Surviving COVID-19
Variables of Immune Response

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HDE 117/ENT 117

Longevity

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SUMMARY

In this paper, I analyze autopsy reports conducted on deceased COVID-19 patients and supply a breakdown of the body's immune response. The purpose of this paper is to provide a more generalized synopsis of how the body is affected by the virus from the onset of infection to the escalating factors that contribute to cause of death. COVID-19 and SARS-CoV-2 are referenced countless times throughout this paper, but they should not be used interchangeably. The name of the pathogenic virus is "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2), and the name of the illness is called COVID-19 and is the common usage in forms of discussion. This paper only scratches the surface of the virus's complexity and its effects upon the body and societies around the world.

INTRODUCTION

On December 31, 2019, the first case of the novel coronavirus was reported in Wuhan, China (Fan, J. et al., 2020). The first case of the virus reported in the United States was January 22, 2020 (Stokes EK. et al., 2020). Within 22 days, SARS-CoV-2 had traveled across the Pacific in less than a month to invisibly wreak havoc upon countries so woefully unprepared. Within a manner of months COVID-19 has managed to bring some of the most powerful countries in the world to heel. Economies and health care systems across the world continue to be devastated by an adversary only 60 to 140 nanometers in diameter (Wiersinga. et al., 2020). On February 11th, 2020, the International Committee on Taxonomy of Viruses (ICTV) formally identified the virus as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). On March 11, 2020 the World Health Organization classified COVID-19 as a worldwide pandemic and global health crisis (WHO, 2020). The most recent data from the CDC has confirmed that the U.S. has over 4 million cases. This is significantly higher case count than reported in some of the most populated countries in the world such as Brazil and India (Johns Hopkins University, 2020). Health care systems across the nation and around the world are overwhelmed by the infected. Many perish due to either a lack of resources or accurate and efficient testing.

