spermatogenesis, and decreased activities of 3β- and 17β-hydroxysteroid dehydrogenases were observed with concomitant accumulation of cholesterol (Chinoy et al. 2005a). Also in 2005, Chinoy showed that epididymis cell damage and damage to the testes in mice induced by fluoride and aluminum were reversed by vitamin C (Chinoy et al. 2005b).

Barbier's Review Article Summarized

Aluminum is a ubiquitous environmental toxicant which is exposed to humans by multiple routes, including orally, topically, and parenterally. Considerable published data provides several likely bases upon which the pathophysiology is based (Barbier 2010).

The Kennedy et al. Review Article Summarized

Just as lead in terra cota pipes for public water supplies may have posed serious unexpected health risks in ancient Rome, so too does lead, Al, F, and HFSA (hexafluorosilicic acid) in public water supplies, e.g. that found in Flint, MI (Flint, MI link). Bio-sequestration of heavy metals by living tissue has been postulated. Importantly, pH dependent speciation and reactivity of NaF and silicofluorides in public water supplies may disrupt hydrogen bonds and hydrogen bond cooperativity and impair G-protein signaling by providing catalytic mimickry of biological phosphorylation reactions, wherein AlF_x species act as transition-state analogues of phosphoryl moieties in biological transphosphorylation reactions (Kennedy et al. 2016).

Of particular note, especially for policy-makers (see the second paper, "Plan B..." by James Lyons-Weiler in this issue of the *IJVTPR*), is the undeniable association between neurotoxicity and neurobehavioral pathology, for which the events in Flint, MI are a microcosm (Masters 1998, 2003; Masters et al. 2016). The "generally recognized as safe" (GRAS) mantra fails because of the concept of synergistic toxicity and non-linearity of the typical dose-response (Kennedy et al. 2016). The human central nervous system has a strong tendency to "sequester" heavy metal environmental toxicants, including aluminum salts and gadolinium salts, both of which have been identified in human brain tissue on MRI and histopathological evaluation (Iadecola 2015; Mold & Exley 2019; Alkhunizi 2020). Also, of note, the undeniable neurotoxicity is associated with neuro-immune toxicity, and has been described as Shoenfeld's syndrome, also referred to as the "Autoimmune-inflammatory syndromes induced by adjuvants" (ASIA; see Shoenfeld and Agmon-Levin 2012). We propose that human tissues of ectodermal embryological origin are biophysically predisposed to bio-sequestration of heavy metal environmental toxicants. Cells of ectodermal origin include pluripotent stem cells, brain cells, reproductive cells, and immune cells. Fortunately, cells of ectodermal origin appear to be high in their level of L-ascorbic acid (Ang 2018), unless of course, the subjects were rendered scorbutic by one or more environmental toxicants, with associated oxidative stress, poor dietary intake of vitamin C, such as was likely to be the case in Flint, MI (Flint, MI). The embryological envelopment of ectoderm by mesoderm and endoderm is biophysically-driven (Brodland 2002).

Results

In this section, we present our proposal as to how environmental toxicants pose distinct risks of disrupting biological group transfers of the non-enzymatic type, i.e. the type of group transfers which logically had to occur long before the advent of biomacromolecules on Earth, i.e. the prebiotic/primordial planet Earth. We present herein a conceptual framework for chemical evolution, biological complexity, and biological diversity, that is biophysically based on homo-chiral molecular morphology in the sequence: water → carbohydrates → nucleic acids → proteins → lipids → glycosaminlglycans → glycosphingolipids → etc. We propose further, that of the earliest carbohydrates, L-ascorbic acid, an oft-studied "vitamin", played a central role based in catalyzing non-enzymatic group transfers.

In agreement with Baccolini's theory of life (2015), it is logical to infer that in the beginning "small and fast" took precedence over "big and slow" and in a "carbohydrates first" sequence to chemical evolution, L-ascorbic acid was likely to be one of the earlier molecular entities to emerge. Under the NGTC and ascorbolysis framework, L-ascorbic acid is postulated to undergo reversible photo-oxidative "super-activation" in the presence of activated ortho/para spin states of water and photo-sensitization by the redox active transition metal, specifically certain oxidation states of highly polarizable essential ultra-trace mineral, copper. We propose herein that in a moderately acidic, mildly oxidative, relatively hydrophobic microenvironment, L-ascorbic acid, its 2-O-substituted derivatives, and its butenolide oxidation products, undergo photo-oxidative super-activation to form radical species that initiate, propagate, and terminate radical chain reactions, in quantum phase-coherent manner, wherein homo-chirality, stereo-, regio-, and chemio-specificity is externally-driven by the handedness of external torsion fields, in a non-adiabatic, open, dissipative environment. Under this hypothetical framework, water plays a central role. Water, itself, is capable of oxidation catalysis in presence of certain redox active transition metals (Rudshteyn 2018). In combination, activated "spin water" is postulated to lower the free energy barriers via quantum nuclear tunneling, effectively flattening the free energy landscape for chemical biology. In this scenario, ever increasing complexity is gained at a cost of dissipation of heat to the environment, in an open dissipative system which exists far from thermodynamic equilibrium.

We will focus on our proposed mechanism for the toxicity of human exposure to various species of fluoride, aluminium, and EM radiation. A large body of published research provides the scientific basis for the assertion that fluoride species, in vivo, have a pleiotropic supramolecular basis for their toxicity which arises largely by disrupting hydrogen bond coopertivity in vivo, in many microenvironments (Froede 1985; Murphy 1992; Kentsis 2004; Strunecka 2012). The magnitude and kinetics of this disruption is thought to be strongly pH- and solvent dependent. A corollary assertion is that the biological activity of L-ascorbic acid is strongly influenced by hydrogen bond cooperativity, both intra- and inter-molecular (Berg 2015; Ebrahimi 2016). The systematic detail underlying the ascorbolysis hypothesis is beyond the scope of this paper, but we can briefly give the reader an overview of the concept and its underlying theoretical basis.

(i) Assignment of nucleophilic "radical philicity" to the L-ascorbic acid free radical

(a) (b)

Figure 7. (a) Calculated incremental spin density map from DFT study of O'Malley (2001) showing the most favorable hydrogen bond acceptor sites for the radical (-150.0 kcal/mol electrostatic potential contour) for the R-hydroxytetronic acid radical (reproduced here from O'Malley (2001) with permission of the publisher); (b) our proposed "intra H-bonded" mono dehydro ascorbic acid free radical depicting the mesomer with the greatest nucleophilic radical philicity.

(ii) Ascorbolysis – what is it?

Ascorbolysis may be thought of as a possible mechanism by which chemical biology "evolved" so as to provide the UNMR with a means of responding in a reversible generalized adaptive response to environmental stress. The adaptive response takes the form of branching cascades of phase-coherent radical chain reactions within an open, dissipative, non-adiabatic system which complies with the second law of thermodynamics. The system is proposed to be externally-driven by EM energy and information from sunlight which has been transduced by activated ortho/para populations of "spin-water" (Glemza 2000; Tikhonov 2006; Horke 2014; Kilaj 2018; Chaplin 2020). Quantum mechanical tunnelling "flattens" the free-energy landscape for genomics, proteomics, lipidomics, and glycomics. Circadian rhythms are imparted to the system by the redox active, photo-sensitizer and time-keeper, the essential ultra-trace mineral, copper. The radical chain reactions are initiated by the unimolecular dismutation of L-ascorbic acid which generates the L-ascorbic acid free radical and DHA without net oxidation or reduction (Deutsch 1997). The first of two serial propagation steps is proposed to occur by means of the L-ascorbic acid free radical reacting in an S_N2 mechanism with any of the myriad endogenous electrophiles, providing 2-O-substituted derivatives of the L-ascorbic acid free radical. The products of the first chain propagation step represent photo-oxidatively super-activated mixed anhydrides which are postulated to possess electrophilic radical philicity. In the secpmd of two propagation steps, the super-activated reactive transients (radical cations) react chemio-, regio-, and stereo-specifically, with any of a myriad of endogenous biological nucleophiles, in a reversible acid-catalyzed proton-coupled nucleophilic attack (PCNA) S_N2 reaction, with the L-ascorbic acid free radical, acting as a resonance-stabilized (mesomerically-delocalized) leaving group.

The L-ascorbic acid free radical can then dismutate to terminate the radical chain reaction. Each step in the radical chain reaction is postulated to proceed via intramolecular 1,4 hydrogen atom transfer ("intra 1,4 HAT") mechanism. Added hydrophobes and amphiphiles are proposed to "induce intramolecularity" for inner sphere hydrogen atom transfer, wherein moderate acidity effectively "labilizes" hydrogen atoms at the 2-, 3-, and 4-positions of the gamma-lactone ring system according to the GCMS studies of John Deutsch (see Deutsch et al. 1994; and Deutsch 1997, 1998a-d). The

rate-limiting step for the radical chain reactions is thought to be homolytic cleavage of the O-H bond at the 3-position of the gamma-lactone ring system. Electronegativity of the various pnictogen-based and chalcogen-based functional groups being transferred is thought to influence the kinetics. The "intra 1,4 HAT" mechanism suggests nuclear quantum mechanical tunneling (McKenzie 2014) along the path of the pre-equilibrium H3-O2 hydrogen bond whose vibrational modes are likely to have been activated cooperatively with the four additional intramolecular hydrogen bonds identified in the global minimum structure for L-ascorbic acid reported by Rolf Berg in a UV/IR Raman and DFT study (2015). Figure 8 depicts one of the many radical chain reactions proposed to be catalyzed by the L-ascorbic acid free radical.

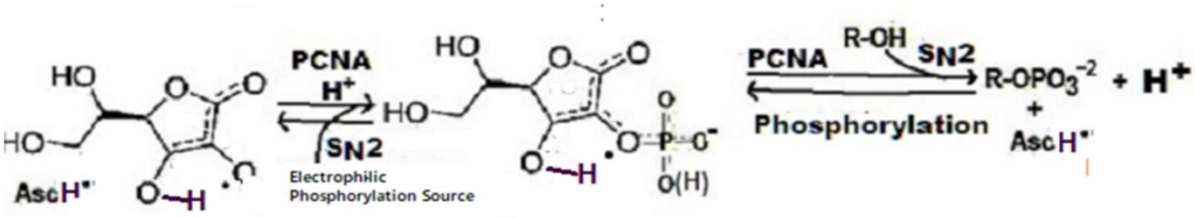


Figure 8. Proposed radical chain propagation steps in phosphoryl group transfer via ascorbolysis (non-enzymatic group transfer catalysis by L-ascorbic acid), i.e. the proposed basis for the "fluid genome" (Maewan Ho 2013). Reversible, auto-catalytic cascades of radical chain reactions provide non-enzymatic kinase-like and DNA/RNA polymerase-like function. The scheme is generalizable to group transfer catalysis of many chalcogen- and pnictogen-based functional groups, thereby occupying a central role in the UNMR. We postulate that ascorbolysis provides a means for non-enzymatic oxidative phosphorylation in eukaryotes, including humans during inflammatory states. The proposed mechanism would enable non-enzymatic ATP production and post-translational modification of proteins during inflammatory states, e.g. within cancer tissues many of which are characterized by a Warburg shift to anaerobic glycolytic energy metabolism and inflammatory states characteristic of non-skeletal fluorosis, oxidative stress, and endothelial dysfunction, e.g. cancer, ischemia, and sepsis (Oudermans-Van Stratton et al. 2014).

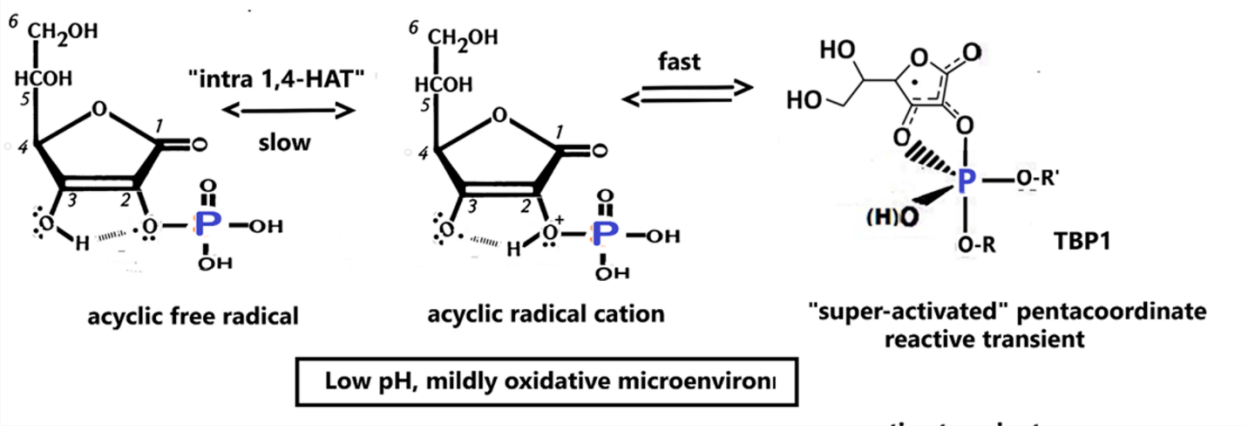


Figure 9. Pre-equilibrium intramolecular H-bonding precedes oxidative photo-activation, followed by (a) rate-limiting homolytic cleavage of the O-H bond at the 3-position accompanied by intramolecular 1,4 hydrogen atom transfer with formation of a radical-cation during charge reorganization ("umpolung" catalysis; Schmittel 1990, 1994) and orbital steering towards the "sigma hole", quantum tunneling; and (b) subsequent fast cyclization to form a cyclic pentacoordinate phosphorus free radical. The trigonal bipyramidal cyclic pentacoordinate free radical reactive transient is then able to pseudorotate following Westheimer's rules (1968), with "flattening" of the free energy landscape. In the low pH, mildly oxidative, relatively hydrophobic aqueous microenvironment the super-activated cyclic pentacoordinate phosphorus reactive transient is able to stereo-specifically, regio-specifically, and chemio-specifically phosphorylate endogenous nucleophiles, including RNA, DNA, and proteins, behaving much like a primordial molecular motor, e.g. a non-enzymatic RNA polymerase, or nuclease in the reverse direction.

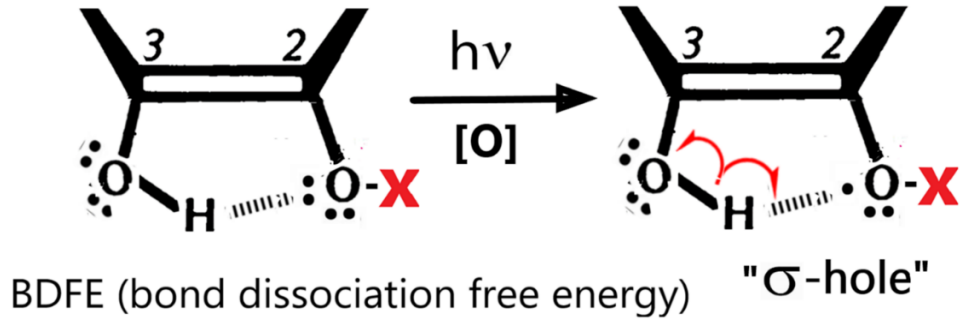


Figure 10. Proposed oxidative photo-activation of AA during uni-molecular first-order dismutation and Group Transfer Catalysis

Ascorbolysis is our proposal for a redox active vinylogous, hyperconjugated variant of acidolysis by L-ascorbic acid (vitamin C), its derivatives, and its butenolide oxidation product (Merriam-Webster; Penczek 2008; Deutsch et al. 1994). An understanding of the distinction between acidolysis and ascorbolysis is crucial. Acidolysis is reversible, general acid catalyzed, and solvent dependent. Whereas, ascorbolysis is reversible, general acid catalyzed, solvent dependent, and redox active (redox potential dependent). In the 1970s, Davidson demonstrated several examples of auto-catalytic acidolysis in the study of various analogues of phosphoenol pyruvate (PEP; this was done in his dissertation work in 1976; also see Davidson & Kenyon 1980). In 1961, Lichtenthaler wrote an excellent review article on the chemistry of enol phosphates (Lichtenthaler 1961). See IUPAC Glossary (Penczek 2008) for acidolysis. The Merriam-Webster definition of acidolysis is useful (Webster Definition). Early proof of concept was provided by the seminal work of Ralph Mumma (1968), who made the remarkable discovery that the 2-O-sulfate derivative of L-ascorbic acid can act as an efficient sulfurylating agent, both in vitro, and subsequently, in vivo (Verlangieri & Mumma 1973). Non-enzymatic sulfurylation of cholesterol forms the ubiquitous, and biophysically-pleiotropic, amphiphilic natural product, cholesterol sulfate (Strott 2003). Further proof of concept was provided when Egami & Hatanaka employed the 2-O-sulfate-L-ascorbic acid derivative in the non-enzymatic sulfurylation of chondroitin (Hatanaka 1976). Of particular note, Frederic Mercier's group, in their study of human stem cell "niches" in the subventricular zone of the hippocampus, referred to as CNS "fractones", made the remarkable discovery that heparin sulfate proteoglycans (HSPGs) of CNS fractones are deficient in sulfur, when the brains of autism subjects were studied histopathologically (Mercier 2012).

(iii) The necessity to challenge conventional wisdom

In several conference proceedings, Davidson and colleagues (2015a-c) inferred the need for a universal sulfurylation factor, in vivo, and proposed a radical-anion structure for such an agent. The original proposal in 2015, however, was critically-flawed by failure to consider the moderately acidic pH range, mildly oxidative, relatively hydrophobic microenvironment in which ascorbolysis, charge reorganization (umpolung) catalysis (Schmittel 1990, 1994), and proton-coupled nucleophilic attack (Hamer et al. 2015), upon photo-oxidative super-activation and intra 1,4 HAT, are most likely to occur. The lipophilicity and physicochemical properties of small molecules are known to be affected by the presence of intramolecular hydrogen bonds (IMHBs; Chen et al. 2019, 2020; Abraham et al. 2020). NMR methods offer convenient alternatives to use of partition coefficients (logP methods) for analysis of IMHBs (Abraham et al. 2020). Chen et al. have recently developed a full *in silico* (computational) linear free energy approach to accurately "predict the effects of organic compounds

on environments and the physicochemical properties of organic compounds", *including neutral organic compounds* (Chen et al. 2020). We assert that the physicochemical properties of the neutral organic compounds, L-ascorbic acid, the L-ascorbic acid free radical, and their neutral lipophilic derivatives affect inflammatory tissue microenvironments in such ways as to substantially affect human health. The global minimum DFT structure obtained by Berg (2015) for L-ascorbic acid had no less than *5 intramolecular hydrogen bonds*, which we assert imparts increased lipophilicity to the molecule. Of particular note, was a 2.751 Å H3-O2 hydrogen bond, which was notably lacking in several calculateed DFT structures for the *L-ascorbate mono-anion*.

The original embodiment of the ascorbolysis hypothesis was critically-flawed by reason of falling into a "rabbit hole" of conventional wisdom, the widely-held longstanding view that the redox biology of vitamin C is dominated by that of the L-ascorbate mono-anion at physiological pH. For readers wishing to consider this topic in greater detail, a large body of published data is recommended, whose scope is beyond that of the present paper (Warren & Mayer 2008; Warren & Mayer 2010a-b; Mayer 2011; Du & Buettner 2012; Saouma & Mayer 2013; Tu & Njus 2017; Njus et al 2020; Sajenko et al 2010; Karković Marković 2020; Handayani 2020). A single-minded focus on the ascorbate mono-anion and the ascorbate anion-radical effectively (a) marginalize studies of the vitamin in the moderately acidic pH range, (b) confounds the conclusions reached in large randomized clinical trials (RCTs), and (c) "starves" NGTC, ascorbolysis, and the UNMR from a source of protons.

Whereas, ascorbolysis postulates that intra 1,4 HAT, i.e. the diagonal cross relation (CR) path on a "box diagram" for HAT under Marcus' theory of proton-coupled electron transfer (PCET), is the favored reaction path within moderately acidic, mildly oxidative, relatively hydrophobic microenvironments. Intra 1,4 HAT is postulated to represent an "inner sphere", first-order process, with a "tight" transition state, and large negative activation entropy in the moderately acidic pH 4-6 range. According to Mayer, "HAT reactions typically have $\Delta S^\circ \cong 0$ because there is no change in the charges of the species involved and little change in their sizes" (Warren & Mayer 2008, 2010a-b; Mayer 2011). We suggest, however, that large negative activation entropies during ascorbolysis are likely to be associated with *intramolecular* 1,4 hydrogen atom transfers and substantial charge reorganization ("umpolung") catalysis which we propose occurs in the anabolic direction of reversible ascorbolysis (see Figures 3, 9, 14, 18b, and 23). The mechanism we propose for ascorbolysis is substantially based on entropic charge reorganization. The effective molarity of the postulated path for hydrogen atom transfer is predicted to be very high, and the likelihood of nuclear quantum mechanical tunneling along this path is likewise predicted to be very high. Neutral uncharged free radicals and radical anion species lead via charge reorganization to radical-cation intermediates and transition states in the anabolic direction of the proposed reaction coordinate for ascorbolysis and the UNMR. In the catabolic direction of reversible ascorbolysis/UNMR, the opposite sequence of charge reorganization would be likely to prevail, within inflammatory microenvironments, which are typically low in pH and high in oxidative stress. Thus, in this theoretical framework, inflammatory states are likely to favor the anabolic direction over the catabolic direction of non-enzymatic group transfers, as long as adequate L-ascorbic acid is provided, and environmental intoxicants (e.g. NaF, silicofluorides, aluminum salts) and EM pollution are avoided.

Warren and Mayer obtained a better fit of their model with experimentally obtained rate constants when Michael Abraham's parameters accounted for kinetic solvent effects which enabled the

prediction of a wide range of rate constants for HAT under the cross relation path of the Marcus theory of PCET (Warren & Mayer 2008, 2010a-b; Mayer 2011). The ascorbolysis hypothesis fails unless all three microenvironmental parameters (pH, redox potential, and hydrophobicity) are considered. Additional multi-component cyclic voltammetry studies of the type recently reported by Handayani (2020) can in principle be designed to prospectively control for all three environmental parameters (pH, redox potential, hydrophobicity) as well as comparisons of kinetics within activated ortho/para spin water (see Figure 11). Multi-component Pourbaix diagrams (plots of pH or pKa versus redox potential) might yield unexpected results, perhaps confirming existing theories, validate new ones, or suggest alternate avenues to explore.

