

Public Health | Review

COVID-19 and the Unraveling of Experimental Medicine - Part I

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Introduction

Two years into the pandemic, with the number of deaths over five million globally and vaccine-resistant variants continuing to multiply, scientists are in the midst of the most dangerous and ill-conceived experiment in the history of medicine. Pinning their hopes on the success of new mRNA-based vaccines that stretch all conventional notions of a vaccine, and which were hastily released without adequate efficacy and safety trials, they seek to take the wind out of the sails of a full-blown pandemic without fully understanding either the means by which individuals develop resistance to the coronavirus or by which herd immunity is attained.

Throughout the pandemic the vaccine has dominated conversation based on its potential to stimulate the synthesis and release of antibodies that bind to viral antigens and neutralize their effects. Hundreds if not thousands of scientific articles document their role in the COVID-19 syndrome and yet the relationship between such antibodies and long-term immunity remains tenuous at best. The fact that the viral syndrome resolves in a significant number of individuals without antibody production or that they disappear from the serum over a matter of weeks to months raises serious questions as to their role in conferral of long-term immunity.

Equally, the appearance of vaccine-resistant viral strains or breakthrough infection in recently vaccinated individuals draws a clear line between protection and immunity. While

the vaccine appears to temporarily boost resistance, it cannot be said to confer long-term immunity. We are thus led to distinguish between antibody-induced protection and natural immunity. This raises questions as to whether mass vaccination will be sufficient to bring closure to the pandemic.

Given such facts it is perplexing that the vaccine issue has taken center stage at the expense of a wider scientific and social dialogue regarding potential solutions. Many physicians have expressed concerns over the efficacy and safety of the vaccine. Numerous others have advocated for prophylaxis and early intervention with cheap and widely available medicines like hydroxychloroquine or ivermectin, both of which have support in the medical literature. The mantra 'evidence-based medicine' has been bandied about in the medical community for decades but it is clear that the current approach to the pandemic is much less about facts and more about perspective.

In this three-part series on the SARS-CoV-19 catastrophe, the first pandemic of the new millennium, we examine the complex interactions between the biological and social domains and how they have so far been impacted by current practices. The outcome of such adjudications will likely influence how future pandemics are approached.

In the present article we examine the dynamic nature of pandemics and raise questions concerning the nature of herd immunity and individual susceptibility. Equally we point to various pandemic-related phenomena that

researchers have described but cannot satisfactorily explain based on current understanding of immune function. The pandemic has laid bare the cracks and flaws of contemporary medical theory and practice. We advance a dynamic energy-based functional framework to explain various clinical and pathologic phenomena related to COVID-19 infection.

In the second segment we examine broadly implemented approaches intended to limit transmission and spread of the viral vector such as lockdowns, social distancing and masks as well as current hospital-based treatments and examine the role they play in viral-mediated dynamics. We examine the new vaccines and the impact they have had on the evolution of the pandemic. Finally, in the third installment we examine the path not taken, the overlooked home-based treatments that provide a highly effective alternative to institutionally-sponsored modalities which, when implemented in a timely fashion, dramatically reduce pandemic-related morbidity and mortality.

Into the Abyss

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), began in early 2020 and has persisted for nearly 2 years. Like earlier pandemics it has recurred in a series of waves which have been ascribed to seasonal influences and to the appearance of new viral subtypes but, unlike the influenza pandemics, which typically lasted for 18–24 months, the COVID-19 contagion seems destined to persist well into the 2–3 year range if not longer [1].

All pandemics—a term used to indicate global spread of disease—share common features: they usually begin abruptly and unexpectedly, often in the winter months, frequently in Asia, and continue in a waxing and waning pattern until they spontaneously self-extinguish, which is attributed the rise of herd immunity, a widespread state of resistance to the infectious agent. It is presently unknown what percentage of recovered persons in a population is necessary to attain such a refractory state.

Whether the infectious agent is influenza or SARS-CoV-19 all pandemics are driven by the same dynamics: spontaneous emergence of an antigenically novel viral strain or subtype possessing an optimal blend of transmissibility (infectivity) and virulence (pathogenicity) that spreads and interacts within a population of susceptible individuals. Both attributes in tandem are essential: many viral strains freely disseminate but lack pathogenicity; others, like the original SARS-CoV in 2004, are highly virulent but lack the capacity for rapid spread. Since the overwhelming majority of infected individuals develop immunity to the virus it is axiomatic that virulence is inversely related to resistance and only represents a heightened state of susceptibility [2,3].

Viral replication occurs only in susceptible cells. Infection begins with attachment of a viral particle to the cell membrane during which its antigenic surface element, the so-called spike protein, binds to specific receptors. SARS-CoV-2 attaches to the ACE-2 receptor, the same entry vehicle employed by the original SARS virus. A recent study found that the affinity of SARS-CoV-2 for the ACE-2 receptor is 10–20 times that of the original SARS which accounts for its heightened infectivity. Upon attachment the virus enters the cell, sheds its coat releasing its RNA cargo, and initiates the replication process. Newly formed RNA strands self-assemble and acquire envelopes and spikes from the cytoplasm and/or cell membrane. Within hours after infecting the cell a single viral particle can generate hundreds of virions which emerge from the cell and seek out susceptible cells to infect [4–6].

Either during or between pandemics, the virus continues to interact with its hosts which become an eternal reservoir. It evolves and morphs on the basis of spontaneous mutations in its glycoprotein surface coat which consequently alter its infectivity or virulence. This ongoing, largely invisible zoonotic experiment is called antigenic drift. While most spontaneous viral mutations end as failed experiments every so often a new subtype emerges that possesses enhanced transmissibility or virulence thus forming the basis for new waves within a pandemic or epidemics in between pandemics. Epidemics usually remain geographically and temporally confined due to a wall of pre-existing immunity among individuals within the population [7, 8].

Confounding pandemic-related issues is the black box problem, the sheer impermeability of the pandemic to statistical analysis. The actual number of cases and mortality rates can never be known and any tally is only a crude estimate. Asymptomatic infections, under-reporting of mild viral syndromes, inaccessibility to organized healthcare, and the disinclination of many to report the illness obscure the true magnitude of COVID-19 in the population. This leads to underestimation of prevalence and inability to accurately gauge mortality rate [9–11]. As in earlier influenza pandemics actual infection rates are believed to be at least 3–4 times higher than the reported caseload [12–14].

The dynamically evolving landscape of the pandemic acts as an ever-present destabilizing force that inevitably thwarts ad hoc social measures intended to control viral spread. As the number of cases surges so too does antigenic drift and the potential for emergence of variants with enhanced transmissibility and virulence. Chance mutations in the SARS-CoV-2 spike protein may confer upon it the capacity to evade neutralizing antibodies and gain more easy entry into cells [15–19]. Such new variants are now in circulation. To compound the problem there is uncertainty as to the duration of vaccine-mediated antibody-induced protection [20–22].

Factors described above highlight the impossibility of containment of viral spread. Humans, now a primary reservoir for COVID-19, insidiously transmit the virus. Individuals who do not develop symptoms do not necessarily escape infection and individuals who develop infection shed the virus for variable periods, both before the onset of symptoms and often for weeks afterward [23–26]. This ignores the contribution of animal reservoirs. By the time a local outbreak is recognized, such as the recent omicron variant, it has already been circulating for weeks and in short order other scattered outbreaks are belatedly recognized. Presently in the US the majority of newly reported cases with the omicron variant are in fully vaccinated individuals [27–30].