SARS-CoV-2 VIRAL PATHOGENESIS

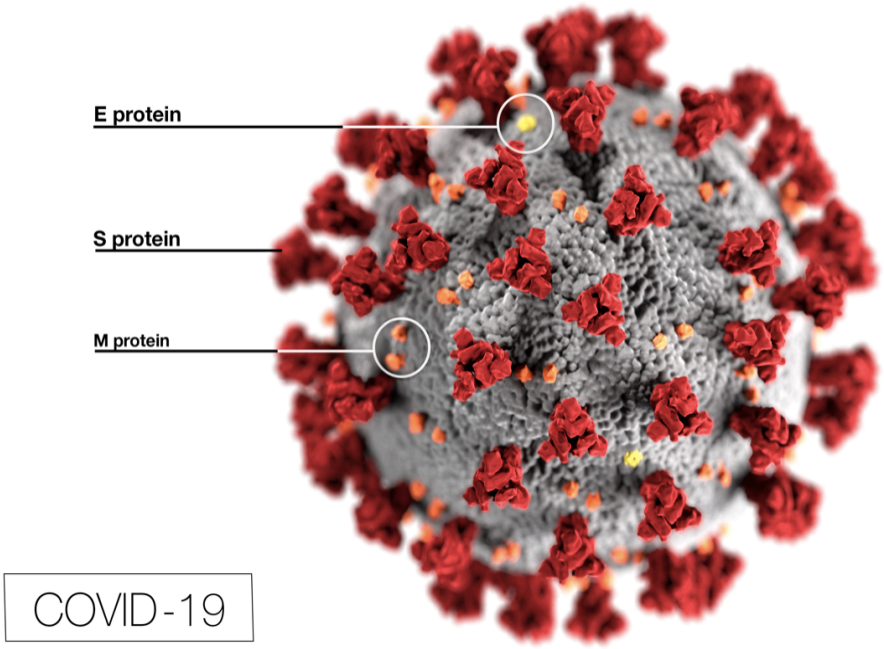
Innate Immunity

Our innate immune system is composed of barrier tissues and cells specialized for defense against pathogens (HMX, 2020). Barrier tissues are the first line of defense, and inside barrier tissues reside sentinel cells, which are capable of consistently recognizing repeated exposure to pathogen associated molecular patterns (PAMPs). The sentinel cells release pro-inflammatory mediators like cytokines, chemokines or histamines and cause the blood vessels to circulate, inviting more immune cells from the surrounding tissue into the blood stream (HMX, 2020). Cells such as neutrophils or monocytes differentiate into macrophages and migrate from the blood stream and phagocytose (eat) the pathogens. Neutrophils will undergo programmed cell death referred to as apoptosis. Macrophages will continue to phagocytose the rest of the pathogens and restore homeostasis by consuming the dead neutrophils (HMX, 2020).

Infection occurs when these viral pathogens in respiratory droplets from a sneeze or a cough enter a person's mouth, nose, or eyes and attach to the ACE-2 receptors in the nose, throat and especially the lungs. Like any virus, SARS-CoV-2 cannot replicate on its own and instead it hijacks the body's own cellular machinery. The virus inserts its own genetic information into the host cell to produce more copies of itself until the cell bursts and dies, spreading more of the virus around the body to infect more cells (Drexler, 2011).

Infection of the host cell consists of the following 5 steps: attachment, penetration, biosynthesis, maturation, and release. Once a virus binds to host receptors (attachment), it enters host cells via endocytosis or membrane fusion (penetration). Once the viral contents are released inside the host cells, viral RNA are transported by protein molecules in the host cell's cytoplasm and travels into the nucleus for replication via the nuclear pore complex (NPC). Viral mRNA then makes viral proteins (biosynthesis). Lastly, novel viral particles are made (maturation) and released (Yuki. et. al., 2020). This innate immune response is not as effective against SARS-CoV-2 due to the various proteins displayed in Figure 1, an ultrastructural morphology rendering, provided by the Centers for Disease Control and Prevention (CDC) Image Library on February 10th, (CDC, 2020).

Figure 1: This innate immune response is not as effective against SARS-CoV-2 due to the various proteins displayed in Figure 1, an ultrastructural morphology rendering, provided



by the Centers for Disease Control and Prevention (CDC) Image Library on February 10th, (CDC, 2020). The SARS-CoV-2 virus contains "M (membrane), S (spike), E (envelope), and N (nucleocapsid)" which envelope the virion and act as a defensive shield (Yazdanpanah, F. et al., 2020). The S or Spike viral surface protein which consists of two subunits (S_1 and S_2), bind to the host cell Angiotensin converting enzyme 2 (ACE2) receptors (Yuki. et. al., 2020). The primary role of ACE2 is the breakdown of the angiotensin II (ANG II) protein into molecules that neutralize the harmful effects of angiotensin II. ANG II is responsible for increased inflammation and death of alveolar cells in the lungs which reduces oxygen uptake. When the S (spike) protein of SARS-CoV-2

binds to the ACE2 receptors they inhibit the ACE2 from doing its job of regulating the ANG II allowing the ANG II to freely damage tissue in the lungs. These ACE2 receptors are naturally present on the surface of the lung's epithelial cells and other organs throughout the body, but the virus's S protein use these receptors to penetrate the cell membrane and replicate inside host cells. The nucleocapsid (N protein) is another viral surface protein of SARS-CoV-2, which inhibits interferons (IFN1 and IFN-β) responsible for cytokine production (Lee & Ashkar, 2018). But if the signals for regulating pro-inflammatory response are disrupted by the pathogen's surface proteins, the innate immune response becomes hyperactive and self-destructive. A malfunctioning innate immune response also compromises an adequate adaptive immune response (Yazdanpanah, F. et al., 2020).