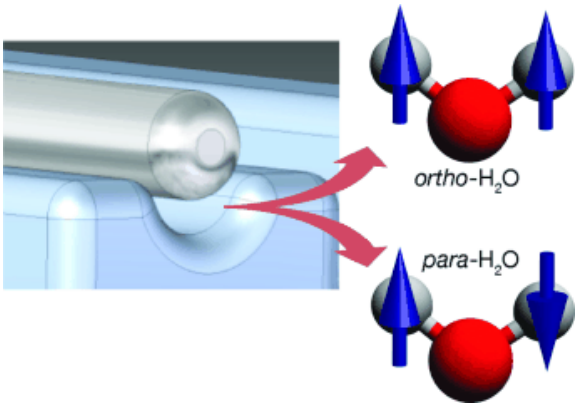
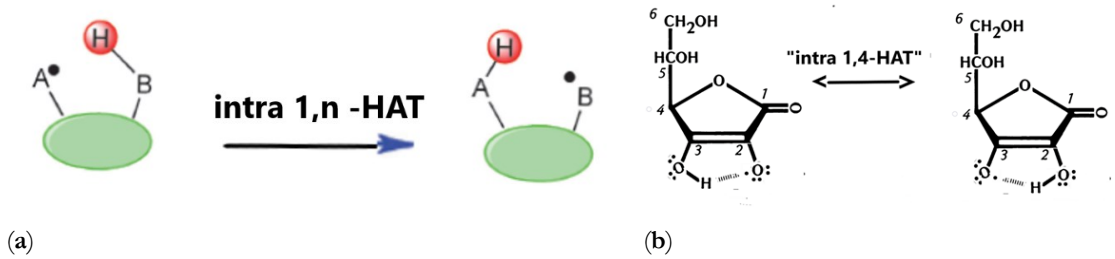


Figure 11. Depiction of ortho and para nuclear spin states of "spin water" reproduced here from Horke et al. (2014) with permission of the publisher.

We argue herein that use of the term "physiological pH" should be abandoned because of its vagueness. Physiological pH is now known to be dynamical and heterogeneous in both time and space (Gebicki 2018; Tsai 2014). Lipid/water extraction coefficients are greater for hydrophobic derivatives of L-ascorbic acid than for their conjugate bases. Truly "free" radicals are neutral, uncharged species which would favor relatively hydrophobic microenvironments to a greater extent than radical-anions. The L-ascorbic acid free radical in the moderately acidic pH 4-6 range has also been inappropriately marginalized by conventional dogma in favor of the L-ascorbate radical anion. Even today, the term "ascorb(ate)" is often conflated with that of vitamin C (L-ascorb(ic) acid). In our view, this practice must be abandoned. The distinction has considerable significance, both retrospective and prospective. The suffix "*-ate*" connotes the conjugate base of the free acid. It is simply misguided to conflate the terms ascorb*ate* and ascorb*ic*. Inflammatory states are moderately acidic states (Tsai 2014).

We propose herein that the moderately acidic, mildly oxidative, relatively hydrophobic inflammatory microenvironment induces "intramolecularity" of L-ascorbic acid (vitamin C), i.e. induces intramolecularity of pre-equilibrium (precursor) hydrogen bonding and intramolecularity of hydrogen atom transfers, and charge reorganization, followed by fast bimolecular (S_N2) proton-coupled nucleophilic attack. Whereas, the stable isotope labeled GCMS studies of John Deutsch (1998a-d) and the recent multi-component cyclic voltammetry study by Handayani (2020) suggest that the oxidative degradation of vitamin C is actually *promoted* within a neutral to alkaline pH range. To wit, the gamma lactone ring of dehydroascorbic acid (DHA) has been shown by Deutsch's work to be more susceptible to ring-opening and subsequent oxidative degradation than the gamma lactone ring of L-ascorbic acid and that of the L-ascorbic acid free radical. We, therefore, ppropose that the in vivo biological activity of vitamin C is dominated by that of the L-ascorbic acid free

radical due to its central role in NGTC, ascorbolysis, and the UNMR, as a supramolecular (biophysically pleiotropic) generalized adaptive response to environmental stress. Testing of these hypotheses, of course, is called for.



(**a**) (**b**)

Figure 12. The "intra 1,4 HAT" depictions: (a) Adapted from Nechab (2014) with permission of the publisher; (b) Proposed "intra 1,4 HAT": stabilizing the "dismutation" of AA and DHA. Proposed stabilization of the ascorbic acid free radical in the dismutation and non-enzymatic intermolecular group transfers via mesomerism and entropically-advantaged (Page & Jencks 1971) intramolecular-1,4-hydrogen atom transfer ("intra-1,4-HAT") in low pH, mildly oxidative aqueous micro-environment.

In our current conception of these processes, we assert that the in vivo redox properties and chemical reactivity of vitamin C is dominated by that of its free acid, i.e. that of L-ascorbic acid and the L-ascorbic acid free radical in the moderately acidic pH range (ca. 4-6). An inflammatory microenvironment is thought to be typically mildly oxidative, relatively hydrophobic, and moderately acidic. We propose that inflammatory states are likely to promote (a) intramolecularity of precursor pre-equilibrium hydrogen bonding, and (b) intramolecular 1,4 hydrogen atom transfer, denoted "intra 1,4 HAT" following Nechab's nomenclature for intramolecular 1,n hydrogen atom transfers (Nechab 2014) upon photo-oxidative super-activation of L-ascorbic acid and its 2-O-substituted derivatives. Upon oxidative super-activation, the vibrational modes of the O-H bond at the 3-position are postulated to predispose to rate-limiting (slow) homolytic cleavage of the O-H bond at the 3-position and nuclear quantum tunneling along the path of the pre-equilibrium H3-O2 hydrogen bond (McKenzie 2014; Berg 2015), in the direction of a "sigma hole", i.e. a singly occupied sp3 hybridized oxygen orbital at the 2-position, formed upon photo-oxidative super-activation. We suggest that the large solvent- and pH- dependent kinetic isotope effects (KIEs) observed by Stanko Uršić's group (Karković Marković 2020) might be better explained by the mechanism and *pH-dependent speciation* proposed herein for nuclear quantum mechanical tunneling by intra1,4 HAT of the L-ascorbic acid free radical during the initiation, propagation, and termination steps of the radical chain reactions we describe as ascorbolysis.

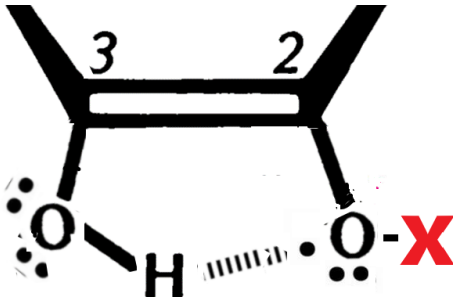


Figure 13. Proposed structure of "intra H-bonded" oxidized AA derivatives provide a novel putative class of reactive transients (AA radical derivatives). This class of AA radical derivatives is proposed to provide the biophysical basis for

branching cascades of radical chain reactions described historically as the UNMR, initially described by Selye as the "general adaptation syndrome" (1950). This class of radical derivatives of L-AA is thought to possess electrophilic radical philicity and their presence, in vivo, is likely to represent an electrophilic reserve capacity for responding to environmental stress, e.g. environmental sources of exogenous interfacial water stress (EIWS) described by Davidson and Seneff (2012), and by Davidson, Lauritzen, and Seneff (2013). Today, many sources of environmental EM pollution pose potentially-detrimental effects to the biological water dynamics represented by the recently discovered ortho/para spin states of water, described loosely as "spin water" (Mamrashev 2018).

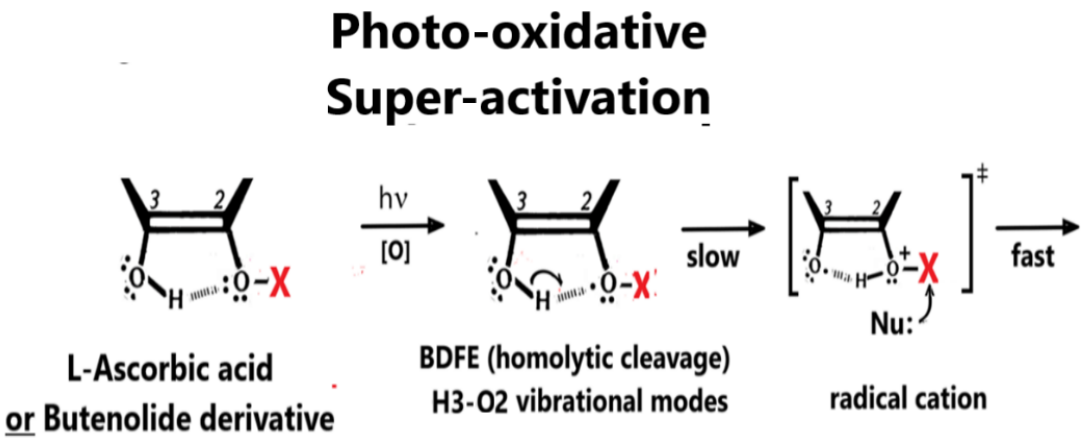


Figure 14. Generalized reaction scheme for the photo-oxidative super-activation of L-ascorbic acid derivatives and butenolide derivatives under moderately-acidic, mildly oxidative, relatively hydrophobic conditions, The hydrophobic effect is postulated to induce intramolecularity of the five precursor pre-equilibrium intramolecular hydrogen bonds in the global minimum DFT structure of L-ascorbic acid predicted by Berg's UV/IR Raman and DFT study (Berg 2015). It is likely that the vibrational modes of L-ascorbic acid interact cooperatively in the relatively hydrophobic, moderately acidic pH 4-6 range. It should be mentioned that Ebrahimi's quantum theory of atoms in molecules ("QTAIM") study (Ebrahimi 2016) predicted hydrogen bond cooperativity of L-ascorbic acid and also predicted the presence of an H3-O2 hydrogen bond which plays a central role in the ascorbolysis hypothesis. In the moderately acidic pH 4-6 range, (a) hydrogen atoms are labilized at the 2-, 3-, and 4-positions (Deutsch et al. 1994); (b) charge reorganization ("umpolung") catalysis (Schmittel 1990; Schmittel 1994); and (c) proton coupled nucleophilic attack ("PCNA"; see Hamer et al. 2015) are postulated to represent central mechanistic tenets, herein.

Pioneering work by Takebayashi et al. (2007) led us to propose that sluggish, "slow and continuous" radical scavenging by 2-O-substituted L-ascorbic acid derivatives, generate reactive transients, short-lived radical species (Takebayashi 2007), for subsequent propagation steps in radical chain reactions of non-enzymatic group transfers during inflammatory states. Branching cascades of non-enzymatic group transfer during inflammatory states are proposed, herein, to provide a plausible physical chemical basis for the so-called UNMR, a process studied by Selye in 1950's and 60's (Selye 1950, 1966, 1967, 1968) employing histopathological characterization of inflammatory states in small animal models of human disease. Hauss also studied (Hauss 1962, 1969) inflammatory changes in the extracellular matrix in response to inflammatory states, which were ultimately described as the Sanarelli-Shwartzman Phenomenon (SSP), subsets of Selye's thrombohemorrhagic phenomena (THP), which of note, include the hemorrhagic fever viral pathophysiology, e.g. that of Dengue and Ebola outbreaks. It remains to be determined whether the current global COVID-19 pandemic represents a consumptive coagulopathy of the microvasculature which typify the SSP (Davidson et al. 2015b).

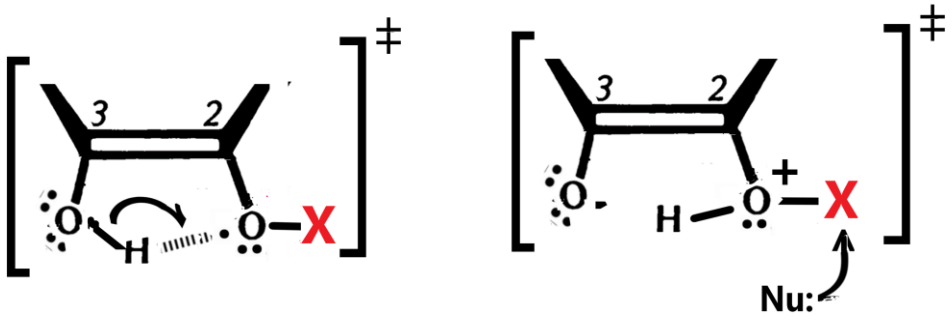
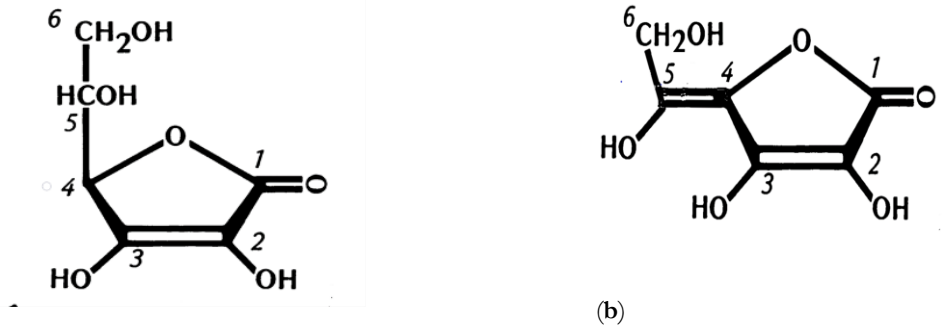


Figure 15. Proposal for "intra 1,4 HAT": Putative rate-limiting (slow) step in ascorbolysis

Central to the ascorbolysis hypothesis is the acidity, oxidative potential, and hydrophobicity of the inflammatory tissue microenvironment. These conditions are postulated to favor the anabolic direction over the catabolic direction of biological group transfers. For example, inflammatory states are thought to promote the anabolic direction to post-translational modifications (PTMs) of proteins, and pre-transcriptional/pre-translational modification of polynucleotides, chromatin, and histone proteins, e.g. cytoproliferative events necessary for assembly and function of the meiotic spindle during human germ cell maturation.

In 2019, Zhou et al. demonstrated that vitamin C can protect against human meiotic failure in human oocyte maturation. Under the ascorbolysis hypothesis, L-ascorbic acid provides a source of hydrogen atoms for the first-order, uni-molecular dismutation and non-enzymatic intermolecular group transfer to endogenous nucleophiles in the acidic pH range. Branching cascades of auto-catalytic, general acid catalyzed radical chain reactions of regio-, stereo-, and chemio-specific quantum phase-coherent functional group transfers in response to inflammation, effectively provides a plausible potential basis for a unified theory of human health, disease, evolutionary resilience, and genomic stability.



(**a**) (**b**)

Figure 16. (a) L-ascorbic acid with numbering convention, structure is used as template in this paper with permission of the American Chemical Society (Crawford 1982); (b) Butenolide early oxidation product of L-ascorbic acid, in acidic aqueous media with $Cu2^{+}$ oxidant, identified by John Deutsch and colleagues GCMS study (1994).

We further propose that the toxicology of NaF and the silicofluorides in public drinking water is highly-likely to disrupt the 5 intramolecular hydrogen bonds identified by Rolf Berg's UV/IR Raman and DFT study (Berg 2015). Of note, a particular intramolecular hydrogen bond identified in Berg's global minimum calculated DFT study, i.e. the H3-O2 hydrogen bond between the hydrogen atom

at the 3-position and the oxygen atom at the 2-position of the gamma lactone ring system, is called to the readers' attention. *This particular intramolecular hydrogen bond was not found in the calculated DFT studies of the L-ascorbate mono-anion.* This is a non-trivial point, because according to the evolving ascorbolysis hypothesis, the pre-equilibrium hydrogen bonding of L-ascorbic acid is thought to predispose, in the presence of activated water, sunlight, added hydrophobes, and trace quantities of the essential ultra-trace mineral copper, to photo-oxidative super activation of L-ascorbic acid, forming the L-ascorbic acid free radical, which is proposed to be resonance stabilized by mesomerism (Neta 1972; Went 1988; Kerber 2006) of the hydrogen atom at the 3-position, upon homolytic cleavage of the O-H bond at the 3-position. Such mesomerism (resonance delocalization) follows the path of the pre-equilibrium intramolecular H3-O2 hydrogen bond. Cooperative vibrational modes of the O-H bond at the 3-position, upon photo-oxidative "super activation" results in a reactive transient, i.e. the entity referred to historically as the "semidehydroascorbic acid free radical" (Deutsch 1998a).

Chinoy's prior work establishing the reversibility and rescue of fluoride toxicity with vitamin C, gives us the opportunity to propose, herein, how environmental pollution might impair ascorbolysis and human chemical evolution. We propose that non-enzymatic group transfers are disrupted by NaF and silicofluorides in the water supply and fluoride in toothpaste, at a cost of inducing both skeletal *and non-skeletal* fluorosis in humans which we propose entails the disruption of hydrogen bond cooperativity necessary for non-enzymatic biological group transfers, necessary for the UNMR, hence necessary for biological complexity, diversity, and morphogenic determinants.

Initial hypothesis testing is underway and promising early results have been found. When unpasteurized, fresh dairy cow milk, is exposed to NaF containing emulsions found in toothpaste, visible differences in protein layering by high resolution still frame and time lapse photography have been observed when activated "spin water" is compared with ordinary water as a control. It is suggested that the unfolded protein response (UPR) is induced by fluoride species. Whether these observations are direct effects of the fluoride species upon protein folding, perhaps associated with a decrease in carrying capacity of water manifested by the zeta potential, or indirect effects of fluoride species upon interfacial water dynamics previously stabilized by L-ascorbic acid and the L-ascorbic acid free radical, are yet to be determined. Further experiments are underway comparing the replicative life span (RLS) of yeast in the presence of NaF and silicofluorides, comparing visible changes by high resolution still frame and time lapse photography in activated to ordinary water control. Subsequent experiments will examine the reversal and rescue by vitamin C from the effects of NaF and the silicofluorides.

A parallel set of experiments comparing the results with and without the presence of 5G radiation might demonstrate differences in folding of milk proteins associated with PTMs, catalyzed non-enzymatically via ascorbolysis, associated with differences in carrying capacity of water observable on the macro scale, hence discernible by microscale microscopy and macroscale photography. Nanoscale experiments might also be conducted employing newer technologies such as atomic force microscopy (AFM).

Discussion and Conclusions

(i) The rationale for proposing a mechanistic change at the inflection point of the biphasic pH-potential diagram for vitamin C: acidity promotes inner-sphere dismutation, whereas neutral to alkaline pH promotes outer-spere disproportionation

Seminal work by John Deutsch in the 1990s clearly established that L-ascorbic acid behaves very differently in the acidic pH range of ca. 4-6 than it does at neutral to alkaline pH (Deutsch 1994, 1997, 1998a-d) which motivated us to propose that a mechanistic change is likely to occur in the acidic pH range, at the inflection point of Bielski's classically-shaped sigmoidal pH-potential diagram (Bielski 1981). In 1997, in acidic aqueous media, Deutsch reported very compelling stable isotope labeled GCMS studies of an interconversion between L-ascorbic acid and L-dehydroascorbic acid (DHA) catalyzed by Cu2+ (cupric) ions. Importantly, the non-exchangeable site deuteriums of Deutsch's deuterium-labeled L-ascorbic acid became distributed at equilibrium under acidic conditions between L-DHA and L-AA, without net loss of label at the non-exchangeable deuterium-labeled 6-position of the gamma-lactone ring system and the kinetics were observed to be first-order.

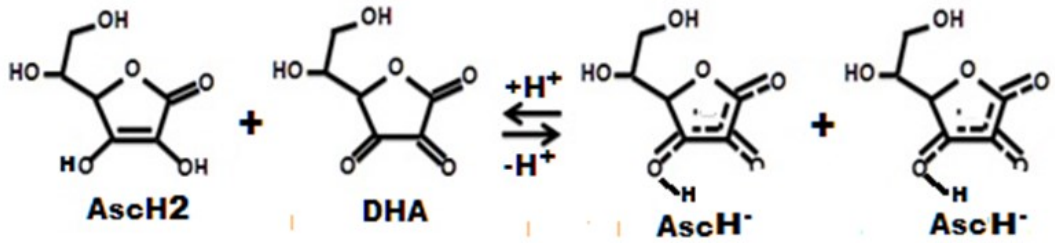
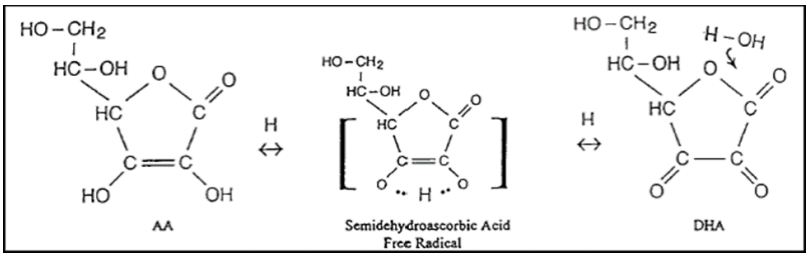
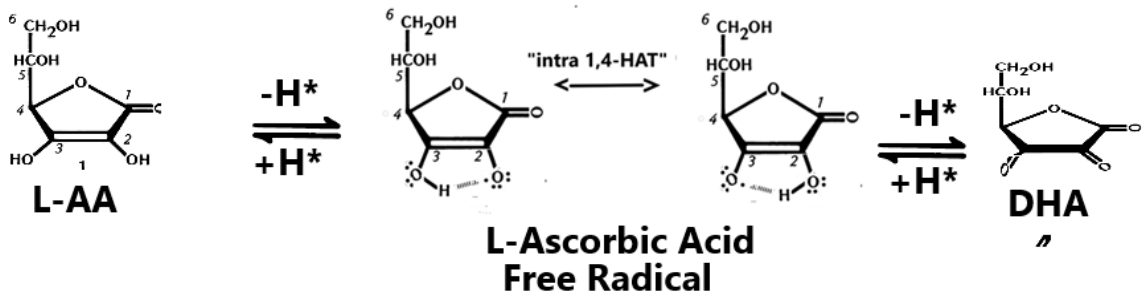


Figure 17. Putative bimolecular "disproportionation" reaction for the L-ascorbic acid free radical. While such a mechanism would follow second-order kinetics, this mechanism is not compatible with Deutsch's stable isotope-labeled GCMS study (Deutsch 1997), wherein his kinetic data were clearly first-order without net loss of label at the non-exchangeable deuterium-labeled 6-position.



(a)



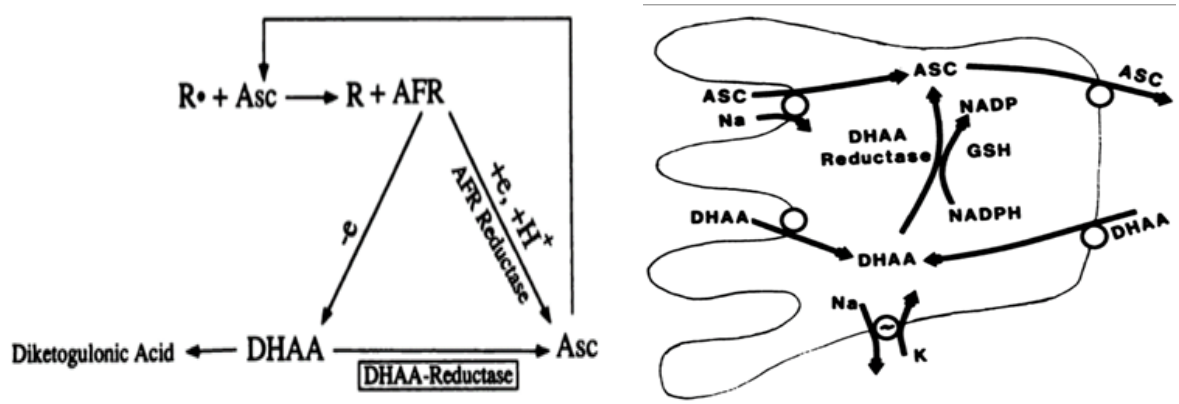
(b)

Figure 18. Mechanistic depictions of the proposed "dismutation" of L-ascorbic acid in the moderately acidic pH 4-6 range. (a) John Deutsch's depiction of proposed "dismutation" (our terminology) of AA and DHA in acidic aqueous media via an L-AA free radical intermediate, referred to historically as "semi-dehydroascorbic acid free radical", reproduced here with permission of publisher (Deutsch 1998a); (b) Our rendering of the proposed dismutation of L-ascorbic acid via "intra 1,4 HAT" upon "labilization" of hydrogen atoms at the 2-, 3-, and 4-positions of the gamma lactone ring system reported by Deutsch's stable isotope labeled GCMS studies in 1994, 1997, and 1998.