Broadly applied interventions such as masks, lockdowns and social distancing temporarily alter transmission dynamics, producing flattening of incidence curves, i.e., the number of newly infected individuals in a specified time period, but do not affect resistance or immunity. It is relevant in light of current social measures enacted during the COVID-19 outbreak that such policies were regarded as ineffective during earlier influenza pandemics [31]. By the same token, mass vaccination programs may produce curve flattening by temporarily boosting resistance; breakthrough infections in vaccinated populations, however, are widely recognized suggesting vaccines do not confer long-term immunity [32–35].

As viral mutation rates increase the length of vaccine-induced protection conversely shortens and breakthrough infection rates begin to climb. Under such conditions how does herd immunity gain a foothold in the population [36]? A related issue concerns the problem of ‘leaky’ vaccines: they confer protection but allow continued transmission of the virus and potential emergence of highly virulent strains. Such dynamics are present in other viruses [37–39].

Attempts to control the pandemic amount to a never-ending game of one-upmanship with scientists continually in search of new vaccines that, inevitably, will be rendered ineffective via antigenic drift. Mass vaccination attempts to hit a rapidly-moving target but invariably leads to round after round of booster initiatives nipping at the heels of newly-emergent variants.

Of equal concern regarding such new variants is the phenomenon of reinfection in previously COVID-19 infected individuals. Reports of second and third rounds of infection in previously infected individuals have appeared [40–49]. That individuals successfully overcame a primary infection and were subsequently reinfected points squarely to rapid evolution of the virus. Most reinfections are mild and, if anything, only serve to boost pre-existing immunity. Nonetheless it is further evidence for antigenic drift and raises questions as to what is yet to come.

The silver lining inside the reservoir problem and impossibility of containment: individuals with asymptomatic or mild infections freely disseminate the virus and, ultimately, serve as a primary means by which herd immunity is attained. Given that up to 90% of infected individuals are either asymptomatic or mildly affected it seems only logical to employ this vast pool of individuals in the quest for herd immunity especially since it is going to occur in any event. The silent spreaders—the asymptomatic, mildly affected, and unvaccinated—serve to enhance collective resistance within the viral reservoir.

In Influenza: The Last Great Plague, William Beveridge notes that in the severe influenza pandemics of the 20th century up to 50% of the population never developed manifestations of the disease [50]. Some of this is likely related to asymptomatic and mild cases that were never reported but this factor alone seems unlikely to account for such a large portion of the population. At the time of this writing (12/21) there were 266,504,411 reported COVID-19 cases across the globe which, given a population of 7.8 billion, translates to only about 3.4% of the population. In the US the corresponding figure is 14.6% based on 48,982,584 reported cases out of 333,781,277 people [51]. Why are infection rates this low if SARS-CoV-2 is so transmissible?

One large meta-analysis with over 77,000 subjects examined secondary transmission within households and found an overall secondary infection rate of 16.6% with a range from 15.4–22.2%. Transmission rates were higher in symptomatic versus asymptomatic cases, adult versus children contacts, among spouses than other family members, and in households with one contact versus three or more contacts [52–54].

Such unexpectedly low rates of transmission implicate preexisting innate immunity within broad segments of the population. A recent study found humoral immunity in the form of reactive antibodies to the SARS-CoV-2 spike protein in previously uninfected individuals [55]. Such innate protection is especially prevalent in children and adolescents, a population in which symptom expression is typically either absent or mild. This background of resistance in selected individuals likely forms the basis of herd immunity and it is this innate capacity which must be expressly amplified in the population in order to bring the pandemic to a halt. Given such considerations why would scientists immunize children against COVID-19 infection?

One the most glaring epidemiological features of the COVID-19 pandemic (and of earlier influenza outbreaks) is the problem of differential susceptibility. Why are certain segments of the population so disposed to developing severe disease while others such as children are minimally affected? How does one account for the disproportionate morbidity and mortality among the elderly, males, certain

ethnic groups, and those with pre-existing conditions like obesity, hypertension, diabetes, and chronic conditions such as cardiac and renal disease [56-73]? It is puzzling that this disparity has not raised more eyebrows much less demanded satisfactory explanation for it points unambiguously in a direction that virologists and vaccinologists seem to have overlooked.

In a recent clinical study, we established for the first time in contemporary medical science the existence of a complex electromagnetic field in the human body [74] and in subsequent papers documented the dynamics of an aether-mediated energy field taking origin in the cardiovascular system through the contraction and dilation of the heart [75-77].

During systole electrical currents streaming through cardiac nerves are infused into the heart muscle and blood and, through interaction with iron stores in these tissues, induce generation of a magnetic field and subsequent outward diastolic motion of the cardiac and arterial walls. Such outward movement generates negative intraluminal pressures, i.e., a suction force, which draws blood forward through arteries and veins thus accounting for spiral flow currents seen in these vessels [78-85].

It has been recognized since the 1980s that diastole is the primary and determinant phase of the cardiac cycle [86-88]. This is so because it is the period of active energy infusion into the blood. Impaired outward motion of the heart and arterial walls, known as diastolic dysfunction, is prima facie evidence of diminished energy influx into the blood. Numerous reports link diastolic dysfunction to diverse conditions like obesity, hypertension, diabetes, coronary artery disease, autoimmune disease, chronic heart failure and chronic kidney disease, the very same conditions associated with increased morbidity and mortality rates after COVID-19 infection [89-113]. All these conditions, as well as the COVID-19 syndrome itself, including both symptoms and cellular disturbances, reflect a primary energy deficiency in the blood-borne energy field.

Not only has the pandemic caught science off-guard and unprepared but it has revealed grave deficiencies in current medical theory and practice. The existence of a blood-borne energy field in living bodies was first described by Roman physician Galen around 200 AD and had been accepted as fact by all physicians until it was arbitrarily discarded by experimental scientists in the 18th century. To make matters more complicated, the reigning immune theory, first advanced around the turn of the 20th century, has been unable to account for phenomena commonly associated with COVID-19 infection and scientists are now back-pedaling and waffling. The pandemic has shaken the foundations of cellular and molecular science.

The Antibody Problem

In the years surrounding the turn of the 20th century when modern immune theory took shape, experimental immunology was bitterly divided between two scientific factions, a group of biologically oriented experimentalists at the Pasteur Institute in Paris, under the influence of Jules Bordet, who asserted the primacy of cellular events in the immune response, and a German camp, under the lead of Paul Ehrlich, who forcefully argued for the primacy of antibodies as the determinant mechanism in the expression of immunity.

As immunologist Arthur Silverstein points out in his acclaimed work *A History of Immunology*, the two groups conducted intellectual warfare in the scientific literature seeking to undermine the other's position, in many cases performing the same experiments, and attempting to demonstrate how their own theory was better able to explain results. By the end of the first decade of the 20th century the molecular perspective had gained a decisive edge and the cellular orientation fell into disfavor for the next half-century, a period Silverstein calls the Dark Age of experimental immunology [114].