Adaptive Immunity

B Cell Response

The innate immune response is not particularly equipped to combat pathogens that are especially complex and vicious because the innate immune response is non-specific and will attack anything they identify as an invader. The adaptive immune response can target pathogens more precisely and powerfully by using proteins called antibodies produced by B-cell lymphocytes that bind to antigens on the surface of pathogens (HMX, 2020). Adaptive immunity can more efficiently handle foreign pathogens like a virus because antibodies can see through the debris of proteins and dead cells left by the cytokine storm. Antibodies uniquely bind to antigens acting as a beacon for the adaptive immune response to home in on the invading pathogen (HMX, 2020). More importantly adaptive immunity has memory and learns how to become more effective by retaining its response to pathogens so that they can be even quicker at eliminating them after repeated exposure (HMX, 2020). Widespread pandemics like COVID-19 occur because of a lack of protective antibodies in populations that have never been exposed or vaccinated against the specificity of SARS-CoV-2 (HMX, 2020). There are 4 ways that antibodies attack pathogens: neutralization, complement fixation, opsonization, and antibody dependent cellular cytotoxicity. During neutralization, antibodies immediately bind to the surface antigens of a pathogen preventing pathogen entry and infection of host cells. Complement fixation is when antibodies are responsible for inviting complement proteins to bind to the antigens of the pathogen. This process coats the pathogen in attack proteins that can either initiate the complement cascade leading to cell lysis, the breakdown of the cell, or it can induce the third stage, opsonization. During opsonization, proteins called opsonins bind to the invading pathogen, acting as markers for phagocytotic cells like Macrophages to identify and consume the pathogen. Lastly, Antibody dependent cellular cytotoxicity (ADCC) is the

process by which antibodies recognize the antigen of a pathogen and signal for Natural Killer cells (NK cells) to release cytotoxic molecules which kill off the virally infected cell (HMX, 2020).

T Cell Response

T cell lymphocytes form the basis of cellular immunity. Consequently, they are more effective than innate immune or B cell response, at targeting intracellular pathogens like viruses (HMX 2020). Shiv Pillai of Harvard Medical School states that antibodies see everything. Antibodies are easily distracted by clouds of virus or viral proteins, so it's up to the blind T cell lymphocytes to ignore the surrounding virus and eliminate the infected host cell at the source. T cells develop in the bone marrow and mature in the thymus. As naïve T cells circulate the lymph nodes and spleen, they express T Cell Receptors (TCR) that recognize cell surface peptides (antigens) attached to MHC molecules on the surface of a specific pathogen (HMX 2020). The dendritic cells work to activate the adaptive immune response by ingesting viral proteins and turning them into cell surface peptides that bind to MHC molecules, forming peptide-MHC complexes. The TCR of naïve T cells recognize the peptide-MHC complexes and activate the T cell. For T cells to become active, they also need to bind to proteins from the dendritic cell via co-simulation. They then undergo clonal expansion and differentiate into effector T cells (HMX 2020). Effector T cells are also referred to as cytotoxic T lymphocytes (CTLs) and travel through the body to hunt down peptide-MHC presenting pathogens and killing the infected cells by releasing cytotoxic molecules (HMX 2020).

Angiotensin-converting enzyme 2 (ACE2) is the primary receptor of SARS-CoV-2 and it attaches to the type II alveolar cells. Type II alveolar cells are responsible for secreting surfactant and maintaining homeostasis in the alveoli, the gas exchange hubs of the lungs. The adaptive immune response is stimulated by the recognition of pathogen-associated molecular patterns (PAMPs). Within 1-2 weeks after infection the B cells produce antibodies while T cells simultaneously increase pro-inflammatory cytotoxic molecules in a forceful attempt to eliminate the virus (Yuki. et al., 2020). The uptick in Interleukin cytokines abbreviated as IL-1, IL-6, IL-8, etc. do not kill the virus. Instead, they cause harm to the body and weaken the body's overall defenses against the virus because they flood the body with pro-inflammatory substances which "chronically increase the stimulation of T cells, resulting in a cytokine storm and T cell exhaustion" (Yazdanpanah, F. et al., 2020). T cell exhaustion not only means that the virus is overwhelming the body's antibodies but is also draining the strength out of the T cells ability to eliminate the virus at the source of infected host cells. SARS-CoV-2 is a "High-grade chronic viral infection because it decreases the responsiveness of T cells leading to a decreased effector function and lower proliferative capacity" (Yazdanpanah, F. et al., 2020). T cell exhaustion is also