> Certain experimental data imply there is more to the antioxidant effect s of AA than simply the reversible AA:DHA reaction. For instances, it has been reported (32) that solutions of DHA better prevented cupric ion-induced low-density lipoprotein oxidation than AA. The mechanism of this effect is unclear since AA is readily oxidized to DHA and *both AA and DHA should provide a source of DHA. However, the formation of AA to DHA generates the semi-DHA-free radical (25) which wouldn't be present if DHA were the starting material*. The situation is further obscured by rapid hydrolysis of DHA to DKG or other degradative products (26). After a short time, a DHA-containing solution will con- tain other species which could contribute importantly to the overall antioxidant capacity. (Deutsch 1998a; italics added by Davidson and Winey)

(ii) The L-ascorbic acid free radical is the key to understanding the oxidation of vitamin C

An important clue to solving this long-standing mystery may be found in the literature (Rose 1993). See Figure 19.



(**a**) (**b**)

Figure 19. Excerpted figures and captions from Rose (1993) are reproduced here with permission of publisher. (a) "A possible scheme by which a free radical species (R 0 is neutralized by single-electron transfer with a scavenger, in this example, ascorbate (Ase). This results in a detoxified product, R, and the ascorbyl free radical, AFR. Pairs of AFR

disproportionate to form one molecule of dchydro-L-ascorbic acid (DHAA) and one Ase. DHAA can undergo a biologically irreversible opening of the lactone ring to form the inert product, diketo-L-gulonic acid; alter- natively, it can be reduced to the useful Asc"; (b) "A working model that describes intestinal absorption of ascorbic acid (Ase) and dehydro-L-ascorbic acid (DHAA) in animal species that require it in the diet (primates and guinea pigs). At the luminal border, Asc is transported against a gradient by a Na•-dependent mechanism and DHAA is transported down a gradient by an Na•-independent process. Cellular DHAA is maintained low by GSH/NADPH-dependent enzymatic reduction. At the basolateral membrane, transport of each form of the vitamin is down an electrochemical gradient. Note that ascorbate is a mono- valent anion and DHAA is uncharged. The cell interior is 30-60 mV negative with respect to the extracellular fluid. The model also accounts for renal handling of ascorbate in mammalian species that synthesize the compound from glucose as well as those that absorb it from dietary sources as a vitamin." (Original caption from Rose 1993.)

(iii) Enzymatic "mimicry" of NGTC?

It should have come as no surprise to us that the answer to fathoming the prodigious supramolecular biological activity might be found on considering how ancient NGTC might be mimicked by enzymatic catalysis. Arriving at the conclusion that the L-ascorbic acid free radical provides the key to solving a long-standing mystery and source of confusion in the published literature, was tricky, complicated by the fact that Deutsch's stable isotope labeled GCMS studies in acidic aqueous media in the presence of different oxidants was spread out over several papers between 1994 and 1998. His data are *very important chemically and clinically*, however, and it is well-worth the effort to try to explain them. Upon reconsideration of Deutsch's data, we propose that the reaction is aptly described as a uni-molecular dismutation reaction and, importantly, we further propose that the mechanism likely proceeds by means of an intramolecular 1,4 hydrogen atom transfer, denoted "intra 1,4 HAT". We have adopted Nechab's nomenclature, for the general case, intra 1,n HAT (Nechab 2014). The intra 1,4 HAT mechanism proposed herein (see Figure 18b) is very distinct kinetically and mechanistically from that of the oft-cited historical bimolecular (second-order) mechanism proposed by Bielski for the "disproportionation" of vitamin C (Deutsch et al. 1994; Deutsch 1997; Bielski 1981).

> Cupric ion, on the other hand, formed only trace amounts of the *m/ z* 607 product. Over time, cupric ion (but not hydrogen peroxide) formed relatively large amounts of a six carbon species with four derivatizable sights, a single retention time, *and no disturbance of the hydrogens on the carbon at position 6*. (Deutsch 1994; italics added by Davidson and Winey).

When viewed in total, these many seemingly disparate historical experimental, theoretical, and clinical observations, call for a unified theory. Such a theory has been proposed in the paper about "the initial common pathway to inflammation, disease, and death" (Davidson et al. 2012). Its corrolaries account for health, anti-ageing, and longevity. In any case, it is understood that the meiotic spindle apparatus during mammalian germ cell maturation and replication places greater demands upon biosignaling systems than are required for mitosis (Ahmad 2016; Yu 2018; Zhou 2019). Under the NGTC/ascorbolysis/UNMR framework, it is very reasonable to expect that L-ascorbic acid would play a central role in mammalian reproductive biology, including that of fruit bats, Guinea pigs, and humans.

(iv) Are we inadvertently "starving" ascorbolysis from a proton source?

It warrants mention that widespread dietary supplementation with L-ascorbate anions, various conjugate base salt forms of vitamin C, might actually be deleterious to health, by effectively

overloading our bodies with salt, e.g. sodium or calcium and "starving" the body for an adequate source of protons needed for ascorbolysis. Importantly, several endogenous and exogenous 2-O-substituted derivatives of vitamin C have been identified intracellularly (Eguchi 2003; Saitoh 2004), e.g. the 2-O-glucopyranosyl- and the 2-O-phosphate-substituted derivatives. If as we propose in the present study, that one of the primary, heretofore undescribed, roles of vitamin C in human physiology is actually to provide for non-enzymatic group transfer catalysis, dietary supplementation with naturally-occuring polyphenolic anti-oxidants, flavonoids, and anthocyanins, may provide the great benefit of effectively sparing vitamin C from the comparably menial role of being a "sacrificial" antioxidant. Under the NGTC framework, weak organic acids and hydrophobes, such as anionic amphiphilic surfactants, e.g. lauric acid, capric acid, etc. may play an important role of retarding the formation of DHA, whose ring-opening and downstream degradation is promoted at neutral to alkaline pH (Handayani 2020; Deutsch 1998a-d).

(v) Inconsistent results of intravenous vitamin C (IVC) randomized clinical trials (RCTs)

It is generally accepted that NaF, aluminum salts, and silicofluorides increase oxidative stress in biological microenvironments (Zhang 2007; Chouhan 2008; Agalakova 2012). Thus, many of the inconsistent results from RCTs may be due to failure to control for the presence of NaF, aluminum salts, and silicofluorides in the drinking water of the study subjects enrolled. Failure to control for baseline blood levels of L-ascorbic acid may be an additional source of inconsistent results. The incidence of subclinical and marginal scurvy is thought to be high, and is rarely if ever diagnosed (Dalldorf 1933; Rinehart 1942). Smoking-related oxidative stress would predictably confound RCT, although this is usually controlled for, by their exclusion from enrollment.

Perhaps the largest source of variation and inconsistencies between RCTs is related to inadequate control, both within study and between study, of the dose, osmolality, pH, and buffer of the IVC solution infused. Standards for the infusate in high dose IVC RCTs are urgently needed. In our opinion, there are many valid reasons why ascorbate salts should not be employed for the infusions. The L-ascorbate anion is not bio-equivalent to the free diacid, i.e. L-ascorbic acid. From a pharmacological perspective it is very wrong to conflate ascorbate salts with vitamin C (L-ascorbic acid). Their biodistribution and pharmacokinetics differ substantially. From a chemist's perspective, it's an oxymoron.

To summarize, the wide variation in RCTs of IVC are likely multi-factorial, and fall into two main categories: (a) lack of infusate/infusion standardization, and (b) lack of study subject inclusion/exclusion criteria uniformity. The lack of standardization and uniformity between RCTs, results in a worst-case scenario, faulty conclusions, attributable to failure to adequately control for (a) pH- and solvent-dependent speciation of vitamin C, (b) pre-existing subclinical scurvy at baseline, (c) adventitious contamination of infusate buffers by redox active metals, e.g. Cu^{2+} and Fe^{3+} contaminated buffers (Buettner 1988; Buettner 1990; Buettner 1996), and (d) NaF, silicofluoride, aluminum salts, and AlF_x species at baseline and during study. Importantly, use of ascorbate salts would predictably confound RCT results due to their inability to provide NGTC, in addition to increasing the total body burden of sodium, e.g. with use of sodium ascorbate, instead of L-ascorbic acid. Care should be given to the choice of buffer for the intravenous infusion of IVC. Ideally, a pH of between 4 to 6 would be obtained. Buffers and water purification should be standardized between studies in RCTs, so as to avoid the contamination with redox active metals (Buettner 1988; Buettner 1990; Buettner 1996). A lactate or citrate buffer might be considered.

(*vi) In the midst of a persistent global COVID-19 pandemic, what can we lose by hypothesis generation and testing?*

If one were to propose that structural topological motifs in RNA sequences of RNA viruses such as the SARS-CoV-2 pathogen exist which are at all similar to topological motifs, i.e. RNA sequences, found in bacteriophages and RNA viruses, would it be worthwhile to see if Cu2+ and the L-ascorbic acid free radical cleave the polynucleotide at sites dependent on the structural motifs, e.g. CpG or UpA or other sequence? A supramolecular experimental strategy could logically target SARS-CoV-2 either (a) directly, at the RNA level, catalyzing RNA cleavage of specific phospho-diester bonds, or (b) alternatively, targeting one or more of the SARS-CoV-2 translation/transcription factors (Peng 2008) at the protein kinase and sirtuin levels, exploiting potential "vulnerabilities" of the pathogen's replicative life cycle. Under the experimental strategy proposed, the reversibility, supramolecularity, intramolecularity, pH- and solvent-dependent speciation, and reactivity of L-ascorbic acid, the L-ascorbic acid free radical, the 2-O-phosphate-L-ascorbic acid derivative, its radical, and its lipophilic derivatives, in a moderately acidic pH range (ca. 4-6), mildly oxidative, and relatively hydrophobic microenvironments, can be systematically explored.

Precedent for the existence of intracellular AA-2P was amply provided in the prior studies by Eguchi (2003) and Saitoh (2004). The ascorbolysis hypothesis provides a potentially provable supramolecular (biophysically-pleiotropic) means of non-enzymatically regulating gene expression, including perhaps expression of the SARS-CoV-2 genome, and that of similar viral pathogens. Such proof would have considerable clinical translational potential for all medical disciplines. We strongly maintain that AA-2P and many of the 2-O-substituted derivatives of L-AA are not merely pro-drugs for intracellular L-AA as is commonly believed. Instead, a central tenet of the ascorbolysis hypothesis is that the 2-O-substituted derivatives of L-AA provide a distinct class of "slow and continuous" non-enzymatic i*ntermolecular* group transfer factors, in addition to impressive radical scavenging properties (Takebayashi 2007). Of note, several of the 2-O-substituted-L-AA derivatives have shown marked anti-neoplastic and anti-metastatic properties, which are being tested in RCTs. Therapeutic synergies with existing anti-inflammatory agents are anticipated. Difficulties with drug delivery (bioavailability) and pH-stability of such agents may likely be overcome by use of liposomal formulations (Shao 2017) and/or various lipophilic analogues of such L-AA derivatives to provide adequate intracellular, blood, lymphatic, and CSF levels, potentially providing new therapies in oncology and infectious disease.

In the formulation of "Westheimer's rules" in 1968 governing the ring-opening and hydrolytic preferences of cyclic pentacoordinate phosphate esters, Frank Westheimer made the experiential and prophetic declaration: "Five-membered esters of phosphoric acid are strained. They hydrolyze millions of times faster than their acyclic analogs, with ring opening and with retention of the ring" (Westheimer 1968). For this reason, our proposal for NGTC via ascorbolysis by photo-oxidatively super-activated AA-2P radical posits that the super-activation step is relatively slow or sluggish by comparison to the subsequent fast cyclization and ring-opening or hydrolysis steps. See Figure 9 presented earlier.

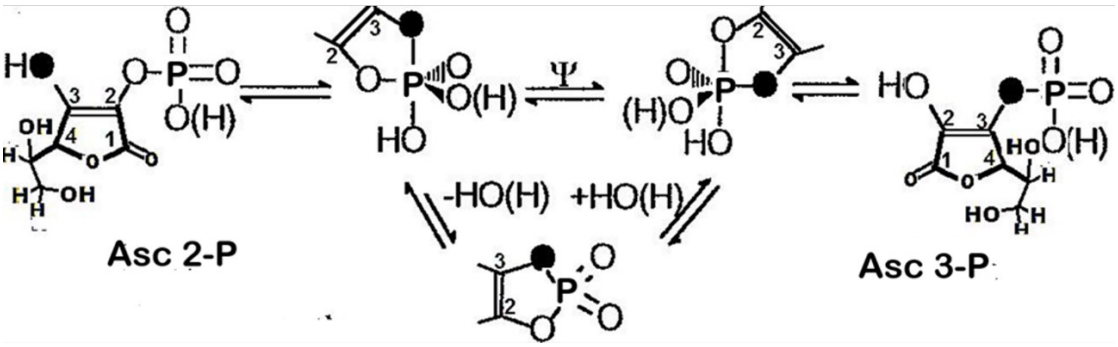


Figure 20. In a scheme adapted from Cameron & Thatcher (1996) for *Berry* pseudorotation (fluxional isomerization, i.e. pairwise exchange of equatorial and axial ligands) of cyclic penta-coordinate sulfates (Cameron 1996; Westheimer 1968; Ugi et al 1971; Davidson & Kenyon 1980; Cabral & Haake 1988; Cass 2006), we propose the following mechanism for intramolecular trans-phosphorylation by the 2-O-phosphate substituted L-ascorbic acid derivative, which subsequently undergoes photo-oxidative super-activation to generate the 2-O-phosphate-L-ascorbic acid radical (see Figure 9 above) which we denote as the "ascorbyl phosphate radical" for brevity. In such a scheme, the cyclic penta-coordinate phosphate derivative and cyclic penta-coordinate phosphate radical derivative lower the activation energy barriers for reversible non-enzymatic transfer of phosphoryl moieties to endogenous biological nucleophiles in the pH range 4-6 (Westheimer 1968; Baccolini 2010). Of particular note, there is a recently published multi-component cyclic voltammetry study (Handayani 2020) to support the addition of hydrophobes and/or amphiphilic anionic surfactants in order to promote and induce intramolecularity of the pre-equilibrium H3-O2 hydrogen bond in a moderately acidic, mildly oxidative, relatively hydrophobic microenvironment. The intramolecular rearrangement of 3-O-acyl derivatives of L-AA to the thermodynamically-favored 2-O-acyl derivatives was demonstrated by Cabral and Haake in 1988. Structure proofs for the derivatives were made by NMR techniques. The intramolecular trans-phosphorylation (rearrangement) was acid-catalyzed and is thought to predict the capacity for reversible, auto-catalytic intermolecular group transfer of acyl moieties, in vivo, as was subsequently demonstrated by Verlangieri and Mumma for the non-enzymatic sulfurylation of cholesterol (Verlangieri and Mumma 1973).

Activation of our endogenous antioxidant defense system, which occurs largely via NRF2 activation and/or KEAP1 inactivation, is highly relevant to developing potentially useful therapeutic approaches to the current COVID-19 pathophysiology, which has been associated with severe inflammatory and oxidative stress in infected victims.

The anti-inflammatory properties of oral, inhaled, and parenteral corticosteroids have shown efficacy. Under the NGTC/ascorbolysis framework, the corticosteroids (hydrophobes) are likely to be of synergistic benefit when administered with lipophilic derivatives of L-ascorbic acid in the pH range of 4-6 (Ohba 1994; Capuzzi 1996; Fan 2004; Miura 2017; Kato 2011; Xiao et al. 2014). Liposomal preparations of L-ascorbic acid and curcumin are likely to also be synergistically efficacious under the NGTC/ascorbolysis framework (Shao 2017). It is conceivable that intracellular ascorbyl phosphate is able to non-enzymatically phosphorylate both serine-40 of KEAP1 (Abed 2015) and serine-276 of NF-kB (Reber 2009), thereby regulating two major transcription pathways, in response to the COVID-19 related oxidative stress, which is likely to be especially profound in patients who might already be suffering from subclinical or marginal scurvy, and often intoxicated with NaF, aluminum salts, and silicofluorides, in an environment which is also replete with EM pollution.

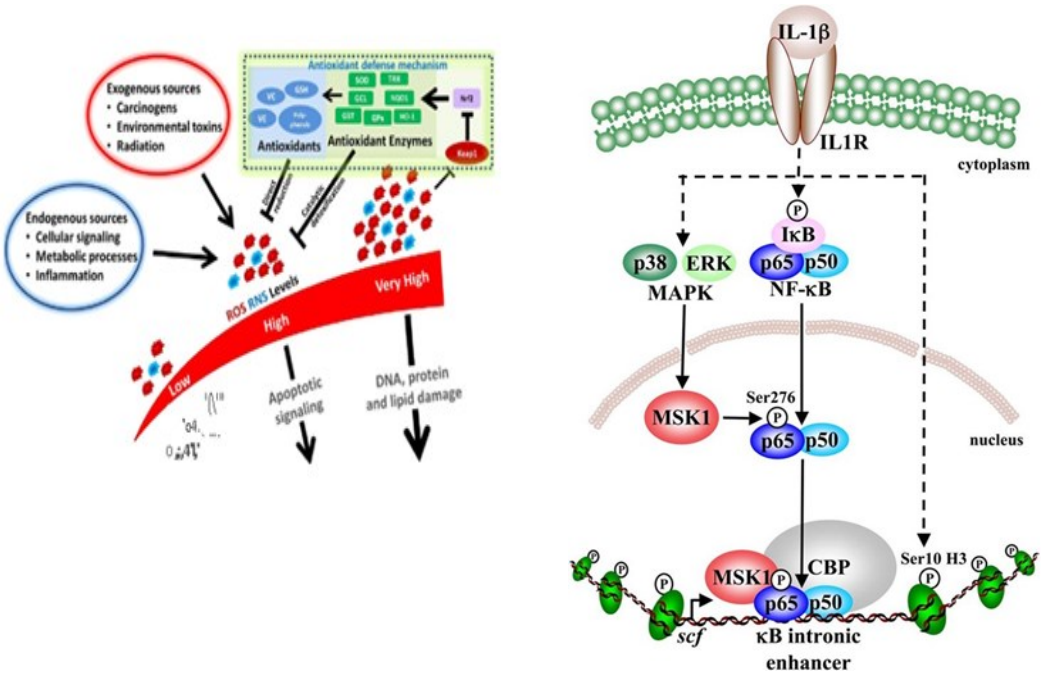


Figure 21. Graphical depictions of potential protein targets for PTMs via reversible ascorbolysis: (**a**) Graphical depiction of NRF2-KEAP1 pathway with NRF2 activation and KEAP1 inhibition reproduced here from Abed 2015 with permission of publisher; (**b**) graphical depiction of the phosphorylation cascade shown to be involved in regulation of the NFκB-MAPK pathway reproduced here from Reber 2009 with permission of publisher. It should be noted that the NGTC/ascorbolysis/UNMR framework, proposes concomitant supramolecular regulation of sirtuin and methylation function, i.e. reversible acetylation and methylation of chromatin proteins via the intermediacy of L-ascorbic acid, the L-ascorbic acid free radical, the 2-O-acetyl-substituted derivative, the 2-O-methyl-substituted derivative, and their photo-oxidatively super-activated radicals, i.e. the2-O-acetyl-L-ascorbic acid free radical and 2-O-methyl-L--ascorbic acid free radical, respectively. See Figures 6c and 6d for proposed structures of the putative free radicals.

According to Abed et al (2015), Keap1-mediated ubiquitination is avoided by phosphorylation of a highly-conserved serine residue (Ser40) in the Keap1 binding domain of Nrf2 (Abed 2015). Thus, at least one kinase is likely required for Nrf2 to dissociate from Keap1. Whereas for the phosphorylation cascade of the NFκB-MAPK pathway multiple kinases are required, whose enzyme pH optima and ATP substrate instability (acid lability), during inflammatory states, suggest the need for intracellular AA-2P. We propose that intracellular AA-2P acts supramolecularly providing the function of many, if not all, "kinases" *non-enzymatically*. AA-2P is proposed to act concomitantly and phase-coherently with putative 2-O-acetyl-L-ascorbic acid and 2-O-methyl-L-ascorbic acid derivatives providing *non-enzymatic* kinase, sirtuin, and methylation functions, respectively (see Figures 6c and 6d presented earlier). Acting in concert, intracellular L-AA, the L-AA free radical, the AA-2P derivative, the putative 2-O-acetyl substituted and 2-O-methyl substituted L-AA derivatives, and their free radicals are proposed to restore genomic stability and rescue from meiotic failure during inflammatory states. In this scenario, endogenous functional group donors, e.g.,ATP, S-adenosyl methionine, and acetyl-coenzyme A would potentially be spared a hydrolytic or oxidative degradative fate during inflammatory and cytoproliferative states. In Figure 8 presented earlier, the first of two propagation steps involves the proposed S_N2 reaction between the L-AA free radical and any of several possible endogenous electrophilic phosphoryl donors, including phosphate monoesters, phosphodiesters, and ATP, Of note, both sirtuin and methylation functions have been implicated in PTMs and "cross-talk" between chromatin and histone proteins (Fischle 2003), much like an intricately choreographed "dance".

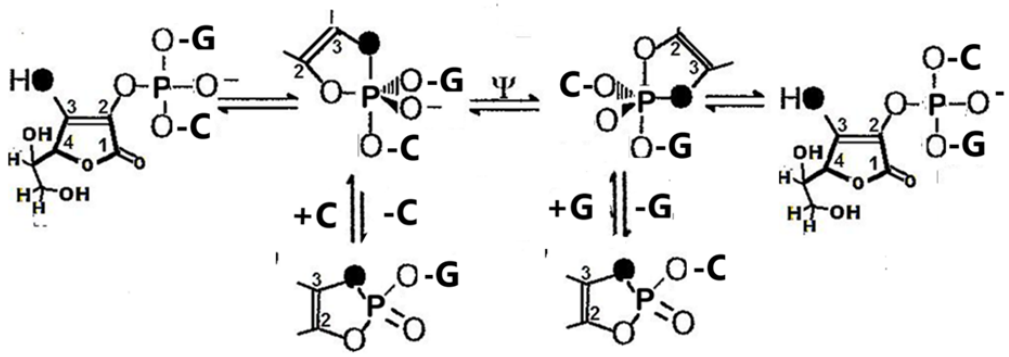


Figure 22. With respect to the current SARS-CoV-2 pandemic, and potential future viral pandemics, we propose that the L-ascorbic acid and Cu2+ in the moderately acidic pH 4-6 range, with added hydrophobes and/or amphiphilic anionic surfactants, may be studied for concomitant supramolecular cleavage of the protein "cloak" (a.k.a. the "corona" or nucleocapsid and spike proteins) and certain motifs in the RNA sequence of the viral pathogen(s), thereby supramolecularly attacking potential vulnerabilities of the protein-"cloaked" moving target represented by the SARS-CoV-2 viral pathogen(s).