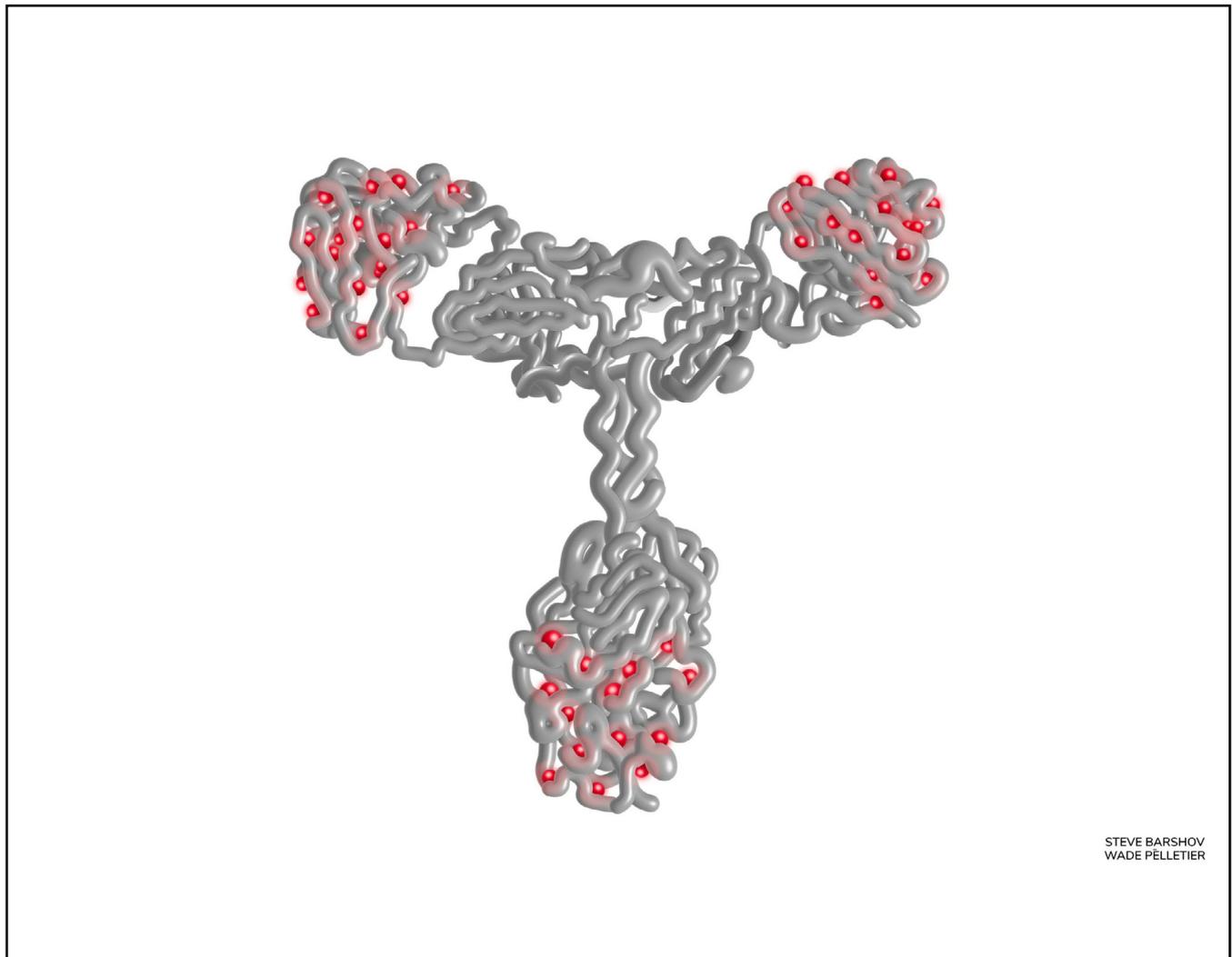
Even within the ascendant molecular camp agreement was far from unanimous. Ehrlich, domineering and dogmatic, one of the early architects of cell receptor theory, argued that the antigen-antibody interaction at the cell surface was based on specific lock-and-key chemical interactions. Over the course of evolution, he claimed, living organisms had acquired an immense antibody repertoire that, during infection, was secreted by immune cells to defend against toxins and bacterial invaders.

By the early 20th century tens of thousands of antigenic substances had been discovered, including many newly synthesized in the laboratory, and various scientists argued that evolution could not have possibly equipped living organisms with a such a vast repertoire of antibodies against an endless array of antigens, some of which had not even been in existence until recently. Researchers like Karl Landsteiner, discoverer of the ABO blood groups, argued against specific lock-and-key chemical interactions and, instead, for a much smaller number of antibodies with overlapping specificities.

Landsteiner asserted that electrochemical forces, not chemical interactions, mediated specific affinity and were the basis of the immune response. Antigen-antibody precipitation reactions were easily explained by colloidal interactions. He and his co-workers found that charged acidic and alkaline colloids not only moved in opposite directions in electrolysis experiments but actively precipitated each other. Interactions were based not on chemical constitution but on physical properties like pH, solubility and temperature. It seems, Landsteiner wrote, 'that this extraordinary type of reaction plays a

particularly large part in living organisms; living substance is mostly made up of colloids' [115]. Landsteiner's claims are now recognized to be correct [116].

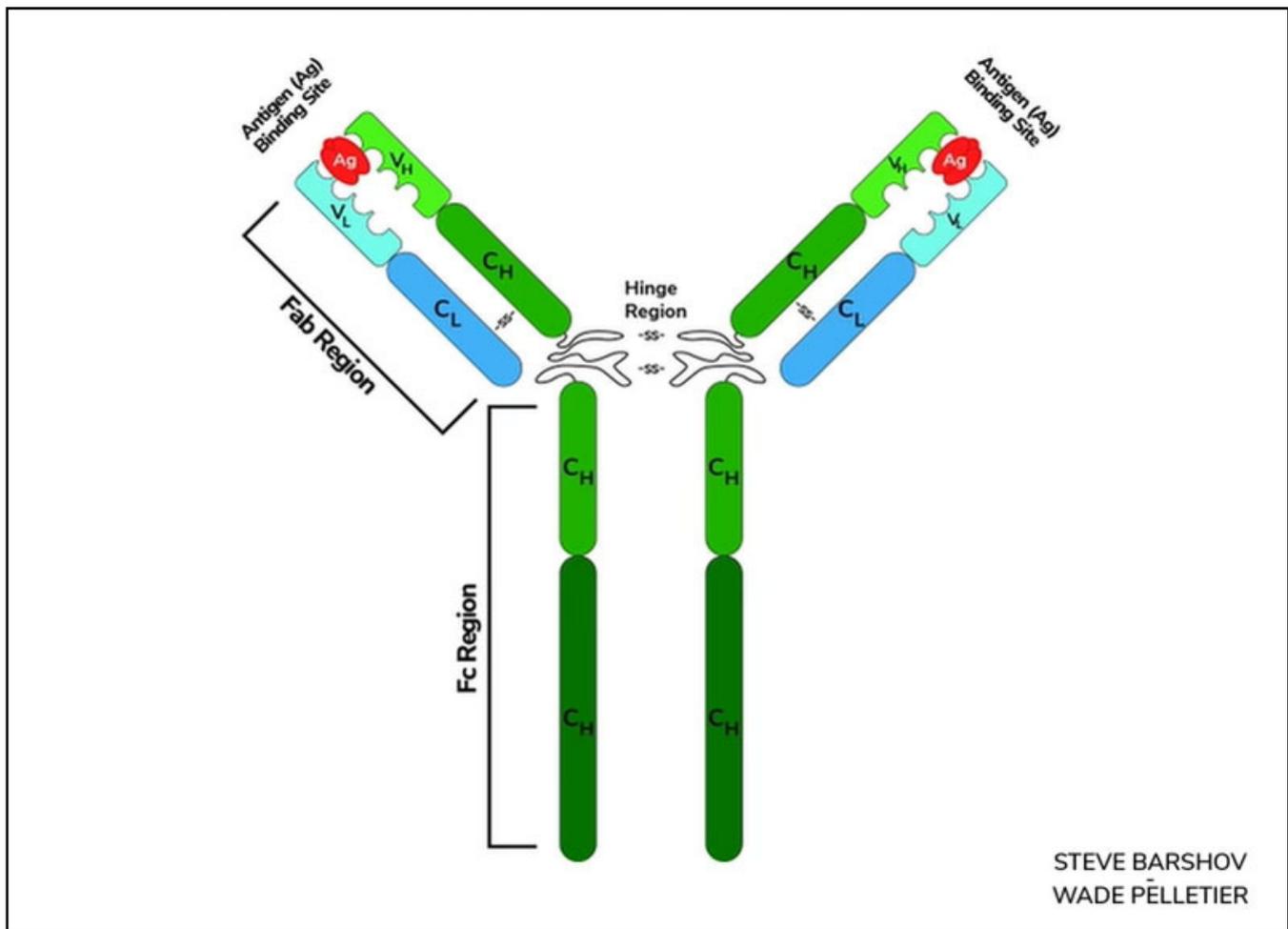
Figure 1. Three-dimensional representation of antibody structure. Red dots indicate binding regions.