linked to an increase in inhibitory receptors that can initiate apoptosis in T cells destroying them and their co-receptors which further suppress the T cells, as well as B cells and NK cells, all of which are white blood cells (lymphocytes). Thus, explaining the general lymphopenia (the lack of lymphocytes) observed in severe COVID-19 cases and the increased number of cytokines (Yazdanpanah, F. et al., 2020).

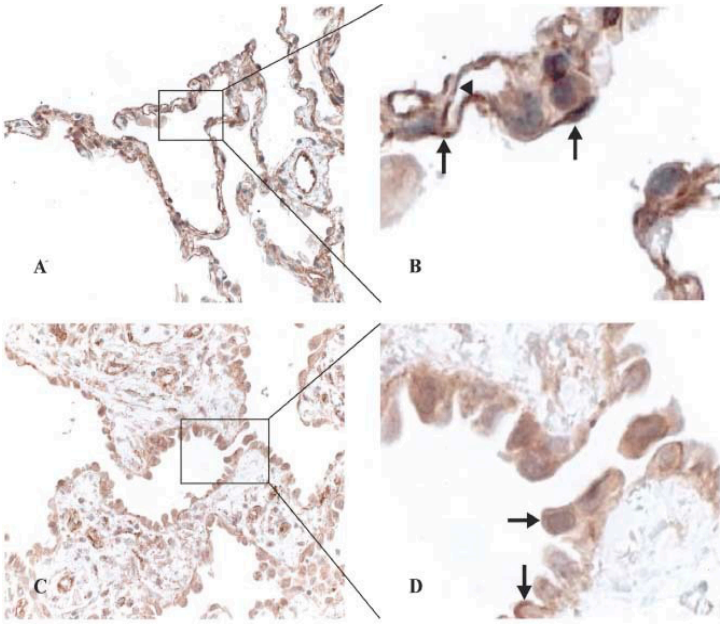
Our innate and adaptive immune system has evolved twice in our known history, but this begs the question, if our immune response has evolved, why has its efficacy not evolved as well? Why does the immune system fail to differentiate between attacks that are destructive to the virus and attacks that are self-destructive? Viral entry and attachment to ACE2 receptors and the vicious cycle of both innate and adaptive immune responses mounting an intense attack by secreting pro-inflammatory substances that invite more lymphocytes to try and kill the virus which release more cytokines and chemokines (Scully. et al., 2020). The downregulation of the ACE2 enzyme results in a cascade of chemical reactions that lead to further inflammation and destruction of cells, weakening and damaging the body's own immune response.

PATHOLOGIES OF A PANDEMIC

COVID-19 Autopsies

Figure 2 shows healthy ACE2 receptors located in the type II pneumocytes in the alveoli of the lungs.

Figure 2



Once the SARS-CoV-2 attaches to alveolar type II cells it propagates within the cells. The majority of viral particles cause apoptosis releasing more self-replicating pulmonary toxins. This results in diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells that lead to pulmonary fibrosis (scaring in the lungs) as seen in Figure 3, a complete contrast to the healthy lung cells from Figure 2 (Mason, 2020).