To more readily grasp the concepts presented (herein), the proposed reaction schemes (Figures 20 and 22, above) ask the question whether a reversible putative primordial/prebiotic reaction might have existed during early chemical evolution, which is evidenced by the published reports of L-ascorbic acid and Cu^{2+} non-enzymatically cleaving bacteriophage, viral RNA, and viral DNA, *including cleavage of proteins* (Wong 1974; Richter 1982; Chiou 1983, 1984). The proposed mechanistic scheme (above) asks the question whether structural topological motifs (Bon 2008; Gan 2003; Koirala 2019), based either on nucleotide and amino acid sequence, or alternatively based on hydrogen bond cooperativity, might expose viral pathogens to vulnerabilities. Fluctuations in protein folding and polynucleotide folding might expose vulnerabilities of viral pathogens to nucleophilic attack by a the L-ascorbic acid free radical. Experiments can be designed to explore the possibility of L-ascorbic acid promoting health, longevity, and anti-ageing (Furumoto 1998; Zglinicki 2000, 2002; Sebastián et al. 2009), while fluoridesaluminum salts, silicofluorides, and EM pollution, synergistically promote oxidative stress, inflammation, disease, immune scenescence, replicative scenescence, ageing, and death.

It should be noted that chiral intermediates, including the formation of chiral centers at the phosphorus atom of 3'-5'-phosphodiesters of RNA are proposed intermediates in Figure 22 above. In 1980, Jeremy Knowles reviewed the biological phosphates, their enzyme-catalyzed phosphoryl transfer reactions, including the synthesis of phosphate mono-esters and diesters with chirality *at the phosphorus atom* (Knowles 1980). Under the ascorbolysis hypothesis, *Berry* pseudorotation of RNA and DNA polynucleotides is intrinsically "chimeric pseudorotation" (Cass 2006), i.e. pro-chiral at the phosphorus atom of the 3'-5' phosphodiester sites. In ortho/para "spin water", chirality-induced spin selectivity ("CISS" discussed earlier) may be operative in the regiospecificity of postulated RNA cleavage, as well as regulating the chirality and stereo-selectivity of the bio-phosphate intermediates and transition states postulated for editing and error-correcting the genome during inflammatory and cytoproliferative states.

Potential Benefits and Applications of the Ascorbolysis Hypothesis

The ascorbolysis hypothesis provides the basis for (a) a novel "radical theory" of oxidative phosphorylation (Schole 1994), and (b) reversible polynucleotide synthesis (Lichtenthaler 1961). The AA-2P derivative of L-AA, acts as a "slow and continuous" intracellular radical scavenger which generate super-activated high-energy mixed anhydride radicals capable of catalyzing reversible non-enzymatic polynucleotide and protein synthesis within a microenvironment conducive to "intra 1,4 HAT", general acid catalysis, and PCNA. Auto-catalytic radical chain reactions that reversibly generate polynucleotides and regulation of gene expression, are predicted consequences of super-activation of vitamin C. Lipophilic derivatives of AA-2P have been reported. It should be possible to rigorously test this hypothesis, e.g. with the mouse macrophage model of ageing developed by Sebastián et al.(2009). According to their results, the STAT5a phosphorylation defect was secondary to the prior oxidation (hydroxylation) defect, i.e. an "oxygenase defect", *both* of which can, in principle, be corrected concomitantly by increasing intracellular L-AA and L-AA-2P levels. Potential therapeutic synergy with vitamins D3, E, and folic acid should be explored..

The elderly and those suffering from chronic inflammatory and degenerative diseases are especially vulnerable to infections with SARS-CoV2. Generally, the elderly typically experience age-related decline in their natural immune function and antioxidant defense system. In principle, they might be effectively "rescued" by means of increasing their intracellular L-AA and L-AA-2P levels. In aged mice, macrophage-related immune function and telomere length were shown to be impaired by oxidative stress, defective oxidation and phosphorylation of the signaling protein STAT5a (Sebastián et al. 2009).

Telomere length has been shown to be a biomarker for ageing and chronic oxidative stress (Houben 2007; Zglinicki 2000; Zglinicki 2002). Intracellular L-ascorbic acid has been demonstrated to slow telomere-shortening (Furumoto 1998). Under the ascorbolysis framework, telomere length is proposed to likely be regulated by intracellular L-ascorbic acid and its 2-O-phosphate substituted derivatives in a manner that might well involve a mechanism similar to those depicted in Figures 20 and 22 (above), wherein Westheimer's rules (preferences) and the quality of the microenvironment influence where the equilibrium lies, with respect to discrimination between "healthy" genes, e.g. long, properly shaped, functional telomeres, as opposed to "unhealthy" genes, such as that of viral pathogens, e.g. Dengue, Ebola, SARS-CoV-2 sequence-based topologies. Just as proteins are thought to fluctuate between folded and unfolded morphologies, so too are DNA and RNA polynucleotides likely to fluctuate between folded and unfolded morphologies. Assembly of the meiotic spindle apparatus must occur in a tightly choreographed sequence of events which must arguably be coherent withmodeling and remodeling of chromatin and histone proteins. Application of a supramolecular therapeutic approach against the SARS-CoV-2 pathogen is an approach which is diametrically distinct from the linear "magic bullet" approaches adopted by most vaccine strategies, at least that was the historical pproach by vaccines against infectious pathogens.

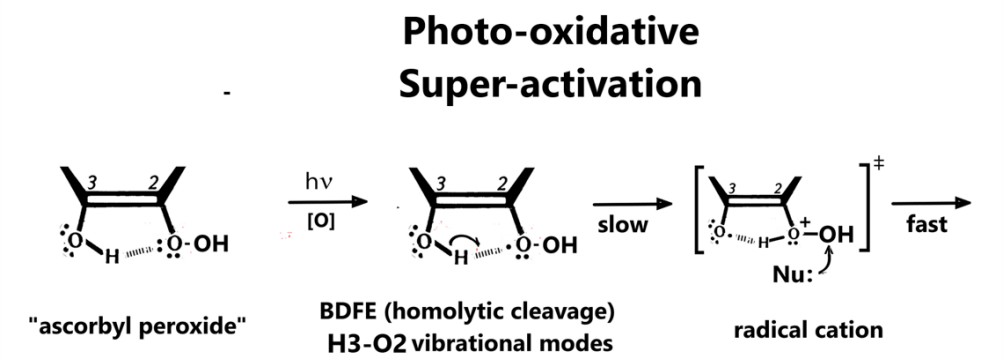


Figure 23. Proposed "Ascorbyl Peroxide" hydroxylation Factor, for provision of non-enzymatic mono-oxygenase function within inflammatory tissue microenvironments.

In any event, the global SARS-CoV-2 pandemic provides the impetus to be pro-active. At such a time, the NGTC and ascorbolysis hypotheses may suggest ways to develop the much needed re-direct for a unified theory of synergistic environmental toxicology in general, and for the known experimental effects of aluminum, fluoride, and EM pollution. It is time for serious and intensive hypothesis generation, testing, and for critical re-evaluation of much of the longstanding conventional wisdom about disease conditions, their causes, and effective treatments.

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Plan B Public Health Infrastructure and Operations Oversight Reform for America

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Abstract

It's not the public that needs more monitoring and oversight: it is the US regulatory agency of public health network and the pharmaceutical companies that run them. In this paper, I provide a blueprint for a bona fide public health infrastructure based on independence of freedom from corporatism.

Keywords: *corporatism, health infrastructure, industry/government partnerships, regulatory oversight and collusion*

Introduction

Since the US CDC was founded, an unholy alliance has infiltrated public health in the US — euphemistically referred to as "industry/government partnerships" and "Not-for-Profit" government entities — the wicked marriage has infused profit motives into US government agencies charged with regulating medical and pharmaceutical industries. Those involved view themselves as agents working toward a "greater good" — notwithstanding, the trappings of perverse incentives and presumed moral dictates, agencies designed by past generations to protect the US population from harm from corporatist tendencies have been completely captured and subverted. Apologists for regulatory capture even laud the "benefits" of collusion between corporations and the agencies that have been designed — and are funded to — provide regulatory oversight (Reiss, 2011). It seems surreal to consider the brazen use and even celebration of the combination of pharmaceutical influences and matters of state. The "revolving door" between corporations and agencies has been widely recognized for some time – including the FDA (Piller, 2018; Kaplan, 2016), CDC (Reuters, 2009; National Public Radio, 2009). Thirty-nine percent of National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel had tied to Pharmaceutical or Biotechnology companies – this was the committee that recommended the expensive Remdesivir over the inexpensive hydroxychloroquine for treatment of COVID-19. Remdesivir is made by Gilead — and eight of the COVID-19 Treatment Guidelines Panel had ties to Gilead.

As well documented as these abuses are, nothing comes of them — even if public health suffers. The scope of its influence on the quality of science that is supposed to inform public health and medical policy is only just now becoming painfully apparent. The US media is likewise utterly captured due to revenue from direct-to-consumer marketing of pharmaceutical products; this quite literally means that the US does not have a free and independent press.

Corporatism Leads to a Regulatory Vacuum

Because corporatism is the prime target of US regulatory agencies, a regulatory vacuum has been created only to be immediately filled by profiteering government "watchdogs" expanding their own political, financial, and regulatory mandate against all challengers, especially the public population they are supposed to be protecting. The need for completely independent "untouchable" research institutions has never been higher, and yet some who have nominated themselves to protect the public interests, actually provide refuge for biased corporate science (e.g., Monsanto reaching into studies by allegedly independent researchers on the safety of glyphosate; McClellan-Roger Exhibit 5, 2019).

The lack of real regulatory backbone is absolute. Incredibly, for example, FDA only required an inert saline placebo in the Moderna's mRNA m1273 vaccine clinical trial after a citizen's group, The "I Can Decide Network" (ICAN.org), petitioned them with a thoroughly referenced piece of work that aimed to improved vaccine safety science by setting it back on its original track.

There is a bulwark system of defenses built up around vaccines (see Oller in this issue) that is patently unscientific to its core. Sadly, the US public have had to resort to litigation to seek justice and compensation for harm caused by corporate products, and such cases are adjudicated on legal merits informed by an increasingly biased body of scientific literature, and in the face of almost insurmountable legal obstacles that have only been increasingly strengthened in favor of vaccine manufacturers since the notorious National Childhood Vaccine Injury Act of 1986 that did nothing to protect children from injuries but did everything to guard vaccine producers from citizen initiated lawsuits. This bias is enhanced by **targeted retraction** — the act of systematic targeting of research studies with results that draw the safety of corporate products into question (Shaw and Oller, 2020). I personally have been involved in the defense of a number of studies that are on par with or superior compared to previous published studies in their rigor of design, execution and analysis. It is readily apparent that 'retraction' of studies has replaced rational discourse in many journals — bringing the validity and reputation of those journals into question.

The bulwark of defenses around vaccines are not defending vaccines themselves — they are defending the power to control the public's perception of vaccine safety, and are thus erected specifically to bias the scientific, medical and lay populations' perception of the quality and rigor of vaccine "safety", actually vaccine "risk and danger", studies. The emergence of organizations such as ICAN — which has chronicled in detail their successes in holding CDC, HHS and the FDA accountable to best practices of clinical research — is the result of harms visited upon the US population caused by regulatory negligence. Without first-hand experience with vaccine injury, the messages of such organizations could not possibly resonate with the public, leading the recent surge in vaccine risk awareness, mass protests, and resistance to mandatory vaccinations without exemptions.

Career "Scientists" Favor Corporate Interests Over Public Health

Over the past three decades, as regulatory capture has increased, a massive public health crisis has emerged. In the US, over 54% of children have a chronic illness – for which they "require" life-long pharmaceutical interventions. Public health disasters such as rampant metabolic disease and diabetes, ADHD, autism, autoimmune disorders, and the rapid spread of COVID-19 due to CDC's failed testing program in March, 2020 – all occurred on the watch of paraprofessional government careerist "Scientists" who have routinely made ill-founded calls for specific public health measures that defy all reason and logic. For example, Francis Collins of the NIH recently called for an early end to COVID-19 randomized trials by vaccination of the placebo group because, in his view "we owe them" the vaccine. This of course would obviate the entire reason for the clinical trials – which includes, to monitor for disease enhancement – ill health caused by pathogenic priming of individuals by prior exposure to a vaccine or an infection – as was seen in all past animal vaccine trials for SARS and MERS. A more rational and scientifically literate ad-hoc WHO committee published an article calling for continuance of the trials specifically because vaccinating the placebo group would make long-term safety signal detection impossible (WHO Ad-Hoc Expert Group, 2020).

In April, Dr. Birx of the Whitehouse COVID Response Team announced that all deaths of individuals with COVID-19 were to be counted as death from COVID-19, blunting the public health tool of reporting and tracking. The assumption that more testing is always better was matched with a corresponding drive to make the medical community and the public believe that RT-PCR tests cannot lead to false positive results, a claim falsified by numerous studies with empirical field false positive estimates that include 11% (Basile et al., 2020), 30% (Lee et al., 2020).

Public health in the US is one -hundred percent focused on the manipulation and control of public perception; they are obsessed with burying any evidence of vaccine risks, and thus our collection of vaccines themselves have become more and more blunted instruments loaded with more and more unforeseen and unstudied risks: we are left with unscientific, irrational responses to COVID-19 leading to staggering economic losses projected to be on the scale of US$16 Trillion dollars – a full ¾ of our GDP (Cutler and Summer, 2020; also see the CHD article in this issue of *IJVTPR*).

Regulatory Capture Means Loss of Liability for Flawed Products

As we now see with COVID-19 vaccines, corporations have learned that making their products appear to be essential to public health can place them closer to the goose that lays a continuous stream of golden eggs – ownership of monopolistic or near-monopolistic of government-contract mandated products free from liability. Right now, liability for vaccine injury in the United States falls to the Department of Health and Human Services— with specific cases adjudicated by Special Masters in the National Vaccine Injury Compensation Program. My personal experiences in the NVICP as an expert have left me simply aghast at how patently unfair that hornswoggle program is: the HHS is at once the defendant and administers the HRSA Table of Vaccine Injuries; their experts and Special Masters remain ignorant of advances in science on aluminum toxicity and in matters of the use of aluminum hydroxide to induce autoimmunity even after being presented with the balance of the research literature. Indeed, one Special Master attempted to bribe me to change my testimony; when I submitted new testimony to the case that included mention that among the materials I

examined, I was morally obliged to include the audio recording of the message tempting me with reimbursement if I took a different approach, the case was dismissed. The lawyer involved was subsequently disbarred due to another matter outside the NVICP.

The opposite model in which vaccine manufacturers, not the HHS, are held liable for vaccine injuries would provide them with critical quality control feedback on the suitability of their product and at the very least protect against product quality decay. It would herald the return of a free market. In the case of vaccines, products such as Merck's MMR vaccines continued to be marketed full in the face of data that made loss of efficacy absolutely clear: entire schools with 100% of students up-to-date on MMR vaccination per the CDC's recommended schedule still experienced mumps outbreak (Hogan et al., 2020).

In the age of COVID-19, we now see vaccine makers seeking additional liability protections — and in some cases being denied those additional protections — and we also see medical facilities seeking passage of legislation protecting them from liability associated with COVID-19 infections. In Pennsylvania, Governor Tom Wolf vetoed legislation that passed the house and senate affording hospitals with liability protections from COVID-19-related illnesses. The rationale for the veto was that it could cause hospitals to lower their safety standards related to COVID-19 transmission — just as pharmaceutical companies have lowered their standards of safety (increasing corresponding risks) related to vaccines. The cycle of unlabeled forward-looking statements without sufficient transparency on the data have led to pump-and-dump stock cycles, allowing company owners to increase their personal wealth without sufficient accountability, not to mention actual oversight, of the often deleterious effects of their products on public health.

Campaign Finance Reform Caused Restrictions and Loss of Human Rights

Corporations with vaccines already on the market are highly motivated to continue their liability-free near-monopolistic hold on the market. Thus, they initiate legislation to restrict existing rights to exemptions (religious and medical). They have gone so far as to pursue, harass, and threaten to disrupt or halt the practice of medicine by doctors who follow federal requirements for informed consent for medical procedures and for human experimentation. Dr. John Piesse's offices in Australia were raided and private medical records were seized so a Pharma-captured medical board could review the exemptions he permitted. In their review, they inadvertently delegitimized their own attempt to legitimize their persecution by finding one — just one, out of all of the past exemptions — to be valid.

Mass Vaccination Programs Are Not Founded on Solid Ethics

The vaccinologists have seized an unearned moral high ground when, in reality, the depravity and disregard they exhibit for the sanctity of human life seems unmatched in modern times.

In a custody court case in Oakland County Court in Michigan, USA, Dr. Stanley Plotkin testified that he had preferentially experimented upon individuals with intellectual disability. The transcript of the testimony (TSG Reporting, 2018), which was never entered into evidence, shows that he participated in multiple vaccine experiments of various groups of disempowered persons without their consent. The relevant part of the transcript reads as follows:

Counselor (Q): Have you ever used orphans to study an experimental vaccine?

Stanley Plotkin, M.D. (A): Yes.

Q Have you ever used the mentally handicapped to study an experimental vaccine?

A I don't recollect ever doing studies in mentally handicapped individuals. At the time in the 1960s, it was not an uncommon practice.

Q So you're saying -- I'm not clear on your answer. I'm sorry. Have you ever used mentally handicapped to study an experimental vaccine?

A What I'm saying is I don't recall specifically having done that, but that in the 1960s, it was not unusual to do that. And I wouldn't deny that I may have done so.

Q Well, in any event, you're not denying that you, that you -- well, there's an article entitled "Attenuation of RA 27/3 Rubella Virus in WI-38 Human Diploid Cells." Are you familiar with that article?

A Yes.

Q In that article, one of the things it says is: "Seronegative mentally retarded children were given RA 27/3 vaccine?"

A Okay. Well, then that's, in that case that's what I did.

Q Have you ever expressed that it's better to perform experiments on those less likely to be able to contribute to society, such as children with handicap, than with children without or adults without handicaps?

A I don't remember specifically, but it's possible. And, again, I repeat that in the 1960s, that was more or less common practice. I've since changed my mind. But those were, that was a long time ago.

Q Do you remember ever writing to the editor of "Ethics on Human Experimentation"?

A I don't remember specifically, but I may well have.

Q …Do you recognize this letter you wrote to the editor?

A Yes.

Q Did you write this letter?

A Yes.

Q Is one of the things you wrote: "The question is whether we are to have experiments performed on fully functioning adults and on children who are potentially contributors to society or to perform initial studies in children and adults who are human in form but not in social potential? (A: Yes) "It may be objected that this question implies a Nazi philosophy, but I do not think that it is difficult to distinguish nonfunctioning persons from members of ethnic, racial, economic, or other groups."?

A. Mmmhmm.

Q Have you ever used babies of mothers in prison to study an experimental vaccine?

A Yes.

Q Have you ever used individuals under colonial rule to study an experimental vaccine?

A Yes.

Q Did you do so in the Belgian Congo?

A Yes.

Q Did that experiment involve almost a million people?

A Well -- well, all right, yes.

The full testimony transcript, available online (ReformedHealth.net, 2020), reveals that the foundation of the vaccine industry and the vaccinologists' disregard for the sanctity of human life was, at the onset of such studies, either missing in action or dead on arrival. Dr. Plotkin's name is emblazoned on the gavel used in ACIP meetings — a committee imbued with direct financial conflicts of interest nearly to a person — whose "recommendations" now carry the weight of the rule of law. Who are these people? They are not elected officials who answer to the voting public. Due to the loss of exemptions to vaccine mandates, their recommendations have become unquestionable decrees — a form of rule over the population that went out of style in 1066 and that was firmly routed from the United State of America in 1776.

The embedded and oft-repeated justification of "the greater good" actually begs the question of utility of vaccines in the prevention and control of disease in the population because, while transmission may be controlled by some vaccines and symptoms merely reduced by others, the true cost of vaccine adverse events is unknowable: to bring forward evidence of vaccine injury might reduce vaccine uptake, threatening the utility of the vaccine in the first place, and the profits of the manufacturers and their now fully captured regulatory partners.

Thus, the net balance of risk is never experimentally tested or demonstrated but is merely presumed to fall in favor of population-wide vaccination. With any ACIP-approved vaccine, the possibility of generating any information to the contrary is stymied at every turn — including meaningful post-market "surveillance". These measures include the use of vaccines or adjuvants as "placebos" during clinical trials. Where the researchers involved in clinical trials of vaccines ought to be using inert saline as a comparison treatment, as shown by the team at ICAN.org (2020) in their report leading to what was called "Placebogate" — the vaccine promoters rely on misleading statements by physicians and the bullying of parents into accepting all the vaccines and "mandates".

They aim to prevent them from gaining access to data on vaccine adverse events. Instead they force reliance on retrospective observational studies which provide association and correlation but which will also eternally deny the discovery of adverse events caused by vaccines. They have placed limits on the Vaccine Safety Datalink, requiring intimidating over-the-shoulder supervision of anyone accessing the data (CDC, 2020). They have also engaged in post-hoc changing of study designs and analysis following result-peeking as in the Destefano et al. study, chronicled in the revelations of such heinous crimes of pseudoscience reported to Hooker by William Thompson (Hooker, 2016). My own in-depth analysis of all of the studies on the vaccine and autism question sent by AAP to President Trump revealed that all of the studies but one were underpowered to detect even a weak correlation, and that one of the studies was likely the product of outright fraud. I even calculated the

number of patients that had to be moved from one group to another to achieve the association given the national prevalence of autism in the population under study.

COVID-19 Has Stimied Progress Toward Reform

By August 2019, the shockingly poor state of vaccine safety science in the US was thoroughly chronicled and the door was opened for discussions. In 2018, Robert F. Kennedy, Jr. had been considered for position in the White House on a Vaccine Safety Commission, an initiative that was turfed by interference by Bill Gates (Newsweek, 2018), who is neither a physician nor a scientist. Attempts by Pharma to repeal exemption laws in numerous states were failing. An attempt to mandate HPV Vaccines in Allegheny County, PA was fought in a lawsuit and ruled null and void ab initio (*Lyons-Weiler vs. Allegheny County Board of Health*, Stipulation). COVID-19 has taken over virtually every inch of legible real estate online. The lives of people around the world are being held hostage with pronouncements "no return to normalcy" by unelected public health servants. These individuals enjoy seriously troubling financial entanglements of their intellectual property and national public health measures. These persons are the same individuals who

- foundered at COVID-19 control with a misleading test in February (see my other paper in this issue)
- flip-flopped on public health measures like masking,
- failed to rigorously follow Federal law in reporting cases and deaths of COVID-19 (Heneley et al., 2020),
- facilitated skipping early COVID-19 vaccine animal trials to avoid vaccine-induced disease enhancement;
- altered standard Phase 2 and Phase 3 trials into Phase 2/3 to reduce the chance of finding adverse events;
- failed to provide rigorous oversight on the false positive rates of qRT-PCR tests for SARS-CoV-2 virus (11%-30%), and
- worked diligently to bury the evidence of efficacy of hydroxychloroquine if used early (see studies compiled at c19study.com).