The antibody is a Y-shaped protein composed of four polypeptide chains, two elongate heavy chains arranged side-by-side forming the 'Y' and two light chains in the limb regions of the 'Y' in parallel with the heavy chains (Figure 1). Functionally it is divided into two polar regions, one in the branched limbs, the antigen-binding site (Fab), which, as expected, is highly variable in amino acid composition and the other, forming the trunk of the 'Y', the constant region (Fc), possessing highly conserved

amino acid sequences, which binds to immune effector cells and activates various functions including breakdown of the antigen. At the junction of the trunk and limbs of the 'Y' is a highly flexible area, called the hinge region, which allows for maximal three-dimensional (3-D) movement of the trunk and limb regions to enable binding of the antibody to both antigen and immune cells [117-119] (Figure 2).

Figure 2. Depiction of functional antibody regions. Two Fab limbs for antigenic binding. The Fc fragment attaches to immune effector cells. The highly flexible hinge region allows for maximal conformational plasticity.



While the linear structure of the heavy and light chains is formed by covalent chemical bonds, the parallel relationship between the two chain types, as well as the overall 3-D configuration of the antibody, is energetic in nature, a result of ionic attraction/repulsion, van der Waals forces, and hydrogen bonding. The polar configuration of antibodies with binding sites for antigens at one end and cell membrane receptors at the other allow for the formation of complex interactions between antigens and cells in which such complexes undergo complex conformational changes that affect cell function. The higher order structure of proteins as well as flexibility and capacity to undergo conformational change is explained largely by their hydrogen bond networks [120-126].

The ability of proteins to dynamically modify their conformation is called allosterism. In such interactions proteins reorganize their spatial configurations to generate dynamic linkages between widely separated domains. In antigen-antibody interactions such interplay requires energetic coupling both within the protein as well as with the antigen and cell receptor. For decades it was widely believed, based on Ehrlich's lock and key hypothesis, that allostery was mediated through structural analogues on

adjacent proteins, but recent studies indicate it is driven solely by energy dynamics [127-136].

It is now acknowledged that a limited repertoire of antibodies is able to interact with an almost endless array of antigens. This is possible since the determinants of such interactions are commonly shared energetic properties distributed over the protein surfaces both at and away from the binding site. In the hydrophilic regions of the complexes, for example, positively- and negatively-charged sites may be drawn into close apposition while two adjacent negatively-charged sites may repel, the degree of attraction and repulsion determined solely by charge strength and distance. All conformational change is energy dependent [137-150].

By the same token binding of the virus to the cell surface is energy-driven. Studies of the SARS-CoV-2 spike protein describe multiple distinct conformational states with different 3-D receptor-binding domain conformations that confer on its exceptional plasticity and adaptability. This property likely accounts for the rapid emergence of new variants. Viral mutations affecting key regions in the spike protein can alter energy distribution and topography

at the binding site allowing for enhanced entry into the cell. Such mutations, in turn, induce conformational changes in the ACE-2 receptor on the cell surface via fluctuations in the conjoined hydrogen bond network with resultant alterations in rigidity and flexibility throughout the complex [151-156].

Such dynamics explain antibody-dependent enhancement (ADE), recognized earlier in the SARS-CoV and MERS-CoV outbreaks and more recently in the SARS-CoV-2 pandemic. It was observed in certain cases that upon attachment of the Fc antibody region to the virus its ability to enter the cell and replicate was paradoxically enhanced with resultant disease severity. ADE has been attributed to poorly neutralizing or non-neutralizing antibodies, i.e., loss of affinity between antibody and virus. At least five structurally-based mechanisms for ADE have been proposed all involving functional changes at the cell surface [157-165]. Occam's razor, which dictates that the simplest answer is usually correct, would point to conformational changes induced by energy deficiency. Such functional incapacity falls under the general rubric of a protein misfolding disorder or what is also called the intrinsically disordered protein state [166, 167].

The common denominator for the various energy-mediated transformations involved in antigen-antibody interactions lead, in turn, not back to the cell and genome but rather into the interstitial fluid space which channels energy between the vascular and intracellular compartments. In recent decades there has been an explosion of research in the physical sciences using x-ray scattering, NMR spectroscopy, and x-ray crystallography to study protein structure and folding dynamics. All the various methods substantiate the key role played by water in protein-related dynamics [168-177].

To be biologically active proteins, i.e., antigens and antibodies, must acquire a so-called hydration shell consisting of multiple surface layers of water molecules often extending up to 25Å from the protein surface. This fluid layer appears to be a critical determinant not only of 3-D protein structure but the folding process itself. Protein misfolding and the intrinsically disordered protein state are mediated via interactions with water. The hydration shell surrounds hydrophilic domains of most proteins and cell membranes and spontaneously organizes into a complex hexagonal lattice-type arrangement, which researchers liken to a semi-crystalline state. Hydration shell water has physical properties distinct from that of surrounding extracellular water including net negative charge, higher pH and increased density resulting in electrical potentials and current flow. The centrality of colloidal dynamics, first advanced in the early 20th century but ignored by cellular and molecular biologists, is now widely acknowledged [178-182].

There are other compelling reasons beyond the energy equation to question the primacy of antibody-related processes in conferral of immunity. Following COVID-19 infection, antibodies rarely appear in the blood before 12 days and sometimes not for 21 days. In many cases symptoms subside before antibodies even appear. Anti-spike protein IgG antibody levels, on the other hand, wane over weeks to months post-infection and by 3-5 months may be negligible [183-192]. By contrast, studies find antigen-specific memory B-cell levels can remain unchanged for 6 months after infection [193]. Such evidence points away from antibodies and toward cellular dynamics in the establishment of long-term immunity.

These conclusions are substantiated by a recent pandemic-related discovery: a significant portion of the COVID-19 infected population, as confirmed by positive polymerase chain reaction tests, never develop a systemic antibody response. Such 'nonseroconverters' range from a low of 5% in one study to a high of 36% in another; three other studies found no seroconversion rates in the 15-25% range. Nonseroconverters tend to have lower disease severity, more rapid viral clearance and lower blood inflammatory marker levels [194-199]. Findings point to the critical role non-lymphocytic WBC subsets like macrophages and neutrophils play in the early immune response. Other evidence points squarely in the same direction.

Individuals with more severe disease have higher neutralizing antibody levels than asymptomatic or mildly affected cases [200-219]. Hospitalized individuals have neutralizing antibody levels up to 3000-fold higher than less affected or recovered subsets [220-223]. No satisfying explanation has emerged. Another study found obese individuals with the metabolic syndrome, the same population with worse clinical outcomes, also have higher antibody responses [224]. This is to say that mildly affected and asymptomatic individuals, those with the best clinical outcomes, paradoxically have the lowest antibody responses.