Figure 3

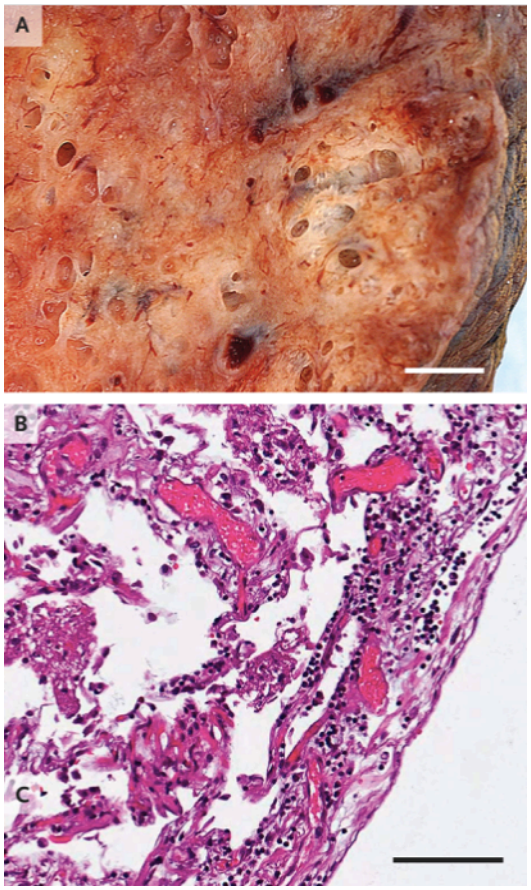


Figure 3 shows "Lymphocytic Inflammation in a lung from a patient who died from Covid-19...Panel A (the scale bar corresponds to 1 cm). The histopathological examination, shown in Panel B, revealed interstitial and perivascular predominantly lymphocytic pneumonia with multifocal endothelialitis (hematoxylin–eosin staining; the scale bar corresponds to 200 μm)" (Ackermann et al., 2020). As the virus ravages the body some patients rapidly deteriorate and develop severe inflammation and clotting in the lungs with the development of Acute Respiratory Destress (ARDS). ARDS develops in about 5% of COVID-19 patients, and of all the infected the mortality rate remains around 1 to 2% (Wadman, 2020). Autopsies are beginning to reveal that rather than a singular cause of

death a pack of devils seem to be responsible for higher mortality rates in patients that develop critical cases of COVID-19.

The fallout from the hyperactive immune response disrupts regular oxygen diffusion from the alveoli into the capillaries and then to the rest of the body. This commonly leaves, fluid and dead cells, resulting in pneumonia where patients experience symptoms such as coughing, fever and rapid or shallow breathing (Wadman, 2020). If oxygen levels in the blood continue to drop, patients rely on breathing assistance by a ventilator to forcefully push oxygen into damaged lungs "riddled with white opacities where black space—air—should be" (Wadman, 2020). Presentation of opacities in the lungs indicate the development of pneumonia into ARDS which was found in the autopsy of a 77-year-old man with a history of comorbidities including hypertension and the removal of his spleen (splenectomy) (Barton. et al., 2020). The decedent presented chills and an intermittent fever but no cough for 6 days. On March 20, 2020, emergency medical services responded to a call, stating that the decedent was experiencing weakness, fever, and shortness of breath. In route to the hospital the decedent went into cardiac arrest and died shortly after reaching the hospital (Barton. et al., 2020). A postmortem nasopharyngeal swab was administered and came back positive for SARS-CoV-2. Therefore, medical examiners would require specialized PPE and a high-containment room to perform the autopsy since the decedent is still infectious.