Together, these efforts work ensure that the public *perception* that COVID-19 vaccines will have saved the day- these same public health servants have done so at great indirect costs. With Francis Collins now calling for the end of clinical trials by vaccination of the placebo group, leaving the detection of long-term health consequences of the COVID-19 vaccine program to post-market "surveillance" studies using already failed passive reporting systems (public reporting to VAERS or the VSD), the public health and medical agencies in the US government themselves can be seen as a dire threat to public health.

All of these facts point to a warping of rational translational research to the end of defending the reputation of vaccine science – and, more broadly, the reputation of the abysmal failure of the US public health infrastructure.

When a precursor article to this one was published on the LinkedIn social media website, I was locked out of my account and offered access back into my account if I agreed to surrender my first Amendment rights. I refused, and lost access to 16,000 professional contacts from around the world.

I had and herein again propose a major overhaul of the public health infrastructure in the United States designed to specifically meet the following criteria:

(1) assurance of independent, objective scientific research on all threats to public health;

(2) de-politicization of the matters of public health;

(3) de-centralization of public health to avoid the flaws inherent to centralization, including

   a. limited scope,

   b. groupthink,

   c. and regulatory capture,

(4) full representation of considerations of the impact of public health priorities and measures on all aspects of society;

(5) full, fair, and objective consideration of all reasonable public health measures to public health crises, including certain details of the practice of allopathic medicine;

(6) and assurances of robust and rigorous scientific studies on all manner of public health issues.

Plan B. Decentralization and Depoliticization

Under the current configuration, the HHS Secretary provides administrative oversight to CDC and related operations (ACIP, NVICP) as well has FDA. This configuration not only leads to geographic centralization of public health interests, a certain military risk, but also to restricted allowance of thoughts and paradigms, including groupthink and authority-based reasoning. It also lends itself well to regulatory capture. This configuration, which can be considered Plan A, has failed to provide a vibrant and healthy stewardship of crucial aspects of public health. Minority viewpoints and dissent are quashed. Plan A lacks adaptive flexibility and resilience. Most of it is patently and irreversibly corrupted.

Under Plan B, 80 independent research organizations, all funded directly by the US Senate, geographically located across the United States, would establish a broad base of expertise and provide a full compendium of cultural representation on priority issues of public health. Each research node would serve independently of the others. Redundancy is the point. The charter of each node will be to focus on public health issues relevant to the local, regional and national populations. Independent research focused on all source of high mortality and chronic illness – not just infectious diseases – would be the priority activities. The prime directive of each node would be determined autonomously, reflecting a sampling procedure of public health matters that command attention, guided only by direction toward the goal of understanding the causes and mitigating human pain and suffering.

Each node would exist either independently or in connection to a larger organization, however, its finances must be completely independent. No involvement, partnership, or sponsorship of activities of any kind can be funded by any source other than the US Senate. The net product of these nodes will be an annual independent report on the state of public health in the United States and North America highlighting the issues that cause American citizens to suffer acute or chronic illness of any kind and mortality.

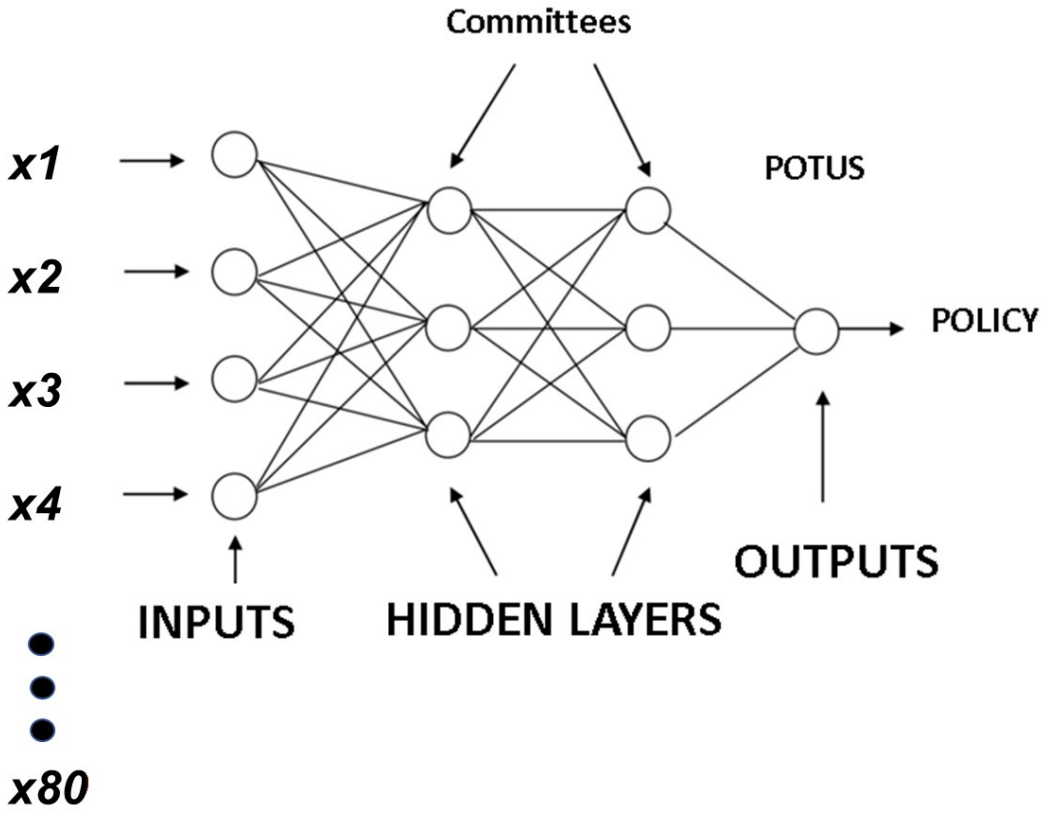

Figure 1. Schematic of the Core Design of Plan B Public Health Infrastructure.

Each independent annual report (IAR) from each node will be provided separately to each US Senate Committee by December 15th of each year. Each US Senate Committee will review each report and issue, by February 15th of each year, their own summary report reflecting the interests represented by that Committee. These Committee Annual Reports (CARs) will be provided the US Senate Intelligence Committee for review by March 15th of each year. The Senate Intelligence Committee will then send a Notice of Intent Report (NIR) to the Governors of each state, the President of the United States, the Speaker of the House of Representatives and to the President of the Senate issuing the determination of the Senate for prioritize actions to address the predominant public health issues threatening the US Public. The House of Representatives will address these issues with Bills as needed.

The decentralized process limits the authority of public health officials and broadens the focus of public health from infectious disease to the most common causes of serious acute and chronic

illness and mortality in a manner that utilize the full intelligencia inherent to representative government. The structure of the proposed process itself is that of a neural network, and thus the entire process is designed to be intelligent and flexibly adaptive to changes in priorities in public health.

Rules Enforcement

All studies undertaken should have a pre-published Data Analysis Plan encrypted for privacy with the key published in a single public blockchain resource following publication. This will allow an external data analysis review that matches the final data analysis plan that was executed to the data analysis plan that was published. Funding to each node should be contingent on independence and freedom from conflicts of interest. Any participating node found to embark on misadventures of profit-based incentives, internally or externally, of any type, including collusion or seeking input from any for-profit entity, should be cut from the network and replaced with a new node in a new geographic location.

The goal is to provide a self-correcting process that replaces the current public health infrastructure, which has gone off the rails. This was foreseen in 2010 by Justice Sotomayor, who wrote, in the dissenting view of the Supreme Court ruling of *Brusewitz et al., vs. Wyeth*, (SCOTUS, 2010), that

"[the court's] decision leaves a regulatory vacuum in which no one ensures that vaccine manufacturers adequately take account of scientific and technological advancements when designing or distributing their products."

It is abundantly clear that there is no free market regulation of vaccines; medical doctors are alleged to serve as "learned intermediaries" between vaccine manufacturers and patients, and they are incentivized to maximum vaccine uptake, and penalized if they do not.

The lack of independence of the regulatory and "research" agencies is blatant, and massive. CDC receives >$25Million per year from Pharmaceutical companies via their "CDC Foundation" In 2000, CDC held a conference to which members of the Pharmaceutical and medical industry were invited – but to which members of the public were not invited – at which it was decided that results showing increase in risk in autism related to vaccination had to be reconfigured before publication. The results were finally published after the data had been tortured extensively (Verstraeten et al., 2003). The product of this so-called "science" – no association – has been used to justify the meeting, but that, of course begs the question of how flawed science can justify an illegal meeting. It's the process of doing the science that is corrupted – and nothing good can come from corrupted processes.

NIH is similarly compromised via the "NIH Foundation", and issues directives on how its employees can "manage" their conflicts of interest.

We know from the crisis in Science that perverse incentives can warp the mentality of some involved in a particular line of scientific inquiry; we also learned from that same coming-of-age realization of the tools used to bias scientific studies such as p-hacking, result peeking. We know from Ioannidis of Stanford University that observational studies can be manipulated by design and analysis to ensure any particular desired result.

It is time to apply across the entire public health enterprise what we already know about the corruption of the pharmaceutical industry and its government regulators and profiteering collaborators. In our mission to return objectivity to science and to the media, we are reminded of the wisdom of Buckminster Fuller:

> *You never change things by fighting the existing reality.*
> *To change something, build a new model that makes the existing model obsolete.*

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Toll-like Receptor 9 Agonists in HPV Vaccine Gardasil9

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Abstract

Gardasil9 is a recombinant human papillomavirus (HPV) 9-valent vaccine, containing purified major capsid L1 protein of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 re-assembled into virus-like particles (VLPs) as the active ingredients. Since the antigens are purified recombinant proteins, in theory Gardasil9 needs a potent adjuvant to generate high and sustained levels of antibodies. Historically, amorphous aluminum hydroxyphosphate sulfate (AAHS), listed as the adjuvant for Gardasil9, was known to require one or more Toll-like receptor agonists, such as the phospholipids in the recombinant hepatitis B vaccine, Recombivax HB®. However, there are no phospholipids in the purified HPV L1 proteins or in Gardasil9. But the Food and Drug Administration (FDA) reports that Gardasil4 does contain recombinant HPV L1-specific DNA fragments, and they may serve as Toll-like receptor 9 agonists in Gardasil9. The author has tested 5 samples of Gardasil9 from 4 manufacturing lots by PCR amplification with a set of degenerate primers followed by heminested PCR or by another 5 sets of non-degenerate nested PCR primers in an attempt to detect all 9 vaccine-relevant HPV type-specific L1 gene DNAs bound to AAHS in the vaccine. Sanger sequencing confirmed the presence of HPV 18, 11, 16 and 6 L1 gene DNA bound to insoluble AAHS nanoparticles, but they were unevenly distributed even within the same vaccine sample. Also, these fragments were at least partially in non-B conformations. Since no L1 gene DNA of HPV 31, 33, 45, 52, and 58 was amplified by the commonly used degenerate PCR primers, the results suggest that these may all be in non-B conformations or may have been removed as contaminants by a purification protocol. Further research is warranted to standardize the HPV DNA fragments in Gardasil which are known to be potent Toll-like receptor 9 agonists.

Keywords: *Gardasil9, Gardasil, HPV vaccine, HPV DNA, non-B conformations, topological conformational change, Toll-like receptor 9 agonist, AAHS, amorphous aluminum hydroxyphosphate sulfate, DNA sequencing*

Introduction

Human papillomavirus (HPV) is the agent of a common sexually transmitted infection according to the Centers for Disease Control and Prevention (CDC, 2019). There are two FDA-approved HPV vaccines, the bivalent vaccine Cervarix and the 4-valent or 9-valent vaccine Gardasil, for its prevention. Both Cervarix (GlaxoSmithKline, 2019) and Gardasil (Merck & Co., Inc., 2019) use

purified recombinant genotype-specific HPV major capsid L1 proteins re-assembled in the form of virus-like particles (VLPs) as their active ingredients (their antigens).

Because the assembled VLPs are purified recombinant proteins, by themselves they are relatively weak immunogens and require the assistance of specially designed adjuvants to generate a robust and persistent immune response as other purified, subunit and synthetic antigens usually do in many newly developed vaccines, as pointed out by the National Institutes of Health (NIH, 2019). In Cervarix, the adjuvant is AS04 (GlaxoSmithKline, 2019), a compound created by combining a Toll-like receptor (TLR) 4 agonist MPL (3-O-desacyl-4'-monophosphoryl lipid A) and aluminum hydroxide. MPL is a detoxified derivative of the lipopolysaccharide (LPS) isolated from *Salmonella minnesota* R595 strain and LPS is a specific agonist of TLR 4. In chemical structure, a single negatively charged phosphate of the linear MPL is bound to the cationic aluminum through an ionic bond so that the free molecular chains of LPS can react with TLR 4 of the immune cells. The MPL within AS04 enhances the initiation of the immune response through activation of the innate immunity, leading according to standard theory to an enhanced cellular and humoral adaptive immune response (Tagliabue & Rappuoli, 2008).

The adjuvant in Gardasil is amorphous aluminum hydroxyphosphate sulfate (AAHS). Each dose of Gardasil9 contains approximately 500 mcg of AAHS as its adjuvant (Merck & Co., Inc., 2019). Both AS04 and AAHS are made from the same starting chemical of aluminum hydroxide (Iyer, HogenEsch & Hem, 2003; EMEA, 2006; Didierlaurent, 2009; Egan, Belfast, Giménez, Sitrin, & Mancinelli, 2009), the hydroxyl groups of which have been partially replaced by phosphate-containing molecules, namely, by MPL, to form AS04 (Tagliabue & Rappuoli, 2008) and by an inorganic phosphate to form AAHS through ligand exchange (Egan, Belfast, Giménez, Sitrin, & Mancinelli, 2009). The crucial difference between AS04 and AAHS is that MPL is a TLR agonist and inorganic phosphate is immunologically inert.

In animal experiments, anti-HPV L1 VLP responses from mice vaccinated with AAHS-formulated HPV16 vaccine have been shown to be substantially greater than those produced by mice immunized with the same antigen formulated with aluminum hydroxide or with aluminum phosphate (Caulfield et al, 2007). In human studies, vaccination with Gardasil has been shown to induce significantly higher early innate proinflammatory cytokine/chemokine responses than Cervarix in women (Herrin et al., 2014). The peripheral blood mononuclear cells (PBMCs) of healthy women vaccinated with Gardasil have been shown to be associated with significant changes in the expression and function of immune innate and regulatory receptors (Colmenares et al., 2012). These results indicate that Gardasil can augment the innate immune response, at a level comparable to Cervarix, if not greater, even though its aluminum adjuvant does not contain MPL. A TLR agonist component equivalent to MPL is neither a part of AAHS, nor mentioned in the description for Gardasil9 (Merck & Co., Inc., 2019). The mechanism by which AAHS exerts its adjuvant effects in either Gardasil4 or Gardasil9 has not been fully explained or published. Although AAHS and other aluminum salts, including various other forms of aluminum hydroxide and also of aluminum phosphate, have been used as vaccine adjuvants for over 80 years, how they work remains largely unknown, or at best the theories that have been proposed are controversial. Recent research progress has led the author, and certain others, to believe that pattern recognition receptors (PRRs) of the innate immune system, particularly TLRs and nucleotide-binding and oligomerization domain

(NOD)-like receptors (NLRs), can modulate and control the generation of humoral and cellular immune responses to vaccination (Maisonneuve, Bertholet, Philpott & De Gregorio, 2014).

Aluminum salts invariably induce cell damage and local inflammation at the site of injection. It has been suggested that at least as an adjuvant in animal vaccination experiments with protein antigen, the cationic aluminum binds the phosphate backbone of the free DNA released from the dying host cells at the injection site of inflammation and transfect the host nucleic acids into the APCs, exerting its adjuvant effects by activation of STING and IFN regulatory factor 3 (IRF3) (Marichal et al., 2011; McKee et al., 2013). Internalized nucleic acids in the APCs are potent TLR agonists in enhancing the desired immune responses (Mohsen, Zha, Cabral-Miranda, & Bachmann, 2017). Internalization of the aluminum salt particles by immune cells may also lead to phagosomal destabilization resulting in the activation of NLR protein NLRP3 (Hornung et al., 2008), probably by inducing the production of endogenous uric acid, which in turn activates NLRP3 within APCs (Kool et al., 2008). All these proposed immunological effects induced by aluminum adjuvants in vaccination follow or are the consequences of generation or release of certain endogenous chemicals as a result of cell damage caused by the aluminum salts at the site of vaccine injection; the real immune mediators are the uric acid and the nucleic acids from the host cells, not the aluminum salt itself (Kool et al., 2008). Based on the studies of Cervarix, HPV vaccines need an exogenous, pre-made, ready-to-use, instant potent TLR agonist immediately available at the time of vaccination to enhance the innate immune responses of the host to overcome the relatively weak immunogenicity of the purified HPV L1 proteins re-assembled as VLPs during vaccine manufacturing (Mach et al., 2006; Frazer, 2018). Such a TLR agonist has not been listed in the Gardasil9 formulation (Merck & Co., Inc., 2019).

Previous testing of 16 samples from different vaccine lots revealed that Gardasil4 contains fragments of HPV L1 gene DNA firmly bound to the insoluble, proteinase-resistant fraction of that vaccine, presumably AAHS nanoparticles (Lee, 2012). Since free DNA released from dying host cells and bound to aluminum salts at the site of vaccine injection is known to be transfected into the cytoplasm of antigen-bearing dendritic cells in promoting MHC class II presentation and enhancing dendritic cell to T-cell interactions as a mechanism of augmenting the immunogenicity of vaccination (Marichal et al., 2011; McKee et al., 2013), the HPV L1 gene DNA fragments bound to AAHS in Gardasil4 are expected to provide such an instant premade TLR 9 agonist to enhance the initiation of the immune response through activation of the innate immunity, leading to an enhanced cellular and humoral adaptive immune response in Gardasil9 vaccination. However, with respect to the efficacy and safety of HPV vaccination, the type and quantity of HPV L1 gene DNA as a TLR agonist have not been defined and standardized for Gardasil vaccines as MPL was for Cervarix. This article reports the technical challenges in using a routine diagnostic PCR protocol for detection of the genotype-specific HPV L1 gene DNAs bound to AAHS in the HPV vaccine Gardasil9.

Materials and Methods

1. Gardasil9 vaccine samples

A total of 5 Gardasil9 vials or manufacturer-prefilled vaccine syringes with intact original packages were submitted to the author's laboratory by health care professionals to be tested for the presence

of HPV L1 gene DNA fragments at the request of their patients or the guardians of their patients. The lot numbers printed on the labels of these vaccine samples were N020139, K001502(x 2, registered as A and B for testing), R000303 and M045743, respectively.

2. PCR and sequencing primers

The sequences of the well characterized MY09 and MY11 degenerate primers and the GP6 primer for PCR amplification of a conserved segment of the HPV L1 gene in routine Sanger-sequencing-based diagnostics (Lee, 2012a) were:

MY09 forward = 5'-CGTCCMARRGGAWACTGATC-3'

MY11 reverse = 5'-GCMCAGGGWCATAAYAATGG-3' (also in heminested PCR)

GP6 forward heminested = 5'-GAAAAATAAACTGTAAATCA-3'

The sequences of additional non-degenerate nested PCR reverse primers, to be paired with GP6 forward primer, referred to as primer R16, R31, R45, R52 and R58, were as follows:

R16: 5'-AATGGCATTTGTTGGGGTAAC for binding site 3'-GTTACCCCAACAAATGCCATT

R31: 5'-GCTCAGGGACACAATAATGGT 3'-ACCATTATTGTGTCCCTGAGC

R45: 5'-ATAACAATGGTATTTGTTGGC 3'-GCCAACAAATACCATTGTTAT

R52: 5'-GCGCAGGGCCACAATAATGGC 3'-GCCATTATTGTGGCCCTGCGC

R58: 5'-GGTCATAACAATGGCATTTGC 3'-GCAAATGCCATTGTTATGACC

All primers were diluted in TE buffer pH 7.4 (Sigma Chemical Co., St. Louis, MO) to a 10 μmolar working solution.

3. Preparation of samples for PCR

After the contents of the vaccine samples were mixed well, an aliquot of 100 μL of the vaccine suspension was centrifuged at ~16,000 × g for 10 min in a 1.5 mL microcentrifuge tube. The pellet was re-suspended and washed twice with 1 mL of 70% ethanol each and the final ethanol suspension was centrifuged at ~16,000 × g for 5 min. The washed pellet was air-dried. The dried pellet was re-suspended in 100 μL of 0.1 mg/mL proteinase K (Sigma Chemical Co., St. Louis, MO) in a buffer consisting of 50 mM Tris-HCl, 1 mM EDTA, 0.5% Tween 20, pH 8.1. The mixture was digested at 45°C - 55°C overnight and was exhaustively washed with the same Tween 20 buffer pH 8.1, 4 times, 1 mL each time and resuspended in 100μL of buffer. After heating at 95°C for 10 min to inactivate any residual proteinase K, a 1 μL aliquot of the washed and heated particle suspension was used to initiate each primary PCR with a pair of MY09/MY11 degenerate primers followed by a GP6/MY11 heminested PCR or a set of nested PCRs.

4. PCR Amplification of HPV L1 Gene DNAs for Sanger sequencing

For the primary PCR, 1 µL aliquot of the washed and heated vaccine particle suspension, 20 µL of LoTemp® master mix containing manufacturer-optimized HiFi® DNA polymerase, magnesium ions, denaturing agents, and dNTPs with stabilizing additives (HiFi DNA Tech, LLC, Trumbull, CT, USA), 1 µL of 10 µmolar MY09 primer, 1 µL of 10 µmolar MY11 primer and 2 µL of molecular grade water were mixed in a final volume of 25 µL in a thin-walled PCR tube for low temperature PCR amplification. The LoTemp® thermocycling steps were set for an initial heating at 85˚C for 10 min, followed by 30 cycles, each set at 85˚C for 30 sec, 40˚C for 30 sec, and 65˚C for 1 min. The final extension was 65˚C for 10 min. A trace of each of the primary PCR products (about 0.2 µL) was transferred by a micro-glass rod to another 25 µL complete PCR mixture containing 20 µL of ready-to-use LoTemp® PCR mix, 1 µL of 10 µmolar GP6 forward primer, and 1 µL of 10 µmolar reverse primer and 3 µL of molecular grade water for heminested PCR or nested PCR. After completion of the primary and the nested PCR, a 5 µL aliquot of the PCR products was pipetted out from each tube and mixed with 2 µL loading fluid for electrophoresis in a 2% agarose gel containing ethidium bromide. The gel was examined under UV light for the PCR product bands in the agarose gel. An HPV 16 plasmid DNA positive control and a no sample negative control (1 µL of water added instead of sample) were included in each primary and heminested or nested PCR run.

5. Direct automated DNA sequencing of the heminested or nested PCR amplicons

For DNA sequencing, a trace of the positive nested PCR products (about 0.2 µL) was transferred directly with a micro-glass rod from the heminested or nested PCR tube into a 20 µL volume of a cycle sequencing reaction mixture consisting of 14.5 µL water, 3.5 µL of 5 × buffer, 1 µL of BigDye Terminator 1.1 (Applied Biosystems) and 1 µL of 10 µMolar sequencing primer solution in TE

Figure 1. Alignment of the ending 65-base sequences of the 181-187 bp amplicons of the Gardasil9 HPV L1 genes defined by the GP6/MY11 heminested PCR primers. The MY11 degenerate primer binding sites are yellow-highlighted. The letters in red color represent single nucleotide polymorphisms which can be used to distinguish the sequences of other HPV genotypes from that of HPV 6 and from one another.