Such findings make no sense unless one accepts that antibodies have only a supporting role in the immune response. Based on available evidence it seems more likely that antibody production is a fallback strategy implemented when primary cellular immune mechanisms are deficient. This inconvenient fact overturns Ehrlich's 120-year-old antibody hypothesis. By the same token it explains why currently employed vaccines stimulate antibody production and confer protection but don't induce immunity.

Internal Digestive System

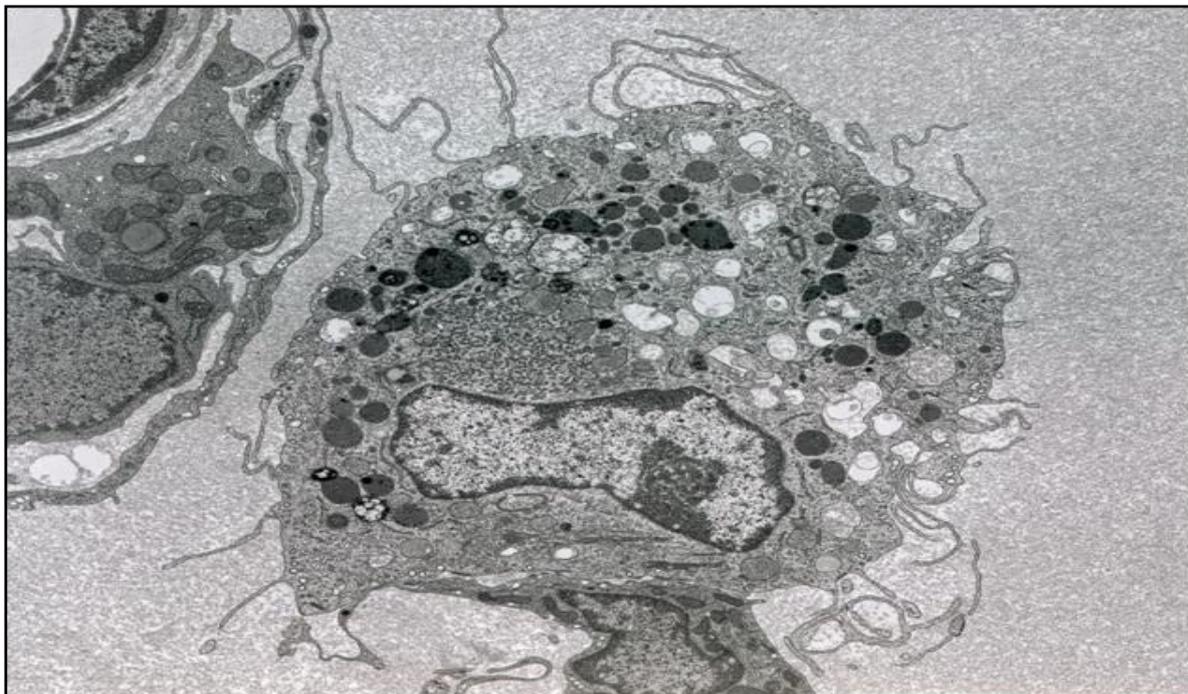
In the 1880s while studying transparent star-fish larvae under the microscope, biologist Elie Metchnikoff

observed cells which appeared to wander about in the tissues. Suspecting they played a role in the breakdown of substances; he introduced a rose thorn into the larva and observed that it was soon surrounded by these mobile cells. Calling them phagocytes or 'eating cells,' he claimed that the functions carried out by these cells was part of a primitive body-wide digestive function that included active host defense [225-227].

Later Metchnikoff injected anthrax bacilli beneath the skin of frogs, which are immune to anthrax, and observed them being engulfed and destroyed by WBCs. Metchnikoff argued that phagocytes play a primary role in host defense and resistance to disease. In a series of papers, he outlined his phagocytosis theory: wandering phagocytic cells possess diverse but functionally aligned processes related to intracellular digestion, namely, engulfment and breakdown of aged or injured host tissue or invading micro-organisms; tissue macrophages and WBCs play a primary role in this integrated functional system; host defense is based on successful containment of pathogens by the phagocytic system. Around the turn of the 20th century Jules Bordet, ardent supporter of phagocytic theory, wrote, 'one of the most significant conclusions that is derived from the work of Metchnikoff is that immunity is a special case of digestion.'

In the 2nd century Roman physician Galen argued that the stomach and spleen formed a nexus of functions related to digestion. From a modern perspective we can conceive these two organs as forming an integrated functional cycle:

Figure 3. Macrophage under transmission electron microscopy.



the stomach initiates digestion of food materials taken in from the outside which, through the blood, are distributed to all parts of the body. The spleen and phagocytic cells on the other hand, initiate the breakdown of substances inside the body and return them via the blood to the liver for recycling and intestines for elimination.

The common link between the internal and external digestive systems is generation of acid and acid-based enzyme systems that catabolize organic materials. Neutrophils and macrophages contain granules laden with digestive enzymes and substances like defensins and cathelicidins that incapacitate bacteria and viruses. The internal digestive system, independent of antibodies, inhibits replication of bacteria and viruses, performs housekeeping functions, and triggers repair of injured tissue. Antibody production is far downstream from where the real action is.

Two main phagocytic cell lines, macrophages and neutrophils (PMNs), carry out digestive functions in the interstitial fluid spaces exactly as Metchnikoff described [228, 229]. Their primary role is engulfment and breakdown of foreign materials, damaged cells and macromolecules [230-233]. Owing to their strategic location in the interstitial fluid compartment macrophages form the tip of the immune spear and play a key role in initiating and terminating inflammatory responses (Figure 3 and Figure 4).

For decades immunologists arbitrarily distinguished between two types of immunity, so-called innate and adaptive forms, one concerned with more general functions and the other with specific antibody-directed defenses. It was widely believed that only adaptive immunity, i.e., the antibody generating subset, possessed memory capable of specific recall of foreign substances but this has been found to be incorrect. Cells of the innate immune system, i.e., macrophages, also acquire new memory-based responses, known as trained innate immunity, that enhance resistance to antigens. The decades-long distinction between innate and adaptive immunity is thus artificial [234-236].

Even the long-held dictum that the primary immune function was to discriminate between self and non-self has come into question. Immune cells like macrophages respond functionally to changing cytokine and metabolite levels in their local milieu, so-called damage-associated and pathogen-associated molecular patterns (DAMPs and PAMPs). Macrophages are highly plastic and, even after differentiating into a particular functional subset, retain the ability to reprogram in response to changing environmental conditions. Consensus has shifted toward the notion of a dynamic, epigenetically-driven state of balance between environmental factors, gene expression and immune function [237-241].

Two opposing functional cytokine groups, pro- and anti-inflammatory, direct all WBC activity and induce macrophage polarization [242-244]. Macrophages form two subsets: pro-inflammatory M1 type polarized by cytokines such as interferon (IFN- γ), tumor necrosis factor (TNF- α), interleukin IL-1 β , IL-6, IL-12, and IL-23. Anti-inflammatory M2 macrophage cells, conversely, are activated by IL-4, IL-13 and, in turn, produce anti-inflammatory cytokines like IL-10 and transforming growth factor (TGF- β). The same pro-inflammatory/anti-inflammatory dichotomy is seen in T-helper Th-1 and Th-2 lymphocyte subsets [245-247].