Figure 4

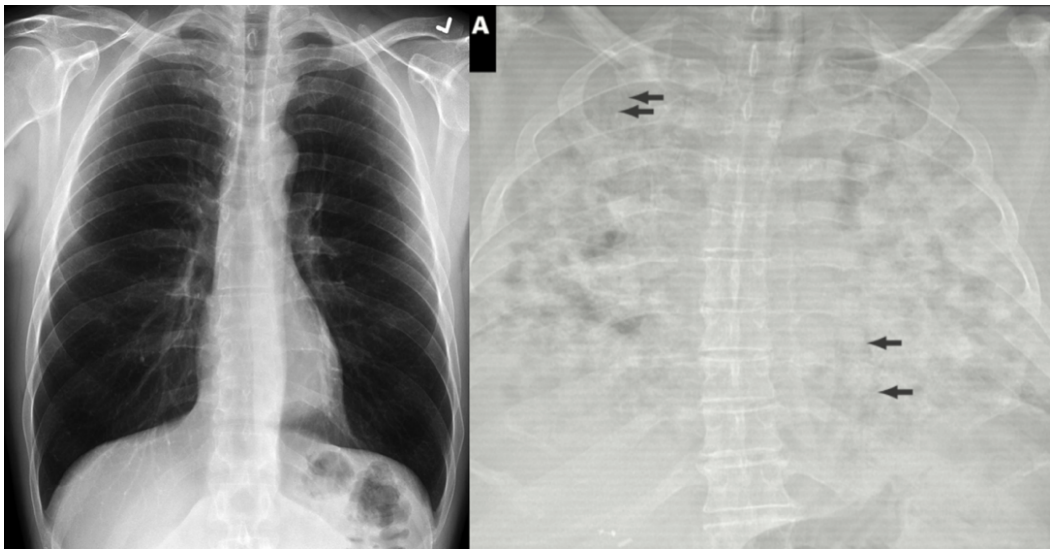
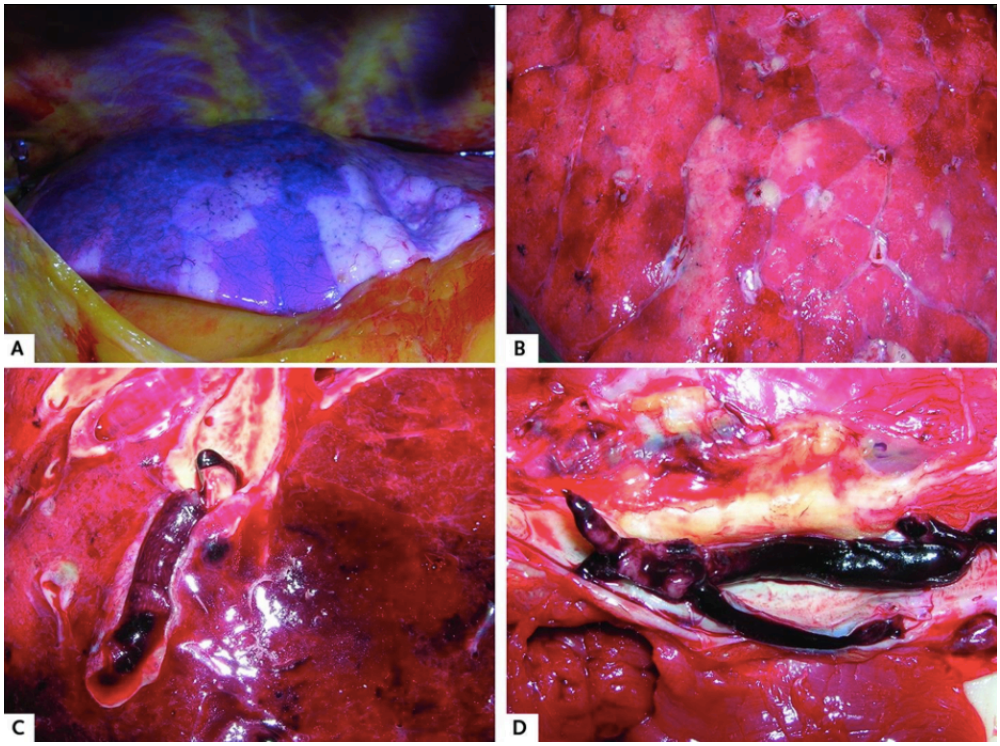


Figure 4 shows the Postmortem radiography comparison between a normal chest x-ray (left) vs. Case 1 decedent 77-year-old male chest x-ray (right), which medical examiners

refer to as a "complete whiteout" of the lungs. This indicates reduced air flow whereas the normal CT of healthy lungs have a black background representing the transparency of free and unrestricted airflow. "Diffuse, dense bilateral airspace consolidations (complete "whiteout"). Multiple air bronchograms are present (arrows). The autopsy in this case showed diffuse alveolar damage" (Barton. et al., 2020). This was the case in the decedent, as it is in most cases of severe COVID-19 where "the greatest severity of CT findings visible around day 10 after the symptom onset. Acute respiratory distress syndrome is the most common indication for transferring patients with COVID-19 to the ICU" (Salehi. et al., 2020).