HPV	Ending 65-base L1 gene sequences of PCR amplicon defined by GP6 and MY11 primers (3'-5')	Size of amplicon
6	GTGGTATCTACCACAGTAACAAACAGTTGATTACCCCAACAAATACCATTGTTATGTCCCTGGGC	181bp
11	GTGGTATCTACCACAGTAACAAACAGATGATTACCCCAACAAATACCATTGTTATGTCCCTGGGC	181
16	GTAGTATCAACAACAGTAACAAATAGTTGGTTACCCCAACAAATGCCATTATTGTGGCCCTGTGC	184
18	GTGGTATCTACCACAGTAACAAATAATTGATTATGCCAGCAGATACCATTGTTATGACCCTGTGC	187
31	GTGGTATCTACCACAGTAACAAATAACTGATTGCCCCAACAAATACCATTATTGTGTCCCTGAGC	184
33	GTGGTATCTACCACAGTAACAAATACCTGATTGCCCCAACAAATACCATTATTATGACCTTGTGC	181
45	GTAGTGTCCACTACAGTAACAAACAACTGATTATGCCAACAAATACCATTGTTATGGCCCTGGGC	187
52	GTGGTATCCACAACTGTGACAAACAACTGATTGCCCCAACATATGCCATTATTGTGGCCCTGCGC	181
58	GTGGTATCAACCACGGTAACAAATAACTGATTGCCCCAGCAAATGCCATTGTTATGACCTTGTGC	181

buffer. After thermal cycling according to the manufacturer's recommendation for 20 cycles, the reaction mixture was loaded in an automated ABI 3130 four-capillary Genetic Analyzer or an Applied Biosystems SeqStudio Genetic Analyzer for sequence analysis. Alignment analysis of a 45 - 60 base sequence in the hypervariable region of the L1 gene excised from the computer-generated

base calling electropherogram was performed against various standard HPV genotype sequences retrieved from the GenBank, using the on-line BLAST (Basic Local Alignment Search Tool) system to validate the specific HPV genotyping and for visual sequence analyses. Throughout the entire period when this study was carried out, no routine diagnostic HPV tests were performed in the laboratory and the procedures of sample preparation for primary PCR, nested PCR and DNA sequencing were performed in different rooms to avoid cross contamination by HPV DNA from other sources.

RESULTS

1. Short-segment L1 gene DNA sequence analysis for HPV genotyping

Based on alignment of the highly conserved sequence with hypervariable regions of the HPV L1 gene of HPV 6 (KX514429), HPV 11 (U55993), HPV 16 (AF125673), HPV 18 (EF202155), HPV 31 (KX638481), HPV 33 (KU550675), HPV 45 (KU049756), HPV 52 (LC373207) and HPV 58 (KY225967), the 9 HPV genotypes included in Gardasil9 can be reliably diagnosed by BLAST analysis of a 45-base sequence immediately downstream of the 20-base degenerate MY11 primer site. The size of the amplicon defined by the GP6 and MY11 primers of these HPV genotypes varies from 181 bp to 187 bp (Lee, 2012a), as shown in Figure 1.

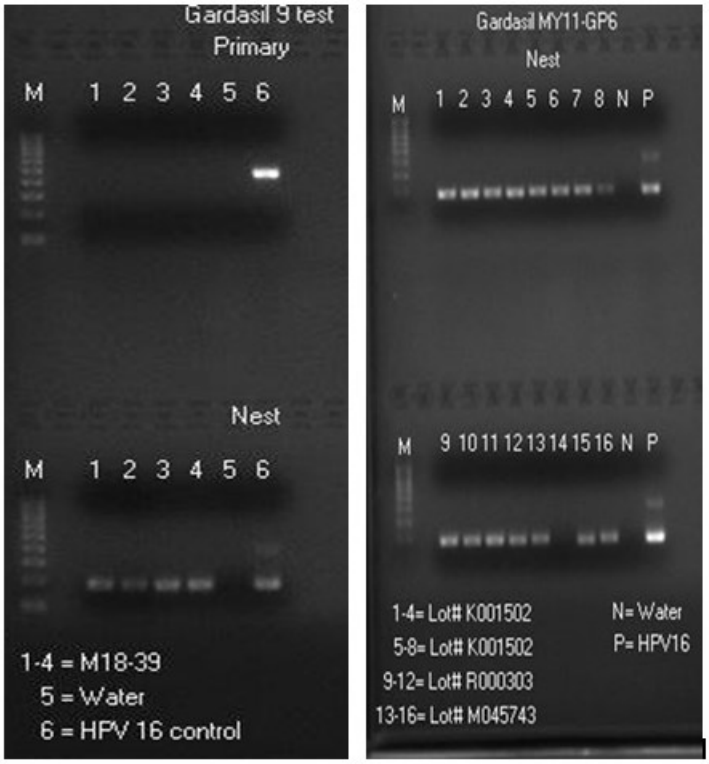


Figure 2. Image of agarose gel electrophoresis showing products of HPV DNA primary and heminested PCR products in the left panel and heminested PCR products only on the right panel. There were four duplicate PCR sets on each of the 5 Gardasil9 digestates.

Left panel: Lanes 1-4 = Lot #N020139 (labeled M18-39) showing 4 invisible MY09/MY11 primary PCR products (upper) and 4 visible GP6/MY11 heminested PCR bands (lower).

Right panel: GP6/MY11 heminested PCR products only. Lanes 1-4 = Lot #K001502(A); Lanes 5-8 = Lot #K001502(B); Lanes 9-12 = Lot #R000303; Lanes 13-16 = Lot #M045743. N=negative, no sample control. P= HPV 16 positive control. M=molecular ruler.

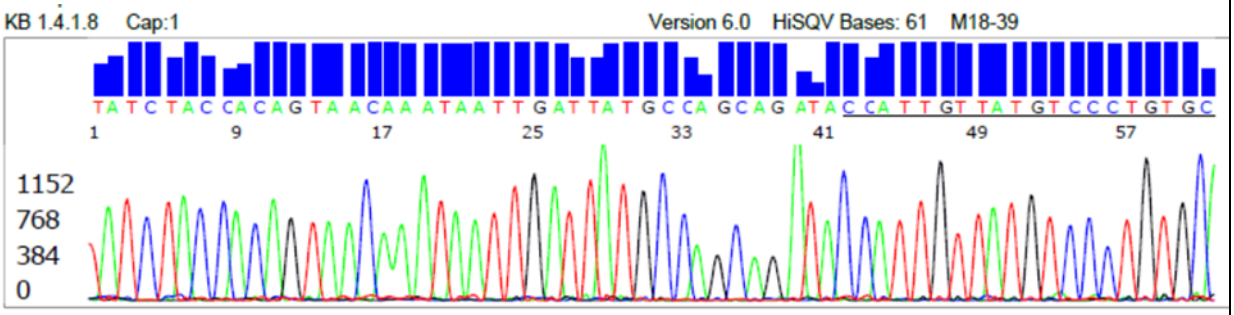
2. Selective amplification of HPV 18 and HPV 11 DNA

Since most invasive cervical cancers are associated with or preceded by persistent infection by one of numerous genotypes of HPV (Wallin et al., 1999; Ciotti et al., 2006), laboratory tests for HPV in specimens obtained from patients have been developed to amplify all clinically relevant HPV genotype L1 gene DNAs by MY09/MY11 degenerate primer PCR followed by GP6/MY11 heminested PCR for initial detection. DNA sequencing is performed on a PCR amplicon for accurate genotyping in follow-up of the patients with persistent HPV infection (Lee, 2012a; Wallin et al., 1999). Theoretically, Gardasil9 may contain 9 genotype-specific HPV L1 gene DNAs, and all 9

genotypes of HPV L1 gene DNA were expected be co-amplified by the degenerate MY09/MY11 primary PCR primers and the GP6/MY11 heminested PCR primers if these DNAs were in B conformation.

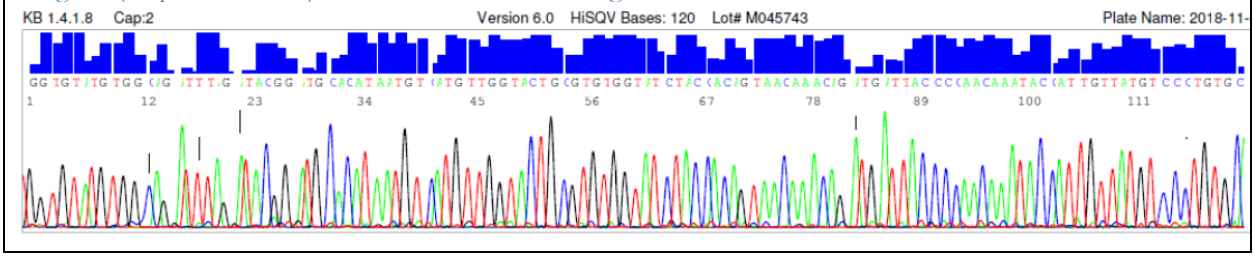
As demonstrated in Figure 2, using 1 µL of washed and heated insoluble nanoparticle suspension as the template to initiate each MY09/MY11 primary PCR followed by GP6/MY11 heminested PCR invariably generated a 181-187 bp HPV L1 gene DNA amplicon, indicating that the HPV L1 gene DNA fragments in Gardasil9 were firmly bound to AAHS nanoparticles, the only water-insoluble and proteinase K-resistant ingredient in the vaccine formulation (Merck & Co., Inc., 2019).

Figure 3. Electropherogram of a segment of HPV 18 L1 gene (Seq ID: EF202155)- MY11 primer underlined.



Sanger sequencing with GP6 primer carried out on all these 20 GP6/MY11 heminested PCR products showed a segment of HPV 18 L1 gene sequence (Figure 3) in 1 of the 4 heminested PCR tubes of Lot #N020139, in 1 of the 8 heminested PCR tubes of Lot #K001502, in 1 of the 4 heminested PCR tubes of Lot #R000303, and in 2 of the 4 heminested PCR tubes of Lot #M045743. A sequence of synthetic HPV 11 L1 gene DNA (Figure 4) was generated with the

Figure 4. HPV 11 – a segment of DNA modified from HPV 6 L1 gene DNA (Seq ID:KX14429) with one A>C, one G>T and two T>A mutations at positions indicated by 4 arrows in creating a synthetic HPV 11 L1 gene (Seq ID: U55993) for vaccine manufacturing.

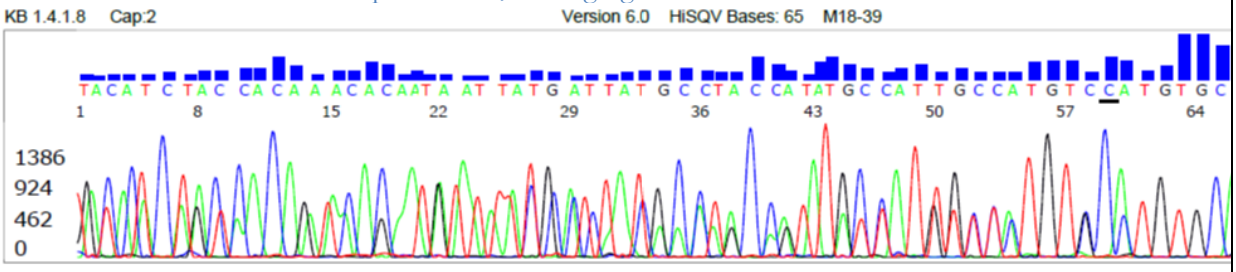


heminested PCR products in 1 of the 4 tubes of Lot #M045743. In other words, Sanger sequencing of 20 heminested PCR products generated only 6 readable DNA sequences. Five of the 6 sequences (5/6) were those of HPV 18 and one (1/6) was that of HPV 11 (synthetic).[3]

3. Multiple HPV DNA sequences generated by MY09/MY11 degenerate primers

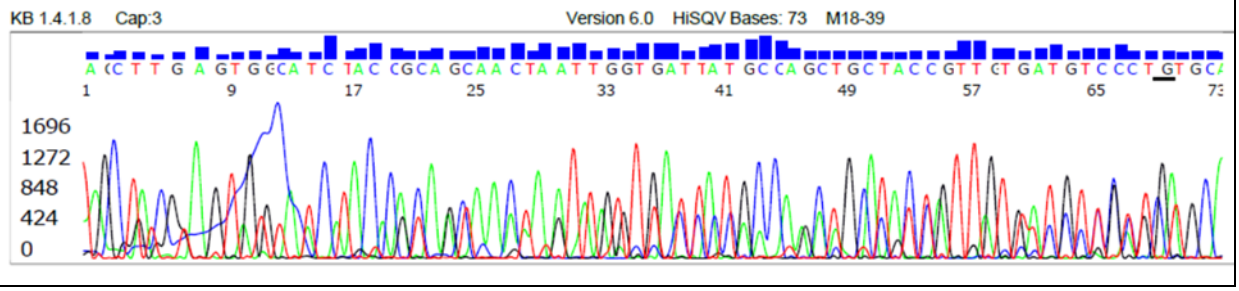
Sequencing with GP6 primer of the 14 GP6/MY11 primer heminested PCR products other than those 6 mentioned above yielded 13 mixed HPV L1 gene DNA sequences. Sequencing of the invisible heminested PCR products shown in Lane 14 (Figure 2) with GP6 primer did not generate a sequence (1 of 4 aliquots from Lot #M045743).

Figure 5. Mixed HPV DNA sequences. At least one PCR amplicon was 6 bases longer than the other(s)- (position 60-65, reading CTGTGC with 2 A-overhangs). The MY11 primer of the shorter sequence started from the underlined base "C" at position 59, reading right to left.



The 13 mixed DNA sequences could be separated into two patterns, each consisting of at least two mixed amplicons, one being 6 bases longer than the other(s), as shown in Figure 5, and one being 3 bases longer than the other(s) as shown in Figure 6. According to the sequence alignment in Figure 1, the unreadable superimposed sequences illustrated in Figure 5 must represent the sequence of an HPV 18 PCR amplicon plus one or more of the 5 HPV genotypes with a 181 bp-long PCR amplicon, all defined by the GP6 and MY11 primer binding sites, because the HPV 18 PCR amplicon defined by the GP6 and MY11 primers is the longest with a clear CTGTGC ending in any

Figure 6. Mixed HPV DNA sequences. At least one PCR amplicon was 3 bases longer than the other(s)- (position 70-72, reading TGC with 2 A-overhangs); the first base "C" of the MY11 primer of the shorter amplicon (reading from right to left) was overshadowed by a big "G" (underlined) of the longer amplicon 3 bases downstream of its first base "C" at position 72.



[33] Editor's Note: The line shown here in purple was inadvertently omitted from the prior version published on July 15, 2020 in *IJVTPR 1*(1), 75-97.

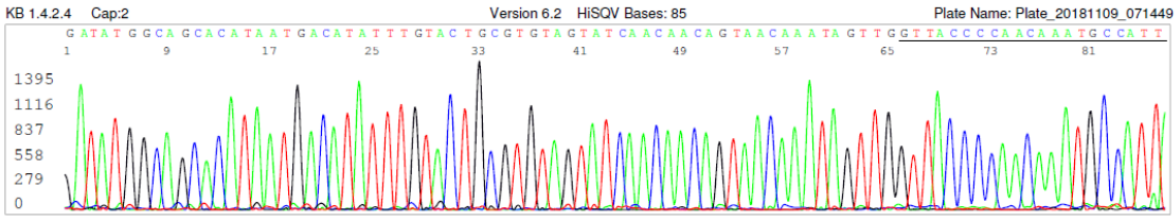
mixed sequence combinations. By the same token, the electropherogram of Figure 6 indicates that there were at least two amplicons in the PCR products; at least one was 3 bases longer than the other(s). Based on analysis the terminal sequences of the electropherograms of Figures 5 and 6, there were at least 3 genotype-specific HPV L1 gene DNA amplicons in the MY09/MY11 primary PCR and the GP6/MY11 heminested PCR products illustrated in Figure 2. One of the 3 was HPV 18, and at least one was an HPV L1 gene DNA with 3 bases shorter and another with 6 bases shorter than HPV 18 in their PCR amplicon sizes defined by the GP6 and MY11 primers.

4. No amplification of HPV 31, 33, 45, 52 and 58 L1 gene DNA by MY09/MY11 degenerate PCR primers

In order to test if there were any L1 gene DNA amplicons of the HPV 31, 33, 45, 52 and 58 genotypes in the MY09/MY11 primary PCR products, each of the 14 primary PCR products generated (see Section ***3)*** which did not yield a single heminested PCR amplicon for successful Sanger sequencing was re-amplified in 5 sets of nested PCRs, each using the combination of a GP6 and one of the R16, R31, R45, R52 and R58 as forward and reverse primers.

The 5 non-degenerate reverse PCR primers were located internal of the MY11 primer binding site of

Figure 7. Natural HPV 16 sequence at primer binding site: GTTACCCCAACAAATGCCATT



each HPV L1 gene and were designed to match a segment of the targeted type-specific HPV DNA (Figure 1). Since the last 9 nucleotides at the 3'end sequence of primer R31 designed for HPV 31 DNA amplification are identical to the sequence of HPV 33 in the corresponding position, no separate reverse primer for HPV 33 amplification was considered necessary.

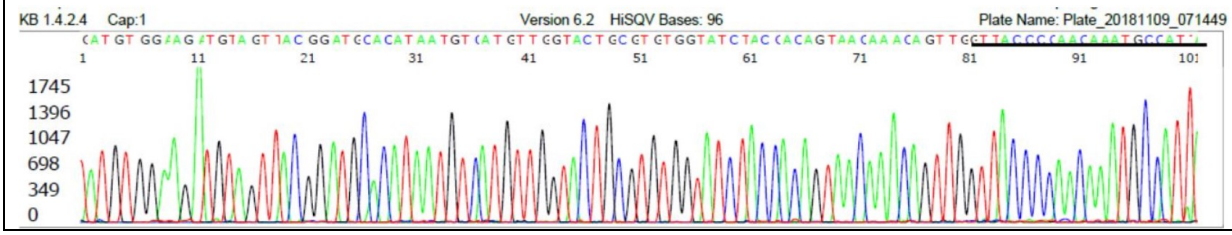
After completion of all 70 (14x5) nested PCRs, each of the 13 primary PCR products which led to a visualized heminested PCR product band consisting of multiple sequences yielded 5 HPV nested PCR product bands at gel electrophoresis, as expected. The primary PCR products as shown in Lane 14, Figure 2 which yielded no visible heminested PCR band also generated no visible nested PCR products. All 70 nested PCR products, regardless of yielding a visible band on gel electrophoresis or not, were subjected to Sanger sequencing with GP6 primer. Visual and BLAST analyses of these Sanger sequencing data did not reveal any PCR amplicons of L1 gene DNA of HPV 31, 33, 45, 52 or 58 in the MY09/MY11 primary PCR products which could be selectively amplified by a pair of non-degenerate nested PCR primers for a successful DNA sequencing. However, these non-degenerate nested PCR primers did selectively re-amplify some of the L1 gene DNA amplicons of HPV 6, 11, 16 or 18 to be used as templates for Sanger sequencing from the MY09/MY11 primary PCR products containing mixed genotype DNAs, as illustrated below.

4.1. In the absence of HPV 16 DNA, primer R16 amplified HPV 6 and HPV 11 L1 DNA

When HPV 16 DNA was present in the mixed genotype MY09/MY11 primary PCR products, the non-degenerate GP6/R16 primer pair selectively amplified the HPV 16 DNA for Sanger sequencing. The R16 primer is 15 bases internal to the MY 11 primer-binding site (see Figure 1) and fully matches the natural HPV 16 binding site sequence (underlined in the electropherogram of Figure 7).

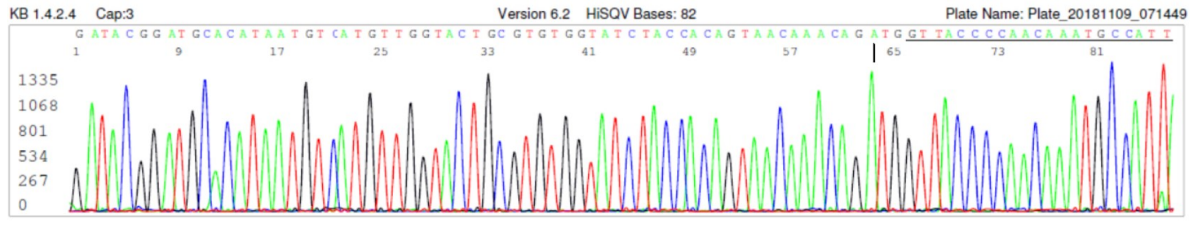
When HPV 16 DNA was absent in the mixed genotype primary PCR products, the non-degenerate R16 primer pair was able to anneal to a segment of HPV 6 L1 gene DNA to generate a template for Sanger sequencing even though there were two mismatched nucleotides between primer R16 and the primer blinding site of the template with one mismatch being at the 3' terminus (primer R16 underlined in electropherogram). The HPV 6 natural primer binding site sequence is placed over the R16 primer with 2 mismatched nucleotides in red color as in Figure 8.

Figure 8. Natural sequence of HPV 6 at primer binding site: ATTACCCCAACAAATACCATT



When HPV 16 DNA was absent in the mixed genotype primary PCR products, the non-degenerate R16 primer was able to anneal to a segment of HPV 11 L1 gene DNA to generate a template for Sanger sequencing even though there were two mismatched nucleotides between primer R16 and the template primer blinding site with one mismatch being at the 3' terminus. Note: The sequence of

Figure 9. Natural sequence HPV 11 at primer binding site: ATTACCCCAACAAATACCATT



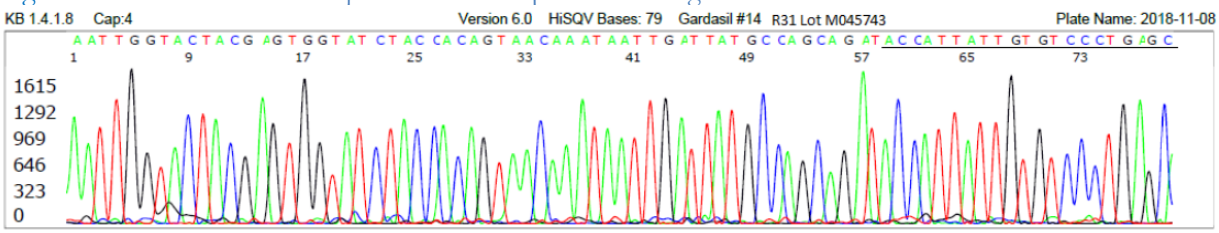
the synthetic HPV 11 L1 gene and the natural HPV 6 L1 gene have the same DNA sequence in this segment except for a T>A mutation indicated by a dark vertical line at 63 in the electropherogram illustrated in Figure 9.