In the early 1950s Belgian cell biologist Christian de Duve described an intracellular membrane-bound organelle he called the lysosome. Later, under the electron microscope, he observed delivery of cellular materials into lysosomes and coined the term autophagy, meaning 'self-eating,' to designate intracellular digestion [248, 249]. In autophagy acid is concentrated in lysosomes and catabolic enzymes activated not unlike that which occurs in the stomach. Autophagy culls aging and damaged cell structures and generates energy during periods of nutrient deficiency [250].

In recent decades impaired autophagy has been associated with a large and growing number of acute and chronic diseases involving inflammation like autoimmune and infectious diseases including COVID-19 [251-263]. From the early 20th century onward scientists never clearly

defined what 'immunity' actually was. Autophagy is the cornerstone of immunity and forms the primary defense against infection as Metchnikoff asserted 130 years ago. Asymptomatic and mild COVID-19 infections, rather than paradigms of heightened 'immunity,' are a result of robust autophagy.

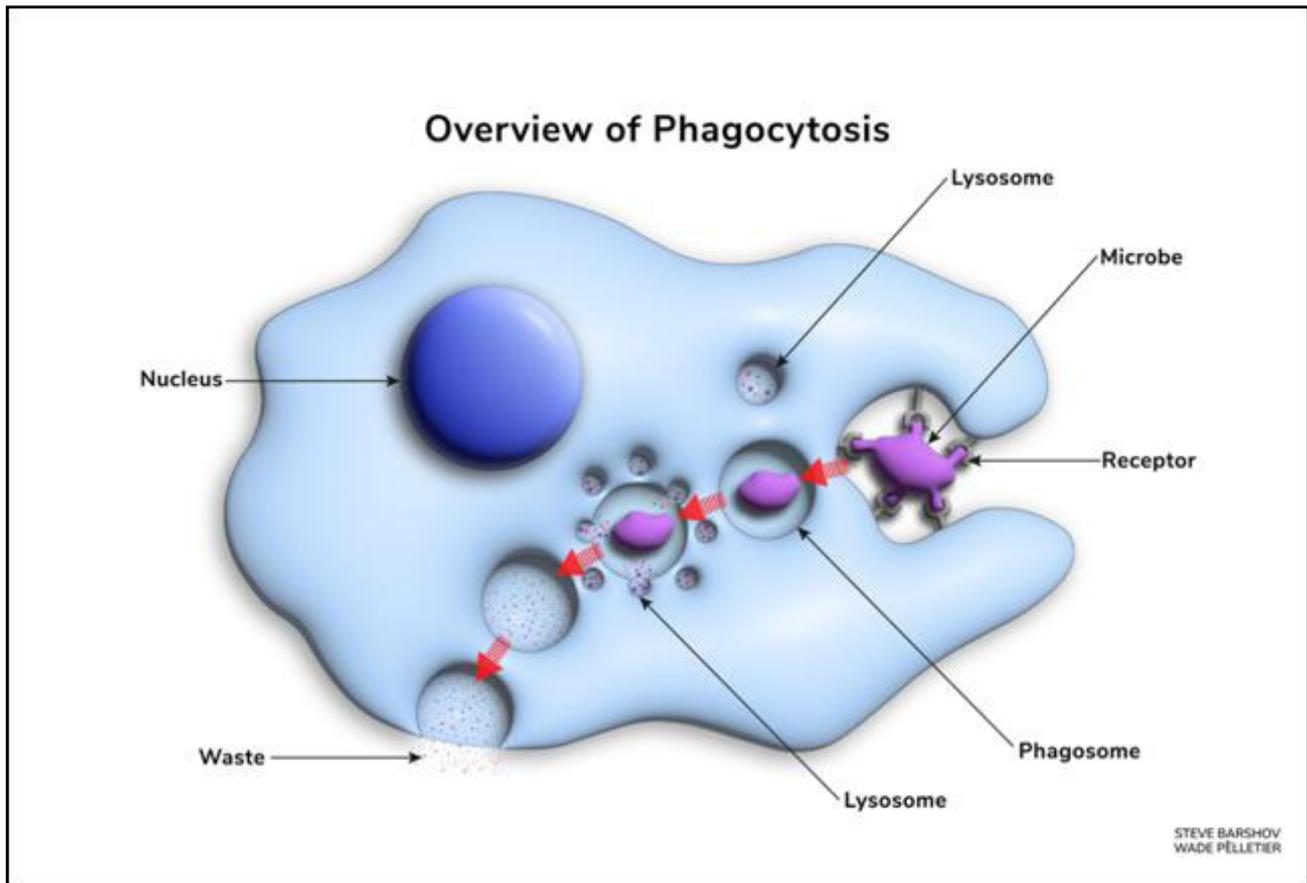
Scientific articles thus suggest autophagy-enhancing substances to treat COVID-19 [264-268]. But autophagy is an energy-requiring process and many symptomatic cases already have impairment of mitochondrial function [269-275]. Such conjoined cellular energy defects involving mitochondria and lysosomes in cells throughout the body, including immune cells are, in fact, precisely what drives inflammation [276-287].

Many infectious agents, including SARS-CoV-2, gain access to the body by colonizing epithelial cells where they attempt to reproduce and disseminate. The primary cellular response to such incursions is induction of autophagy. Microbes are enveloped in a membrane, the phagosome, which fuses with the acid-laden lysosome to initiate the decomposition process. If autophagy in epithelial cells is effective then spread of the infectious vector is prevented; in cases where it is not the agent reproduces, initiates cell lysis, and spills into the interstitial fluid space. During cell lysis, DAMPs and PAMPs as well as cytokines like IFN- γ are released which elicit a local macrophage response [288-290].

Activated macrophages converge at the infection site and initiate phagocytosis to contain further spread. Macrophages possess a multitude of acid-driven mechanisms by which to dispose of the infectious vector: the agent is walled-off in a sealed membrane limiting access to nutrients; release of polypeptides like defensin and cathelicidin destroy the outer bacterial membrane; acid and metals within the phagosome trigger the organism's own self-digestive enzyme systems; the catabolic degradation process amplifies to produce highly reactive substances like nitric oxide and free radicals which further degrade the ingested particle (Figure 4).

If such autophagy-driven mechanisms are successful then spread of infection is prevented and the inflammatory response is terminated via cytokine flux. If, however, the response is deficient then macrophages release additional pro-inflammatory cytokines to elicit support from circulating PMNs and lymphocytes in the blood, the so-called humoral or blood-mediated response. Spread of an infectious process thus involves successive breaches of barrier functions, first in epithelial cells, then macrophages in the interstitial fluid space, related to impaired autophagy. The humoral phase of the response is an attempt to enhance digestive functions by drawing energy and other blood-borne resources to the site of infection.

Figure 4. Sequential depiction of phagocytosis: 1) engulfment; 2) formation of membrane-bound phagosome; 3) fusion with cytoplasmic lysosomes; 4) internal digestion; 5) elimination of waste.



Runaway Inflammation

COVID-19 infection is characterized by three stages: the latent phase during which viral replication and dissemination is punctuated by the release of cytokines and elicitation of the cellular immune response; the amplification phase during which the interaction between viral and immune dynamics becomes systemic resulting in symptomatic and physiologic alterations; the depletion phase in which intravascular energy generation is profoundly impaired with runaway immune-mediated inflammation that triggers spiraling deterioration of clinical and physiological parameters [291-293]. Progression through the three stages is not invariable and disease outcome can be favorably altered by appropriate interventions early in the course of the syndrome.

To understand the complex web of relations that drive runaway inflammation in COVID-19, we must go back to the beginning, both in terms of disease process and the history of medicine. Roman physician Galen, the great western medical synthesizer, unified and systematized all medical knowledge from the time of Hippocrates onward. The primary basis for his humoral system is a blood-borne energy field which mediates all bodily functions.