ARDS in connection to SARS-CoV-2 was first documented in Wuhan, Hubei, China in December 2019 with over 90,000 deaths associated with organ dysfunction, particularly progressive respiratory failure and the formation of blood clots (coagulopathy) resulting in the highest mortality rates (Magro et al., 2020). In an additional autopsy from Hamburg Germany conducted on the first 12 documented consecutive cases of COVID-19 related deaths revealed that not only was there diffuse alveolar damage in 8 out of the 12 patients but there was also a high rate of clotting resulting in death. 75% of patients that died were males within an age range of 52 to 87 years and 7 out of 12 patients autopsied (58%) presented venous thromboembolism, [see Figure 5]. A pulmonary embolism was the direct cause of death in 4 of the deceased (Wichmann et al., 2020).

Figure 5



The formation of clots results in pulmonary vasoconstriction or the constriction of arteries and halting of blood delivery to the arteries and capillaries in the lungs. Blood cannot travel to the lungs so oxygen levels to drop. As a result, a cytokine storm from our hyperactive immune system, occurs, destroying the alveolus and the endothelium and causing clots to form. Smaller clots come together and form a fatal giant blood clot, or the clots can break apart and travel to other parts of the body, causing a blockage and inadequate blood supply to organs or other parts of the body (Magro et al., 2020). If the blood supply to fingers, toes, etc. is cut off by a clot, it is referred to as ischemia and often results in amputation of digits and appendages once the flesh begins to die (Magro et al., 2020).

When SARS-CoV-2 enter the alveolar cells in the lungs via the ACE2 receptors, they can directly attack organs and indirectly cause damage to organs by triggering a hyperactive immune response (cytokine storm) and when the virus or viral particles trigger a cytokine storm it causes further inflammation of the lungs resulting in plummeting oxygen levels and the formation of blood clots in the arteries (Arterial thrombosis). ACE2 receptors are also located in the "oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain" as well as the testes (Hamming et al., 2004). Those that survive the virus are marked by unknown neurological and even psychological lingering effects, and potential reinfection. COVID-19 autopsies show a pressing need for more rapid testing. If people are waiting days or weeks for tests and results to become available, they could have long since become critically ill and died, thus defeating the purpose of testing. Infected individuals could also be asymptomatic—unknowingly spreading the virus to other people and more vulnerable individuals.

Discussion

The variability of this virus is unprecedented, and its virulence is likened to the 1918 influenza pandemic. Droves of studies are published every day and communication between scientists around the world drive the discovery and discussion of therapies, vaccines, and standards of protective practices people should follow to stop the spread of the virus. This is a virus that efficiently exploits weaknesses not only within our innate and adaptive immune systems across sex, age, race and ethnicity, but it also exploits weaknesses within our societies.

The etymological origins of Pandemic are rooted in pandēmos, which is Greek for 'all' (pan)+ 'people' (demos). When simplified, pandemic literally means "all people" but the priorities of leadership across the world reveal that *not all people* suffer the burden of this pandemic equally. With regard to the United States, this quote from the Atlantic's article "Why Some People Get Sicker Than Others" is sufficient; "the damage of disease

and a global pandemic is not a mystery. Often, it's a matter of what societies choose to tolerate. America has empty hotels while people sleep in parking lots. Food is destroyed everyday while people go hungry. Americans are forced to endure the physiological stresses of financial catastrophe while corporations are bailed out. With the coronavirus, we do not have vulnerable populations so much as we have vulnerabilities as a population. Our immune system is not strong" (Hamblin, 2020).

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