4.2. Topological conformational change at the primer binding site led to PCR failure

As for all other Gardasil9 samples tested, four 1μL aliquots were pipetted from one 100μL AAHS suspension derived from a sample of Lot #M045743 to initiate 4 individual MY09/MY11 primary PCRs, followed by 4 corresponding GP6/MY11 heminested PCRs. The heminested PCR products were shown by gel electrophoresis in Lanes 13-16, Figure 2. The MY09/MY11 primary PCR products which generated no visible GP6/MY11 heminested PCR product band in Lane 14 (Figure 2) were re-amplified by a set of 5 pairs of non-degenerate nested PCR primers, and the nested PCR products were re-sequenced with GP6 primer as described above even though the nested PCR products were not visible at gel electrophoresis. Three (3) DNA sequences ending with non-degenerate primer R31, R45 and R58 were generated from the 5 nested PCR amplicons derived from the Lane 14 primary PCR products although the nested PCR amplicons were not visible as bands on agarose gel electrophoresis. These 3 sequences are illustrated in Figures 10, 11 and 12 as follows.

DNA sequencing electropherogram of a GP6/R31 nested PCR amplicon generated from Lane 14 MY09/MY11 primary PCR products, showing a sequence of HPV 18 L1 gene DNA amplified by primer R31. The R31 sequence is underlined; it has one extra nucleotide "A" at the 3' end compared to the degenerate MY11 primer sequence for HPV 18 shown in Figure 3. The natural sequence of HPV 18 with 4 mismatched bases (in red color) is placed over the underlined R31 primer in the electropherogram of Figure 10. This sequence found there indicates that the HPV 18 DNA in 1 of the 4 aliquots from Lot #M045743 was not exponentially amplified by the MY11 degenerate primer **as** the HPV 18 DNA in other aliquots from the same vaccine sample. An R31 primer with a 3'-ACCATT end instead of the MY11 primer with a 3'-CCATT end was needed to yield an HPV 18 PCR amplicon in this aliquot to be used as the template for DNA sequencing. It was previously reported that non-degenerate HPV 16 MY11 primer with 3'-end extension was needed to amplify some of the HPV 16 L1 DNA fragments bound to AAHS in Gardasil4 to generate a visible PCR amplicon for Sanger sequencing because binding of the HPV dsDNA to aluminum salts may cause topological conformational changes at the MY11 primer binding site, turning a segment of the dsDNA into a non-B conformation (Lee, 2013; Lee, 2014).

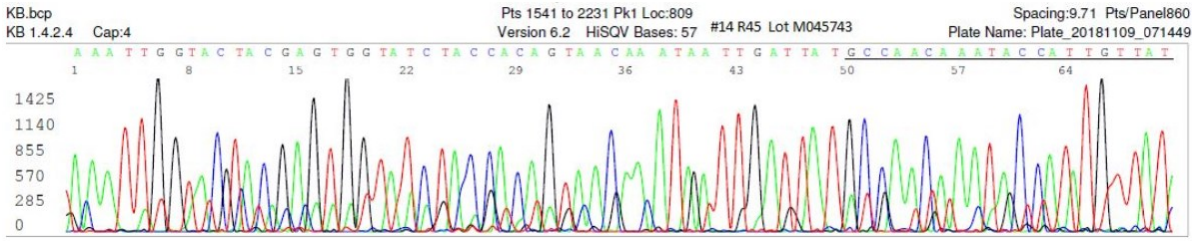
Figure 10. Natural HPV 18 sequence at MY11 primer binding site: CCATTGTTATGACCCTGTGC



It was also found that in the same primary PCR products described above there were DNAs other than those of HPV 18 the sequence of which was shown in Figure 10. As illustrated in Figures 11 and 12 below, the R45 and R58 primers, both shifted internally from the MY11 primer binding site,

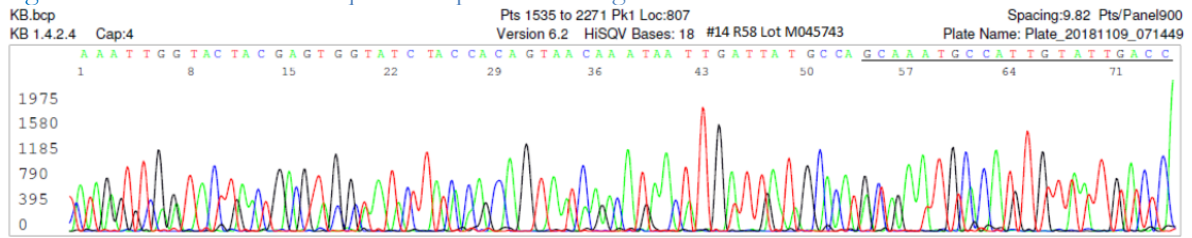
when pairing with the GP6 primer, re-amplified more than one HPV type-specific DNAs which had been prematurely terminated during MY09/MY11 primary PCR due to topological conformational changes at the 3' end of the MY11 primer site.

Figure 11. Natural HPV 18 sequence at primer binding site: GCCAGCAGATACCATTGTTAT



As seen in Figure 11, nested PCR with R45 primer, shifted 10 nucleotides inward compared to the primer used for Figure 10, yielded more than one type of HPV L1 gene DNAs. The computer-generated sequence downstream of the underlined primer in Figure 11 is that of HPV 18 L1 gene. The underlined R45 primer in the electropherogram had two mismatches (in red) compared against the natural HPV 18 DNA primer binding site in this location.

Figure 12. Natural HPV 18 sequence at primer binding site: GCAGATACCATTGTTATGACC



In Figure 12, nested PCR with R58 primer, shifted 6 nucleotides inward compared to the primer used for Figure 10, also yielded more than one type of HPV L1 gene DNAs. The computer-generated sequence downstream of the underlined primer is that of HPV 18 L1 gene. The underlined R58 primer in the electropherogram in this instance also had two mismatches (in red) from the natural HPV 18 DNA primer binding site in this location.

Summarizing, most HPV 18 L1 gene DNA fragments bound to AAHS in Gardasil were in B conformation and readily amplified by the MY09/MY11 degenerate primary PCR primers and by the subsequent GP6/MY11 heminested PCR primers to produce one dominant HPV 18 PCR amplicon as shown in Figure 3, or as one of multiple PCR amplicons as shown in mixed sequences (Figure 5). However, in 1 of 4 tested aliquots from Gardasil9 Lot M045743, the HPV 18 DNA could not be exponentially amplified by the degenerate MY11 primer. The sequencing data presented above showed that replacing the MY11 primer with a non-degenerate primer to re-amplify the

primary PCR products yielded templates for GP6 primer sequencing with 5 different results as follows (the mismatched bases in primers typed in red).

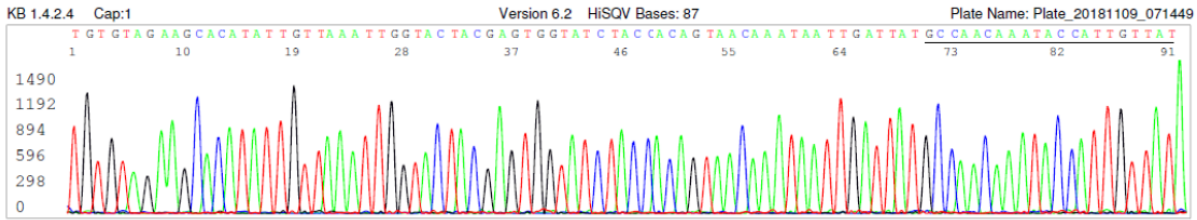
```
AACAAATAATTGATTATGCCAGCAGATACCATTGTTATGACCCTGTGC    HPV18 sequence (ID#EF202155)
                            CCATTGTTATGACCCTGTGC    MY11 No template generated
          GTTACCCCAACAAATGCCATT                     R16  No template generated
AACAAA·····················ACCATTATTGTGTCCCTGAGC    R31 Template generated Figure 10
AACAAA··········GCCAACAAATACCATTGTTAT               R45 Template generated Figure 11
                            GCCATTATTGTGGCCCTGCGC    R52  No template generated
AACAAA·············GCAAATGCCATTGTTATGACC            R58 Template generated Figure 12
```

In the sequence alignment presented above, the highly conserved sequence CCATT for all HPV L1 genes are highlighted yellow in its reference position which is also the ending of the degenerate MY11 primer. PCR primer requires at least 6 nucleotides that match those in the template to initiate a polymerase chain reaction (Ryu, Choi, & Lee, 2000). A mismatch at the 3' terminus is usually not tolerated for PCR amplification. The fact that the MY09/MY11 primary PCR products of the HPV 18 L1 DNA segment in this particular sample aliquot was re-amplifiable by primer 31, primer 45 and primer 58, but not by primer MY11 to generate a template for Sanger sequencing indicates that there was a topological conformational change at the MY11 primer binding site of the AAHS-bound HPV 18 L1 gene DNA, rendering a portion of its DNA with the sequence GTTATGACCCTGTGC (which is underlined in the sequence spelled out above) unavailable for template-directed enzymatic DNA synthesis. Moving the PCR primer inward was necessary to provide a stable primer/template duplex to initiate a template-directed enzymatic primer extension.

4.3. In the absence of HPV 45 DNA, primer R45 amplified HPV 18 DNA

When HPV 45 DNA was absent in the mixed genotype MY09/MY11 primary PCR products, the non-degenerate R45 primer could anneal to a segment of HPV 18 L1 gene DNA to generate a template for Sanger sequencing. There are only two mismatched nucleotides between the R45

Figure 13. Natural HPV 18 sequence at primer binding site: GCCAGCAGATACCATTGTTAT



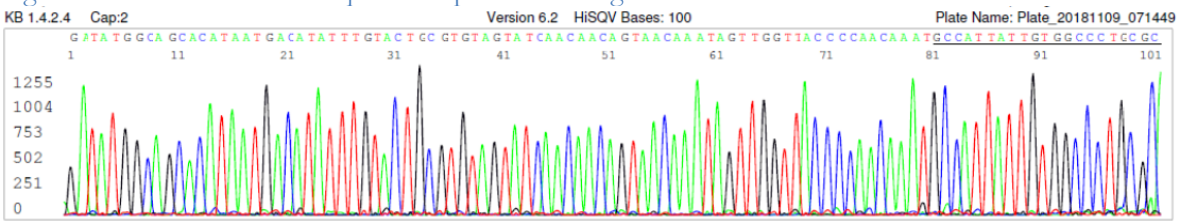
sequence and the natural HPV 18 L1 gene sequence at the primer binding site as shown in Figure 13. There the HPV 18 DNA in a mixed genotype MY09/MY11 with primary PCR products was amplified by a non-degenerate primer R45 (underlined in the electropherogram of Figure 13).

4.4. In the absence of HPV 52 DNA, primer R52 amplified HPV 16 DNA

When HPV 52 DNA was absent in the mixed genotype MY09/MY11 primary PCR products, the non-degenerate R52 primer could anneal to a segment of HPV 16 L1 gene DNA to generate a

template for Sanger sequencing. There is only one mismatched nucleotide (typed in red) between the R52 sequence and the natural HPV 16 L1 gene sequence at the primer binding site as seen in Figure 14. There, only HPV 16 DNA (underlined) in a pool of initial mixed genotype MY09/MY11 amplicons, which were the primary PCR products, was re-amplified by a non-degenerate primer R52 (as underlined in Figure 14).[4]

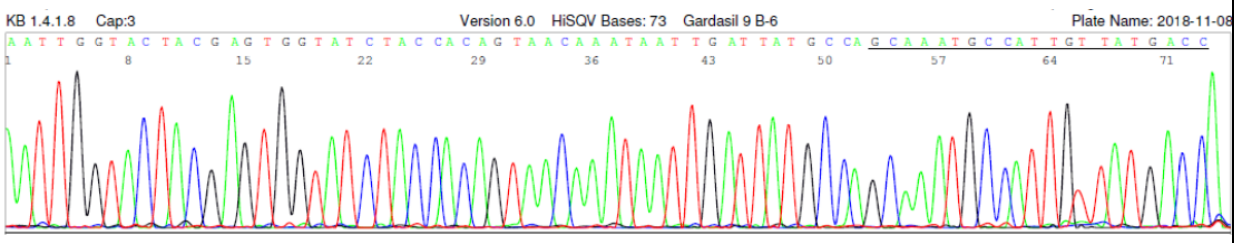
Figure 14. Natural HPV 16 sequence at primer binding site: GCCATTATTGTGGCCCTGTGC



4.5. In the absence of HPV 58 DNA, primer R58 amplified HPV 18 DNA

When HPV 58 DNA was absent in the mixed genotype MY09/MY11 primary PCR products, the non-degenerate R58 primer was used to anneal to a segment of HPV 18 L1 gene DNA to generate a template for Sanger sequencing. There are only two mismatched nucleotides (shown in red in Figure 15) between the R58 sequence and the natural HPV 18 L1 gene sequence at the primer binding site. As seen in Figure 15, the HPV 18 DNA in a mixed genotype MY09/MY11 primary PCR products was amplified by a non-degenerate primer R58 (underlined).

Figure 15. Natural HPV 18 sequence at primer binding site: GCAGATACCATTGTTATGACC



[4] [Author's added note to this version:] This means that there was more than one HPV genotype in the sample being tested. I used a non-degenerate primer specifically designed for HPV 52, in an attempt to amplify an HPV 52 sequence. However, there was no HPV 52 DNA in the sample. Although there were multiple HPV genotypes in the sample, mixed together, only one of them was HPV 16, and only the HPV 16 DNA was amplified in Figure 14.

Discussion

1. HPV L1 gene DNA bound to AAHS in Gardasil9

As advised by the FDA, Gardasil contains recombinant HPV L1-specific DNA fragments. These HPV DNA fragments are not contaminants (FDA, 2011). The current study based on testing 5 Gardasil9 samples and a previous report based on testing 16 Gardasil4 samples (Lee, 2012) confirm that both Gardasil4 and Gradasil9 contain type-specific HPV L1 gene DNA fragments. Since these DNA fragments were found to be in the water-insoluble AAHS particles which were proteinase K-resistant and the DNA remained bound to the proteinase-digested particles after exhaustive washings in TE buffer with detergent Tween 20, the HPV DNA detected must be bound to AAHS via ligand exchange. If so, it can work as a potent adjuvant in Gardasil9 as the phospholipids bound to AAHS in creation of a potent adjuvant for the recombinant hepatitis B vaccine, Recombivax HB® (Egan, Belfast, Giménez, Sitrin, & Mancinelli, 2009). Among the officially listed ingredients of Gardasil9, including the VLPs, AAHS, sodium chloride, L-histidine, polysorbate 80, sodium borate, yeast protein and water for injection (Merck & Co., Inc., 2019), AAHS is the only water-insoluable, proteinase-resistant component.

2. Most HPV L1 gene DNA fragments bound to AAHS are in non-B conformations

Multi-valent Gardasil vaccines are produced by separate fermentation. The purified and reassembled VLPs of each HPV type are adsorbed on AAHS before the monovalent bulk adsorbed products are combined (EMEA, 2006; Merck & Co., Inc., 2019). As recombinant HPV L1 gene DNA fragments are not contaminants, they are not targets for removal as are other contaminants during vaccine manufacturing. Therefore, 9 type-specific HPV L1 gene DNAs are expected to be present in the 9-valent vaccine Gardasil9. However, as demonstrated in the current study, routine MY09/MY11 degenerate primer PCR amplification only generated amplicons of HPV 18, 11, 16 and 6 for sequencing validation in tests of 5 samples of Gardasil9. As in Gardasil4 (Lee, 2012), HPV 18 and HPV 11 L1 gene DNAs in Gardasil9 are most commonly detected, suggesting that these two types of HPV DNA are more likely in B conformation when bound to the AAHS particles. However, as illustrated in Figures 10-12, even HPV 18 DNA can undergo topological conformational change which may interfere with template-directed enzmatic DNA synthesis during PCR amplfication. Successful generation of one single HPV DNA amplicon by PCR as the template for Sanger sequencing does not exclude the possibility that there may be other genotype-specific HPV DNAs also present in any given sample. Previous studies on Gardasil4 samples showed that the AAHS-bound HPV 16 and HPV 6 genotype-specific L1 gene DNAs could not be amplified by MY09/MY11 degenerate PCR primers (Lee, 2012; Lee, 2013; Lee, 2014). The current study on Gardasil9 samples shows that using non-degenerate primer nested PCRs and shifting the primer binding sites inwards could amplify some of the AAHS-bound HPV 16 and HPV 6 type-specific L1 gene DNAs in Gardasil9 which had been replicated by the MY09 degenerate primer as linear PCR amplification products. The failure to detect any type-specific L1 gene DNA of HPV 31, 33, 45, 52 and 58 suggests that all 5 of these specific DNAs may be in non-B conformations. Alternatively, all the L1 gene DNA fragments of the these 5 HPV genotypes in the 4 tested lots of Gardasil9 may have been removed as "contaminants" during the manufacturing process.

3. Topological conformational change of HPV DNA bound to AAHS is genotype-dependent

In all tested aliquots of 5 Gardasil9 samples from 4 vaccine lots, HPV 18 and/or HPV 11 L1 gene DNA fragments can be amplified by the MY09/MY11 degenerate PCR primers, as reported previously on Gardasil4 (Lee, 2012). Only rarely, as shown in Figures 10-12, HPV 18 L1 gene DNA in a fraction of the Gardasil9 shows a topological conformational change. In contrast, the HPV 16 L1 gene DNA fragments were not exponentially amplifiable by the MY09/MY11 degenerate primers, and require non-degenerate primers with a 3'end extension or primers targeting another segment of L1 gene for PCR amplification as reported previously on Gardasil4 (Lee, 2013; Lee, 2014). In the current study, a non-degenerate primer shifted 15 nucleotides inward (R16) from the MY11 binding site generated an HPV 16 nested PCR amplicon for Sanger sequencing validation (Figure 7). An HPV 16 amplicon was also generated when an extra "G" nucleotide was added to the 3' end of the MY 11 primer (R52), as shown in Figure 14. These results suggest that topological conformational change occurred in the HPV 16 MY11 primer binding site 5 nucleotides upstream of the 3' terminus because at least a 6-base matched sequence at 3' end of the primer is needed for template-directed primer extension in enzymatic DNA synthesis (Ryu, Choi, & Lee, 2000). Apparently, when the phosphate backbone of the HPV DNA binds the AAHS, the HPV 16 L1 gene DNA in Gardasil is more prone to topolotical conformational change than the HPV 18 L1 gene DNA at this location.

4. PCR amplification of HPV DNA by primer with a mismatch at 3' terminus

In the absence of a fully matched complementary target, the primer designed to amplify a segment of HPV 16 L1 gene DNA (R16) can initiate a PCR to amplify a segment of HPV 6 DNA (Figure 8) or a segment of HPV 11 DNA (Figure 9) even though there is a single base mismatch at the 3' terminus of a 21-nucleotide primer. A highly processive DNA polymerase can "by-pass" one single terminal nucleotide mismatch in template-directed enzymatic DNA synthesis, a phenomenon which was previously observed and reported when a non-degenerate GP6 primer was used to amplify a segment of HPV 52 DNA (Hong, Lee, Ge & Zhou, 2013).

5. HPV L1 gene DNA as a TLR 9 agonist in Gardasil vaccination

Based on animal and *in vitro* studies of the HPV vaccine Cervarix, aluminum hydroxide makes little contribution to the early innate response stimulated by AS04 and there is no evidence that aluminum hydroxide acts synergistically with MPL to enhance the magnitude of cytokine production or to enhance the infiltration of APCs in the draining lymph nodes 24 hours after injection. Neither does aluminum hydroxide alter substantially the type of cytokines and recruited cells induced by MPL. Both AS04 and MPL, but not aluminum salt alone, can induce TNF-α secretion in monocytes. It is MPL which plays the crucial role in AS04 as a TLR 4 agonist for the stimulation of an innate immune response in Cervarix vaccination (Didierlaurent et al., 2009).

AAHS, also a derivative of aluminum hydroxide, was first used officially as an adjuvant in RECOMBIVAX HB® Hepatitis B Vaccine (Recombinant) in the 1980s (Merck & Co., Inc., 2018). The effect of the adjuvant in the latter vaccine depends on replacing some of the hydroxyl groups of its parent chemical, aluminum hydroxide, with inorganic phosphates by ligand exchange (Egan,

Belfast, Giménez, Sitrin, & Mancinelli, 2009) so that the phospholipid moiety of the viral surface antigen (Gavilanes, Gonzalez-Ros & Peterson, 1982) can bind to the cationic aluminum loosely to serve as a TLR 4 agonist in vaccination (Wong-Baeza et al., 2015), similar to MPL bound to aluminum hydroxide in AS04, in boosting antibody production. For optimum immune response, AAHS needs a pre-made TLR 4 agonist which happens to be the phospholipid part of the viral surface antigen (Gavilanes, Gonzalez-Ros & Peterson, 1982) to fulfill its extraordinary adjuvant effects in RECOMBIVAX HB® vaccination. In other words, AAHS needs a pre-made, ready-to-use TLR agonist to perform its expected potent adjuvant function in a vaccine. However, the re-assembled HPV L1 protein VLPs do not provide a phospholipid. The PCR/sequencing results presented above and the data previously reported (Lee, 2012) indicate that the HPV L1 gene DNA fragments are the only known TLR 9 agonist in Gardasil vaccination as MPL is in Cervarix vaccination. The sequencing data presented in this report suggest that most of the HPV DNAs bound to AAHS in Gardasil are in non-B conformations which can function as long-acting TLR 9 agonists in vaccination because DNA bound to minerals and colloidal particles in non-B conformations are known to resist DNase degradation (Cai, Huang & Zhang, 2006).

TLR 9 is one of the intracellular TLRs situated in the membrane of the endolysosomal compartments of APCs. It samples the content of these compartments for the presence of dsDNA agonists. It is hypothesized that humans developed intracellular TLRs during a long history of vertebrate evolution, principally specialized in viral recognition (Barreiro et al., 2009). Now, TLR 9 serves as an innate immune sensor for viral, bacterial, fungal and protozoan DNA and is also activated by synthetic oligodeoxyribonucleotide (ODN) with a phosphorothioate backbone and an unmethylated CpG motif (Brencicova & Diebold, 2013). Natural TLR 9 agonists are the various kinds of dsDNA with a phosphodiester and 2' deoxyribose backbone, like those found in bacterial and viral genomes or in self-DNA when the latter is delivered to the endolysosomal compartments of the host's dendritic cells (Brencicova & Diebold, 2013), for example as aluminum salt/DNA complexes (Marichal et al., 2011; McKee et al., 2013). Until recently the prevailing paradigm was that TLR 9 recognized unmethylated CpG motifs, which are abundant in bacterial DNA but relatively scarce in mammalian DNA (Krieg et al., 1995). However, it is known now that the dependence on CpG motifs for TLR 9 activation is restricted to synthetic phosphorothioate oligodeoxynucleotides (PS-ODNs), and that natural phosphodiester oligodeoxynucleotides (PD-ODNs) bind and activate TLR 9 via the 2' deoxyribose backbone in a sequence-independent manner (Li, Berke & Modis, 2012).

The resulting immune responses to TLR 9 activation include induction of pro-inflammatory and Th1 cytokines (for example, IL-6, IL-1, TNFα, IFNγ and IL-12). In particular, IL-12 and Type I IFNs induced by pDCs via TLR 9 induce strong Th1 type immunity and CTL cytotoxicity. Stimulating endosomal TLRs is particularly effective at promoting the generation of CTL responses capable of eliminating viral pathogens and cancer (Dowling & Mansell, 2016). A recent human case report demonstrated that complete regression of a widespread cutaneous malignant tumor was achieved after combined systemic and direct intratumoral injection of Gardasil9 (Nichols et al., 2018), suggesting that this vaccine may have therapeutic utility for squamous cell carcinomas which cannot be surgically excised. The only plausible immunological mechanism by which Gardasil9 exerts its therapeutic activity against widespread cancer is through its TLR 9 agonists.