This amounts to saying that all dysfunction is secondary to diminished energy generation by the heart. COVID-19 is a latter-day poster child for Galen's humoral medicine. Functional disturbances associated with COVID-19 infection are mediated by diastolic dysfunction originating in the cardiovascular system and blood. Studies indicate that vascular endothelial cells become infected by SARS-CoV-2 with resultant widespread endothelial inflammation in advanced COVID-19 cases. This has led various researchers to question whether the cardiovascular system plays a primary role in the systemic dynamics of the syndrome [294-301].

The endothelium forms an interface between the blood and peripheral tissues that orchestrates energy-driven functions like vasomotion, vessel permeability, hemostasis, coagulation and fibrinolysis. Diastolic and endothelial dysfunction is widely believed to not only impair organ perfusion but to augment the systemic pro-thrombotic state resulting in arteriovenous macro- and micro-thrombotic events.

The ubiquitous distribution of the vascular tree accounts for the wide range of symptoms and functional deficits from person to person with apparent random involvement of multiple organs like the lungs, heart, kidneys and brain

[302–313]. As indicated earlier, diastolic dysfunction is the common link among comorbid states like hypertension, diabetes, chronic heart and kidney disease as well as obesity, all of which increase the risk for severe COVID-19. The presence of widespread endothelial inflammation involving large and small vessels points to a more than casual relationship between runaway inflammation and impaired energy-generation in the vascular compartment. Inflammation represents a cellular response to deficient energy flow across the cell membrane. Diminished intracellular energy induces mitochondrial dysfunction with a shift from aerobic to less efficient metabolic pathways resulting in generation of reactive oxygen species (ROS), accumulation of acidic metabolic by-products, as well as altered membrane potentials of intracellular organelles including mitochondria and lysosomes [314–320].

The generation of ROS causes structural damage by denaturation of proteins but also induces formation of the stress-related structure known as the NLRP3 inflammasome which is responsible for induction of the pro-inflammatory cytokine storm that accompanies the runaway inflammation of COVID-19. A large body of data indicates that the cytokine storm is associated both with COVID-19 severity as well as mortality rates [321–334]. Blood analysis of COVID-infected patients has shown increased TNF- α and inflammatory interleukins including IL-1 β , IL-2, IL-6, and IL-10 which amplify the already existing endothelial dysfunction. As others point out, there is not one but two storms, the cytokine storm, secondary to widespread mitochondrial dysfunction and a primary, equally impactful ROS storm [335–343].

For decades clinicians have speculated on a possible relationship between viral infection and subsequent development of autoimmune disease. This association has come to the forefront in the SARS-CoV-2 pandemic with numerous reports of viral-induced effects mimicking various autoimmune syndromes [344–348]. The crossover between the two states is strengthened by laboratory phenomena like autoantibodies, neutrophil extracellular traps, and the macrophage activation syndrome.

As with autoimmune disease, a wide array of autoantibodies (autoAbs) directed against proteins like cytokines, chemokines, complement, cell surface proteins as well as RNA and DNA have been described in SARS-CoV-2-infected individuals. Studies find dramatic increases in autoAb activity which, depending on the species of autoAb, may range from 10% to as high as 50%. Such autoAbs likely result from protein misfolding related to energy deficiency leading to loss of antigenic specificity and subsequent cross-reactivity with native macromolecules.

AutoAbs further impair immune function by interfering

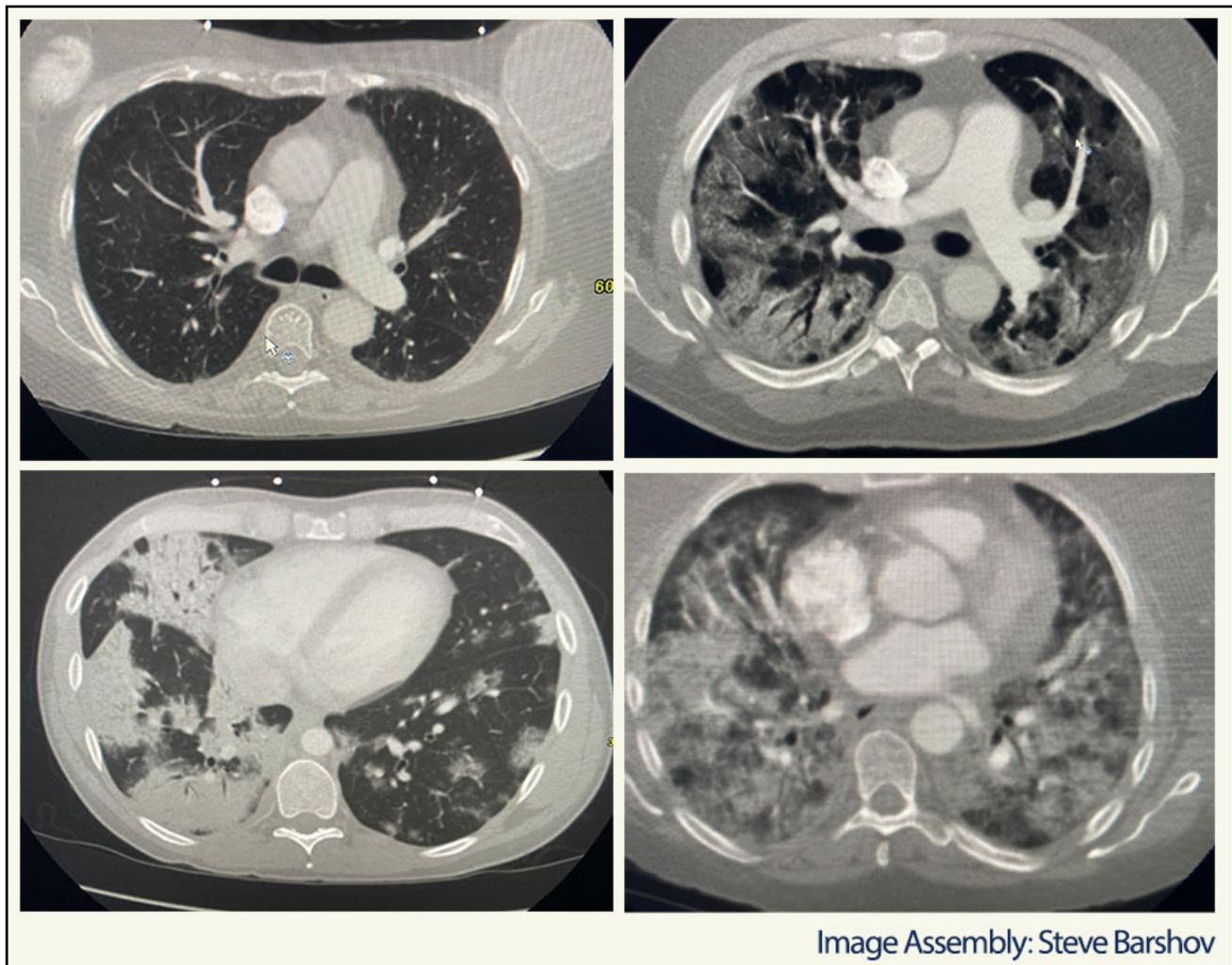
with cytokine signaling and immune cell responsiveness. The presence of autoAbs directed against intracellular structures like nucleic acids points to widescale cell destruction mediated by viral infection and/or cell-mediated processes like apoptosis, pyroptosis or necroptosis, all of which point an incriminating finger in the direction of impaired autophagy [349–355].