6. Any TLR 9 agonist is a double-edged sword

Foreign nucleic acids have been known to be *in vivo* active molecules for more than 50 years (Isaacs, & Rotem, 1963). In the past 10 years, experimental research has been directed towards using synthetic CpG rich oligonucleotides with phosphorothioate backbone as a TLR 9 agonist to stimulate the immune system for possible cancer treatment (Vollmer, & Krieg, 2009) and triplex oligonucleotides, a form of non-B DNA, have been used for targeted mutagenesis (Chin, & Glazer, 2009). It is technically challenging to introduce foreign DNA into the target cells in animal experiments because free natural DNAs after being injected into the animal are quickly degraded by various nucleases in the tissue fluids and are excreted through the kidneys. In contrast, synthetic CpG rich oligonucleotides with a phosphorothioate backbone are highly resistant to degradation by nucleases (Stein, Subasinghe, Shinozuka, & Cohen, 1988). In addition, phosphorothioate oligonucleotides are significantly more hydrophobic than their natural phosphodiester, oxygen-containing counterparts and as a result pass the cell membranes more readily to their intracellular sites of action, *i.e.* the endolysosomal compartments (Juliano, Ming, & Nakagawa, 2012). To introduce natural foreign DNA as a TLR 9 agonist without a phosphorothioate backbone into the target cells of a mammalian host, nanoparticles are usually needed as the DNA carriers, for example in the formulation of DNA vaccines (Poecheim et al., 2015). In Gardasil vaccination, the nanoparticles of AAHS serve as the DNA carriers to bring the HPV L1 gene DNA fragments as TLR 9 agonists into the immune cells. Gardasil has been shown to contain metal nanoparticles in the range of 3-60 nm in size.[5] The metallic elemental compositions of these nanoparticles are CaAlSi, AlSi, SiMgFe, Al,Fe, AlCuFe, FeSiAl, BiBaS, Ti, and TiAlSi as demonstrated by Field Emission Gun Environmental Electron Scanning Microscope equipped with the X-ray microprobe of an Energy Dispersive Spectroscope (Gatti, & Montanari, 2016). All these metal elements, most of which co-exist with aluminum in the AAHS adjuvant, can be in cationic form and bind the phosphate backbone of HPV DNA fragments in the vaccine products, turning the DNA molecules into non-B conformations which may then serve as non-biodegradable long-acting TLR 9 agonists. The aluminum-laden inflammatory cells with activated TLR 9 can enter the lymphatic system, travel throughout the body, cross the blood-brain barrier and merge into the microglial cell population in the brain (Mold, Umar, King, & Exley, 2018). Disorders due to adjuvant-activated TLRs in the form of autoimmune inflammatory reactions in various organs following vaccination have been referred to as 'the adjuvant diseases' (Israeli, Agmon-Levin, Blank, & Shoenfeld, 2009).

The fate of the non-B HPV L1 gene DNA fragments bound to AAHS nanoparticles in the immune cells is totally unknown. Intracellular foreign DNA may have unpredictable and unknown ways to alter the sequences and conformations of the genomic DNA of the host cells (Milot et al., 1992; Doerfler et al., 1997; Würtele, Little, & Chartrand, 2003; Lechardeur, Verkman, & Lukacs, 2005; Bergen, Park, Horner, & Pun, 2008). In addition to being a highly effective long-acting adjuvant in maintaining a sustained high level of anti-HPV L1 protein antibodies and causing autoimmune adjuvant diseases in certain genetically and physically predisposed vaccinees, these intracellular HPV

[5] Editor's Note: The redlined measure showing nanometers (nm) corrects the typographical error of micrometers (μm) in the prior version published on July 15, 2020 in *IJVTPR 1*(1), 75-97.

L1 gene DNA in non-B conformations may also induce a mutagenic and genomic instability effect with far-reaching consequences (Bacolla, & Wells, 2009; Zhao, Bacolla, Wang, & Vasquez, 2010).

Conclusions

HPV DNA fragments bound to AAHS are part of the essential ingredients of Gardasil4 and Gardasil9, and are mostly in non-B conformations. These HPV DNA fragments may function collectively as potent long-acting TLR 9 agonists in augmenting the induction of pro-inflammatory and Th1 cytokines to enhance the immune responses to HPV vaccination. Since the immunological effects of the AAHS-bound HPV DNA have not been studied by the vaccine industry and the HPV vaccine Gardasil9 with its TLR 9 agonists may have immunotherapeutic effects on cancers, further research on the immunological roles of the HPV DNA fragments bound to AAHS as an active ingredient in Gardasil is warranted.

Potential Conflicts of Interest

S. H. Lee is the director of Milford Molecular Diagnostics Laboratory, a CLIA-certified commercial laboratory specialized in developing DNA sequencing-based diagnostic tests implementable in community hospital laboratories.

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Buying and Selling with the "Mark of the Beast"

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> [16] And he causeth all, both small and great, rich and poor, free and bond, to receive a mark in their right hand, or in their foreheads: [17] And that no man might buy or sell, save he that had the mark, or the name of the beast, or the number of his name. [18] Here is wisdom. Let him that hath understanding count the number of the beast: for it is the number of a man; and his number is Six hundred threescore and six. (Revelation 13:16-18, *King Janes Version of the Bible*)

ABSTRACT

The document appended here — an "International Application Published Under the Patent Cooperation Treaty (PCT)" — falls among the many "unprecedented" events witnessed during COVID-19. It was filed June 20, 2019 with the World Intellectual Property Organization (WIPO) under the PCT and its international publication date was March 26, 2020. Some have already scorned the idea that the document appended as the final entry to *IJVTPR* 1*(2)* is at least a partial fulfillment of an apocalyptic prophecy concerning the age-old conflict between good and evil. But it is as real and as relevant to COVID-19 as the vaccines that were envisioned and practically in production before SARS-CoV-2 infected the first human in Wuhan. Now, with the burden of the economic shut-down settling upon the people of the planet, the prospect of pandemics more deadly than COVID-19, has made many fearful enough to forfeit their free will to technocrats ready to manage them like robots. The patent applied for is about the buying and selling of "human necessities". It would authorize the patent holder to use every manner of surveillance of an individual's bodily states, actions, and thoughts to make the buying and selling of necessary products and services, contingent upon certain "work", such as receiving or refusing to receive certain vaccines or meeting other requirements set by the patent holder.

Keywords: *contact tracing, cryptocurrency control, forfeiture of rights, global surveillance, new global monetary system, robotic management, technocratic control*

Global Surveillance Inside Your Body and Mind

The international patent application re-produced here — filed June 20, 2019 and published internationally on March 26, 2020 — is designated as WO 2020/060606. The international publication date came just 10 days after my university, along with virtually all those across the USA

and Canada, and schools at all levels, were locked down. Most of the faculty, yours truly included, were required to resort to 100% online, remote instruction to complete the courses then underway. The hope was that things would change in the following fall of 2020 but that was not to be. Now, as we look toward the start of a New Year, if anything, in many places governments have tightened some of the former restrictions.

The WIPO Publication Number

The abbreviation "WO" is shortened from "WIPO" which is an abbreviation of "World Intellectual Property Organization". The four digits that follow specify the year of the , according to our current calendar which is, of course, 2020 AD — that is 2,020 years "after divinity" which is marked by the historical birth of Jesus Christ. The next six digits, in the case at hand, 060606, can range from 000000 to 999999, under the Patent Cooperation Treaty.

In that context, the patent application reproduced following this article was filed, not by Bill Gates-the-monopolist (Anon 2020g), but by Microsoft, the former company of the erstwhile richest man in the world, Bill Gates, now better known, by many at least, as a benefactor/philanthropist committed to helping save the world from diseases and from over-population with vaccines than as a monopolist (Gates 2010; Oller et al. 2017, 2020). More recently, in 2018 Mark Zuckerberg was called to account defending Facebook against charges of monopolistic power similar to those brought against Bill Gates twenty years earlier (Serwer 2018). In the meantime, however, Gates has distanced himself increasingly from the industry that enabled him, Zuckerberg, Bezos, and Musk to join the elite plutocracy of the uber-rich and powerful. And yet, the convolluted interconnections between vaccines and bioweapons linking the global military-industrial-pharmaceutical complex to the technocrats aiming to create a whole new system of currency invests them with an almost unimagined level of enforcement power. Whoever controls the planned surveillance, setting the rules for buying and selling of human necessities, can dictate actions at the level of individual human beings as never before. Here are a few features of the planned power of control under the systems of surveillance to be associated with the cryptocurrency system.

The Practice of the Invention and Its Surveillance Devices

The general and far-reaching patent application for the technocratic control of future buying and selling, contingent upon "proof of work" — that would be the verified performance of whatever required bodily actions the patent holder may choose to set for the use of the cryptocurrency — is not limited to the particular devices, methods, concepts, etc., described in the patent itself. The authors of the application say:

> These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is understood that other embodiments may be utilized and that structural, logical, and electrical changes may be made without departing from the spirit and scope of the invention. The following detailed description is therefore not to be taken in a limiting sense, and the scope fo the invention is defined only by the appended claims and equivalents thereof. (lines 21-26)

Conspiracy Theory or Fact?

In an evident attempt to "get out ahead" of the apocalyptic nature of the declared intentions in the patent application, a number of "grassroots" blogs (Evon 2020) have sprung up that make out the number "060606" in the published patent application to be a meaningless coincidence: here are a few quotes — but see Sharyl Attkisson 2008 for her evidence that plutocrats have ample power to generate countless "grassroots" blogs and news reports virtually blanketing the planet in what she described as manufactured "astroturf" — suggesting that the patent in focus is completely benign:

> The number WO2020060606A1 contains three "6's" but is obviously not the same as "666". This patent focuses on tracking body activity via wearable technology, such as a smart watch, and makes no mention of implanted microchips. ("Does Microsoft Own Patent '666' About Implanting Microchips in People?" at www.snopes.com by Evon 2020)
>
> Conspiracy theories surrounding Bill Gates have been a huge part of the news cycle, especially amidst coronavirus fears. One such theory stems from a TED video featuring the former richest man in America explaining his fears of an imminent pandemic and how ill-equipped we are to handle it. . . . Citing his connection to Microsoft, and the multitude of conspiracy theories purporting that a group of tech leaders aim to create a global surveillance network that subjugates civilians by planting tracking chips inside them, parts of the internet are convinced a recent patent filing proves these ideas to be true. ("Microsoft, Bill Gates, Patent 666, & Microchipping Humans Explained", Davis 2020)
>
> There is an online war going on between the mainstream media and conspiracy theorist after Microsoft filed "Patent 060606" which the latter have called the mark of the beast from the bible that is going to be implanted in people. ("BILL GATES' 'PATENT 666' SCARES THE WORLD: Is It True Microsoft Has Acquired Intellectual Property To Microchip Humans with the Mark of the Beast in Form of COVID-19 Vaccine…" Grapevine News 2020)
>
> **The origins and allure of the microchip conspiracy theory:** Rich and famous people are frequently the center of conspiracy theories. The fact that Gates is a vocal proponent of public health initiatives long scrutinized by conspiratorial-minded groups only makes him an even riper target. It is possible that the conspiracy theory partly originated from a December study published by a team at the Massachusetts Institute of Technology. The study was funded, in part, by the Bill & Melinda Gates Foundation. The team had developed an "approach to encode medical history on a patient" by including a small amount of dye with a vaccine. The dye, which would be invisible to the naked eye but observable through a specialized cellphone app using infrared light, would keep a record of a child's vaccines. The technique may be especially useful in developing countries, where record keeping is often more difficult. ("Fact check: Bill Gates is not planning to microchip the world through a COVID-19 vaccine", Brown and Weise 2020)

So goes the narrative absolving the authors of the patent application of any potential thought of taking freedoms away from ordinary citizens. Much less would Bill Gates, or the authors of the patent application, even consider injecting micro-chip tracking devices into the human body. Well, yeah, there was that dye. Oh, yes, and according to the researchers at MIT it did contain "quantum dots" (McHugh et al. 2019) — "near-infrared light-emitting microparticles . . . invisible to the eye but [that] can be imaged using modified smartphones". The purpose? "By codelivering a vaccine, the pattern of particles in the skin could serve as an on-person vaccination record" (Trafton 2019 referring to McHugh et al. 2019).

Absolution from Vaccine Related Microchip Inventions

According to proponents of what might be called "the Gates absolution narrative", including unsurprisingly Bill Gates himself (see his denials in Brown and Weise 2020), freeing him from any

association with the Devil, not only is the number "060606" a meaningless coincidence, but it is absurd (I almost said "patently absurd") to suppose that this particular patent application would cover anything like an impanted microchip device to track the history of a person's bodily actions, much less their thoughts and intentions. Gates is quoted by Brown and Weise (2020) as having said in a phone call to him on June 3, 2020, "I've never been involved [*sic* in] any sort of microchip-type thing. . . . It's almost hard to deny this stuff because it's so stupid or strange." Even stranger still — though it may help us understand why it is hard for Bill Gates to deny the "micochip-type thing" — is the fact that the primary supporter of the "quantum dot" research at MIT, listed in the report by McHugh et al. (2019) on the Web of Science site, was the Bill & Melinda Gates Foundation.

Free Will as the Ultimate Issue[6]

Skeptics, atheists, evolutionists of most stripes, and even some "Judeo Christian theologians", but no Muslims that I know of, have contended that the human mind and even the exalted language capacity is purely a product of chance. They argue that the pinnacle of intelligence in the biosphere — though enigmatic as suggested in the title by Berwick and Chomsky, *Why Only Us? Language and Evolution* (2017a) — must be the product of a long and lucky series of accidents that just happened to occur. My late friend, John Omdahl, a geneticist and biochemist of some note, joined me in taking the contrary view (Oller and Omdahl 1994), that chance cannot produce even the simplest form of a true representation as known to any ordinary human being with the language capacity. Chance cannot generate the kind of complexity required. It cannot even get started, much less can it progress through the countless transformations required to generate the infinite connectedness of a single true narrative representation (Oller, Scott, and Oller 2018). What is more, it is interesting to me that the muscle systems over which human beings command the greatest degree of free will are those found in the tongue. In fact, the degree of autonomous free will control exhibited in those systems of muscles is only exceeded by our conceptual ability to produce thoughts of our own making, by virtue of our own uniquely human intelligence. We have more freedom of choice to control our words, and our thoughts, than over any other aspect of our lives.

Whereas many of my colleagues, undoubtedly the vast majority, but not all of them by any stretch, suppose as do Davidson and Winey, in this issue of the *IJVTPR*, that chance can generate the whole complexity of the ecological balance required for life and with it also the powers of thought and language that enable us to consider how such a balance could possibly come about. To support the theme pursued by Davidson and Winey, following the mainstream approach, but with creative adjustments such as their ideas about nonezymatic hydrogen atom transfer assisted by quantum entanglements, they suppose that chance associations can arrange themselves in the kind of balanced dynamism necessary for the existence of the entire present biosphere. Frankly, I believe the mistake in that theory is something like the illusion of an impossible event like the diver who leaps backward from the pool onto the diving board. It is easy enough for a reasonably fit person to tuck and roll from a handstand into a sommersault followed by a return to a standing position. At my advanced age, I believe I can still do that maneuver. However, the best gymnast in the world cannot quite

[6] For an impassioned and intelligible discussion of the freedom that is at stake during COVID-19 and with the coming vaccines, see Robert F. Kennedy, Jr.'s "International Message for Freedom and Hope", at https://www.youtube.com/watch?v=NpMWDCX1yMI (Children's Health Defense 2020).

execute the reverse. It can easily be produced on film, or in the imagination, but not in the real world.

Running the Film Backwards

The evolutionists are not mistaken about change, nor even about it being ubiquitous. Everyone believes in that kind of change because we all see it happening around us all the time. Evolution in that sense is a fact. Things change. We get older. But that kind of observable change, a *bona fide* kind of evolution, trends not toward increasing orderliness and meaning, but toward the antithesis of order (Oller 2010). It invariably trends toward what Shannon called "entropy" — and which Jaynes (1957a, 1957b) proved is necessarily irreversibly increasing in all actual experimental settings and whose proofs generalize to all biological settings (Oller 2014a). In the case of what I have termed "biosemiotic entropy", we find a universal propensity for cumulative injuries to progress to disorder engendering increasing vulnerability to disease, and progressing inevitably to the catastrophic failure of organ systems that we call death. It is not a desirable outcome, nor can it be construed as the source of life.

We can run a film backwards, but time and chance do not flow in that direction, and we cannot make them do so. Time and chance guarantee progress in the other direction — all efforts to produce by chance something that might legitimately be called "negative" entropy are, according to long-standing proofs, doomed to fail. The general error of evolutionists who try to make out disease and death as the basis for the most exalted forms and manifestations of life, is like that of some hounds my father and his brothers used to hunt with: the dogs would sometimes take the "backtrack". In any case, the trail of historical change is not always marked clearly for its direction. The result is that the dogs, going the wrong way, are actually getting farther and farther from their objective. That is pretty much the story for modern theories of origins grounded in Darwin's efforts to use observed change to explain the requisite order that enabled him to observe anything at all — namely his God given language capacity and the freedom to believe and represent his discoveries according to his imaginations. Berwick and Chomsky, I believe, are following the backtrail as well. Their difficulty, like that of the hounds that went the wrong way, is that the deeper they go into the backtrack, the older is the trail, and the more difficult it is to discover and correct their error.

Who Needs Free Will Anyway?

Bill Gates acts as if he believes that human beings are really just robots in the first place, so what could be wrong with treating them as if free will were something of no consequence? Why bother with it? If cryptocurrency robs individuals of choice, so what? In a world totally created and governed, in the final analysis by chance, is freedom of will anything more than an illusion? According to the strictest forms of evolutionary thought, free will either does not exist at all or is a meaningless accident underlining the irony of existence in general. I am reminded here of Christopher Hitchens who is famously quoted as saying: "Yes I have free will; I have no choice but to have it" (Live by Quotes 2020). Apparently, he didn't value it much and neither does Bill Gates. In any event, the international patent application at issue here would take so much freedom from the individuals in the grip of the cryptocurrency as to turn them into virtual robots.

The rub is that, on the side of the patent promoters, freedom of movement and the sanctity of your own skin is in question. If the cryptocurrency plan laid out is implemented as planned according to

those "skilled in the art" — if the plan for a global cryptocurrency is realized — the freedom to make ordinary choices about what to put inside your own body, what to eat and drink, whether to take a medicine or not, whether to go to the doctor or not, and so forth, is about to be taken over by the unseen managers of the cryptocurrency.

With that in mind, the people I am talking to and hearing from, refer to the planned surveillance system described in the patent reproduced here as "diabolical". They see it as having apocalyptic, biblical portent. While claiming to free the human population from the threat of the future plagues being made possible by the deliberate manipulation of deadly pathogens in laboratories ostensibly aiming to prevent what is already happening in COVID-19, the authors of the patent application seek to implement a new global system of commerce that will place all its users almost completely under the control of the plutocrats who own the patent and the invention of the cryptocurrency system. Freedom of will on the part of the ordinary persons using that cryptocurrency will be forfeited, gone with the wind.

Good News for Those Who Refuse the Mark of the Beast

The patent holder for the "embodiment (including firmware, resident software, micro-code, etc.)" but not limited to any of those as "will be understood by those of skill in the art that there are other embodiments that are equivalent to the described embodiments . . . [but] the invention is not to be limited by the described embodiments, but only by the scope of the appended claims" (Abramson et al. 2020) will evidently seek to force the constraints of the new cryptocurrency on everyone. Those who do not conform will be prevented from participating in the buying and selling necessary to normal human existence. So what is a person to do?

Government

With respect to government policy, James Lyons-Weiler has made some excellent recommendations in this issue of the *IJVTPR*.

Banking

With respect to banking and an alternative to the proposed new order with a global cryptocurrency, Catherine Austin Fitts has expressed some thoughts worth consideration in her 47 minute interview with Greg Hunter at https://robinwestenra.blogspot.com/2020/12/catherine-austin-fitts-on-great-reset.html (Hunter 2020).

The Merciful God of Abraham

In my own personal view, there is no hope for any of us apart from the message of the cross: I believe there is a just Creator who is so serious about preserving our freedom of will that he incurred in the body of his only begotten son, the judgment of all our bad choices so we might live by freely trusting in Jesus Christ. I agree with Gottfried Wilhelm Leibniz (1686) who wrote in the 37th principle of his *Discourse on Metaphysics* that

> Jesus Christ . . . alone has shown how much God loves us, and how exactly he has provided for everything that affects us:
>
> • that, caring for sparrows, he will not neglect the rational creatures who are infinitely dearer to him;
>
> • that all the hairs of our heads are counted;
>
> • that the sky and the earth will perish before any change in the word of God or in any of the conditions for our salvation;
>
> • that God cares more about the least of thinking souls than about the whole machine of the world;
>
> • that we need not fear those who can destroy bodies but could not harm souls, because God alone can make souls happy or unhappy;
>
> • that the souls of the just are, in his hands, safe from all the revolutions of the universe, since nothing can act on them except God alone;
>
> • that none of our actions is forgotten;
>
> • that everything is taken into account, even an idle remark or a well used spoonful of water; and, finally,
>
> • that all must result in the greatest well-being for good people, that the righteous shall be like suns, and that we have never experienced or conceived anything giving us a fore-taste of the happiness that God prepares for those who love him.

As I close this issue of the *IJVTPR* during the few days that remain between Christmas 2020 and the first day of 2021, I believe I am seeing change (evolution) on a scale that is more far-reaching and is occurring at a pace never before experienced. It seems we are moving toward the climax of history: in such a context as COVID-19 and at such a time as this, the words recorded by the prophet Daniel as spoken to him by the Angel of the Lord are surely being fulfilled: "But thou, O Daniel, shut up the words, and seal the book, even to the time of the end: many shall run to and fro, and knowledge shall be increased" (Daniel 12:4, *King James Version* of the Bible). There is — in my own personal view, speaking as just one among the billions on the planet, each of us still exercising the freedom to believe as we choose — just one souce of Good News. In my view, during this post-normal age of COVID-19, that source is the Lord Jesus Christ.

This Christmas I believe I heard a more complete exposition than was ever possible before the recent events including COVID-19 were in view. That presentation was the central paprt of the Christmas program and sermon delivered by Joseph Prince and co-workers at Creation Life Church in Singapore and Grace Revolution Church in Dallas, Texas and is available online in its entirety (https://sermons-online.org/joseph-prince/live/christmas-experience-2020). With that in view, I believe our freedom of will is so important and inviolable from the viewpoint of God Almighty in his love for us, that the cross of Christ was the only possible way, and as Leibniz argued in his *Discourse*, it was the one perfect way to provide salvation to us. I love that passage in Psalm 85:10 where it says, "Mercy and truth are met together, righteousness and peace have kissed each other". It all happened at the cross where the judgment owed to us fell on Jesus Christ and him alone. Grace is offered freely to us to receive or not as we choose. For my part I say: What a Savior! Halelujah!

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