Neutrophil extracellular traps (NETS), found in abundance in COVID-19 subjects, are web-like fibrinous structures released by PMNs intended to trap and contain typically intracellular structures like mitochondrial or nuclear DNA, enzymes, and histones that have spilled into the interstitial fluid space. NETs, a feature of autoimmune disorders like systemic lupus erythematosus (SLE), augment cytokine secretion and the pro-thrombotic milieu and are major risk factors for lung injury, multi-organ damage, and mortality in COVID-19 disease. They trigger formation of autoAbs which further amplify the spiral of deterioration. The presence of NETS is a direct consequence of impaired autophagy by immune cells. Sera from advanced COVID-19 patients had lower degradation capacity of NETs than less affected individuals [356–368]. Macrophage activation syndrome, a potentially life-threatening complication of various autoimmune disorders like SLE, juvenile rheumatoid arthritis as well as COVID-19 infection, is characterized by fever, pancytopenia, coagulopathy, hepatosplenomegaly and biliary dysfunction. Through incompletely understood mechanisms the cytokine storm and runaway inflammation trigger activation and expansion of macrophages and NK T-cell lymphocytes. It carries a high mortality rate [369, 370].

In advanced COVID-19 cases microthrombi are present in small- and medium-sized arteries in nearly all organs, including the lungs, heart, brain, and liver and these microthrombi contribute to organ dysfunction and ultimately death [371–376]. Nearly all patients with severe COVID-19 present with bilateral lung involvement (Figure 5). Acute onset of impaired oxygenation occurs in up to 40% of patients with COVID-19 pneumonia and of these about 80% require supplemental oxygenation and about 30% mechanical ventilation. In one large meta-analysis mortality rate in patients requiring mechanical ventilation approximated 50% with rates up to 80% in the elderly and those with multiple comorbidities [377].

COVID-19-related respiratory failure is caused by severe lung injury similar to that seen in ARDS. Injury is not induced by viral infection or replication per se but rather by the dysregulated immune response directed toward the virus [378]. The dominant pattern of injury is diffuse alveolar damage accompanied by platelet-fibrin microthrombi, collapse of alveoli, dilated alveolar ducts, capillary congestion and scattered alveolar hemorrhages [379–382].

Figure 5. The multifaceted appearance of COVID-19 pneumonitis on CT chest scans. Normal appearing lungs upper left.



The heart is a common target organ in COVID-19 immune-mediated pathology and multiple cardiac complications including myocarditis, myocardial infarct, cardiac dysrhythmias and heart failure have been reported. By the same token COVID-19-induced renal failure and neurologic complications like stroke contribute to worsening morbidity and mortality in severe cases [383–392]. Autopsy studies on decedents describe widespread capillary congestion in the lungs and other organs suggesting severe vascular dysfunction [393].

Based on considerations presented in this article in all instances of COVID-19 infection the primary therapeutic imperative should be correction of diastolic dysfunction and energy deficits in the blood, normalization of mitochondrial function to prevent or reverse ROS generation and the cytokine storm and, finally, restoration of impaired autophagy. In the third part of the series, we examine such strategies.

In the current pandemic health care systems have no effective strategy to address SARS-CoV-2 infection early

in its course when it is the easiest, least expensive to treat, and has the best chance of satisfactory outcome. Instead, they left events in this critical window to chance and let matters take their course. From the beginning organized health care set itself up for failure: by the time individuals present to the ED at the local hospital they have often had symptoms for 7-12 days, are in profound energy debt, and already in the cytokine-ROS storm [394]. Each step in the process, from hospital admission, to ICU transfer, to mechanical ventilation, is punctuated by incremental mortality rates.

In-hospital treatment of the syndrome involves steroids to quell inflammation, disease-modifying agents directed at the cytokine storm, anti-thrombotic drugs to inhibit clot formation, and anti-viral agents, none of which address the primary functional events that drive the syndrome and are thus only palliative. This amounts to a profound systemic failure by medical science to appropriately conceive and treat COVID-19 and the SARS-CoV-19 pandemic.

Science on Trial

Pandemics, devastating, destructive natural occurrences, expose weaknesses and deficiencies of the systems in which they interact. It is fair and accurate to say that the pandemic has been broadly mismanaged at multiple levels. Current events will undoubtedly be debated by scientists and historians for decades to come. Nonetheless, take-home points can be distilled so far from the COVID-19 catastrophe.

In 1973, Charles Cockburn, then head of virology section WHO, wrote: 'the influenza virus behaves just as it seems to have done 500 or 1000 years ago and we are no more capable of stopping epidemics or pandemics than our ancestors were' [395]. At this point, two years into the pandemic, there is little evidence to suggest that social or medical interventions have favorably altered dynamics of the pandemic. Indeed, one could question whether they have made it worse. Scientists miscalculated the relentless nature of the pandemic and what was required to achieve herd immunity, or even what herd immunity is.

One year after introduction of mRNA vaccines, with much fanfare, they seem to have widely missed the mark. While proponents claim it provides protection against the virus, such protection is at best temporary. We have observed breakthrough infections 2-3 months post-vaccination in numerous individuals. Vaccination does not confer long-term immunity. It does not impact transmission of the virus and, moreover, contributes to the emergence of new variants. And this does not address the problem of adverse event rates which are now being more widely recognized. Why weren't such issues properly vetted by scientists before introduction of such experimental and potentially dangerous agents?

Clearly, extensive revisions must now be made to the reigning immune theory. Some would argue that this is the nature of experimental science, which is always in flux, always generating new facts, always seeking new insights. But such is not the case in the COVID-19 pandemic: the problem is far deeper and systemic for it involves a perennial inability of scientists to make critical adjudications in a timely and appropriate manner.

To finally recognize autophagy as the primary basis of the immune response 130 years after it was clearly and presciently articulated by Metchnikoff is an indefensible stain on the experimental method. The same can be said for Landsteiner's argument from early in the 20th century against Ehrlich's lock-and-key chemical basis of antibody specificity. Why weren't such issues vetted more thoroughly by the science community? The current paradigmatic crisis in science is nothing but the chickens coming home to roost.

Equally disturbing is the failure of the contemporary medical science community to come to consensus over the flood of evidence pointing to the presence of a body-wide energetic field generated by the cardiovascular system. The dominant systolic-centered model of heart function, which held sway for most of the 20th century, was overturned in the late 1980s, nearly 35 years ago, and diastole is now widely recognized to be the primary determinant of cardiovascular function. And yet scientists continue to peddle their discredited molecular and cellular paradigm as if it were gospel.

By 1970, ten years after receiving the Nobel Prize, Macfarlane Burnet, eminent 20th century immunologist, had soured on experimental medicine. In *Genes, Dreams and Realities* he argued that the contribution of laboratory science in unlocking the problem of disease had come to an end and that further research would amount to little more than filling in of details. Most of the breakthroughs in 20th century medicine, he noted, were observational in nature and not based on experiment.

Burnet claimed that 'too much sensational material was being written about the future significance of discoveries in molecular biology.' He pointed to the increasing burden of chronic diseases and lack of meaningful change in their outcomes in the previous 3-4 decades. Modern science, he wrote, 'is by no means the triumphal march toward perpetual health and well-being' as popular accounts would suggest. And far from stunning breakthroughs he warned that molecular science 'might release some new and nasty problems on a world that already has more than it can cope with.' The SARS-CoV-2 pandemic has laid bare the failures of the experimental method and revealed the emperor to have no clothes.

In the second part of this series, we examine in greater detail the various strategies, including vaccination, that science-based societies have enacted during the pandemic to mitigate its influences. Cockburn's assertion that pandemic dynamics are unstoppable stands unchallenged.

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