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Neurology | Review

COVID-19: Energy, Protein Folding & Prion Disease

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Introduction

The recent recognition of intravascular amyloid formation with deposition of insoluble microthrombi throughout the circulatory system in primary COVID-19 infection or following administration of mRNA vaccines is a pivotal discovery that alters conventional notions about the nature of the underlying pathologic process at play in SARS-CoV-2 infection.

Since early in the pandemic researchers have ascribed the cascade of pathology to intravascular coagulation induced by the so-called cytokine storm and related immune system dysfunction. Alongside the web of deterioration, studies chronicle a range of autoantibodies, a dozen or more in some individuals, directed against proteins like cytokines, chemokines, cell surface proteins as well as RNA and DNA. Antibodies to platelet factor 4, for example, are believed to play a key role in the propagation of clot within the vascular system. While such reports must be regarded as factual, they are merely descriptions that do not, in and of themselves, explain the progressively widening arc of intravascular pathology. The presence of amyloid, however, compels one to fundamentally reconsider the nature of the problem.

Amyloid deposition can occur in any organ of the body and is associated with an increasing number of pathologic states including diseases like Alzheimer's, Parkinson's as well as type II diabetes. Amyloid is composed of single-stranded protein fibrils held together by hydrogen bonds to form the characteristic birefringent β-sheet structure. At least 30-40 proteins have been identified as precursors to the amyloid state but in any given patient or disease condition the amyloid usually derives from but a single type. Protein misfolding is widely regarded to be the primary cause of amyloid aggregation and deposition.

Protein misfolding is now regarded as a leading cause of chronic disease and has been associated with the neurodegenerative diseases, diabetes, cystic fibrosis, sickle cell anemia, as well as various cancers. All functional activities in the body – movement, nerve transmission, molecular transport, secretion, cellular division, enzyme activities and more – are effected by conformational changes in folded proteins. Even the appearance of autoantibodies in the blood during COVID-19 infections can be explained on the basis of protein misfolding.

But the folding of proteins into their three-dimensional functional structure is an energy-dependent process and disruption of intracellular energy availability necessarily

impacts folding. Conversely, accumulation of amyloid as well as the characteristic intracellular aggregates in disease states such as Alzheimer's or Parkinson's reflect impairment of lysosomal function and intracellular digestive pathways, i.e., autophagy, which are also dependent upon sustained energy flow.

In recent decades there has been increasing focus on a rare class of disorder known as the prion diseases, progressive and invariably fatal neurodegenerative conditions. The pathologic chain of events in the central nervous system (CNS) are a result of protein misfolding caused by propagation a pathogenic misfolded form of a naturally occurring protein inside the body.

While little is known of how prion particles propagate through nerve cells or induce misfolding of native proteins, the prion concept itself is extremely useful and would seem to account for how a wide range of protein misfolding conditions ultimately develop and progress. Prion-like mechanisms have increasingly been invoked to explain the origins of Alzheimer's and Parkinson's diseases as well as other conditions including amyloid deposition. Not surprisingly, some have suggested that the SARS-CoV-2 spike protein produces its pathological sequelae through prion-like mechanisms.

In this article we focus on the disturbed energy milieu associated with COVID-19 infection and show how all manifestations of the syndrome, from the earliest prodromal constitutional symptoms such as fever, malaise and lethargy, to more advanced morbid alterations such as intravascular thrombosis and organ dysfunction, can be explained on the basis of a mounting energy debt. Moreover, functional alterations such as autoantibodies, clotting disturbances, and organ failure ultimately trace back to protein misfolding and impairment of conformational change in affected proteins.

Cardiovascular Energy Dynamics

One of the most far-reaching and impactful conceptual turn of events in 20th century medicine occurred in the 1980s without most medical scientists or physicians even recognizing that the ground beneath their feet had begun to crumble. A decisive reshaping of ideas was underway that, ultimately, would render the molecular and cellular framework obsolete. This profound intellectual transformation constitutes what science historian Thomas Kuhn, in his insightful work *The Structure of Scientific Revolutions* (1962), described as a paradigm shift [1].

For much of the 20th century scientists conceived the heart to function in the manner of a mechanical pump, with blood propelled forward through the arteries during the systolic (contraction) phase of the cardiac cycle. The diastolic phase of the cycle, conversely, was believed to represent a period of passive relaxation. This notion was originally advanced by William Harvey in 1628 in his seminal work *On the Motions of the Heart* in which he describes his discovery of the circulation of the blood [2]. Harvey's model was uncritically adopted by English physiologist Ernest Starling in the early 20th century and thereafter became accepted as fact. The problem with Starling's so-called 'law of the heart' is that it couldn't explain how blood returned from the veins to the right side of the heart.

In the early 1980s physiologists discovered negative intraventricular pressures, i.e., a suction force, in the early diastolic phase indicating that diastole was not a period of passive relaxation but, instead, a period in which blood was actively drawn forward through the veins into the ventricular chamber [3-6]. In order for the ventricle to pump blood through the arteries it first has to contain blood. A handful of studies later found the presence of spiral flow currents in arteries and veins which can only be explained on the basis of a suctional force [7-20].

By the late 1980s numerous studies had established the primacy of diastole in the cardiac cycle and, intriguingly, found that impaired outward movement of the ventricular and arterial walls, known as 'diastolic dysfunction,' was the defining feature of a wide range of chronic conditions: hypertension, diabetes, obesity, depression, cancers autoimmune diseases, as well as organ failure syndromes like chronic kidney disease and chronic heart failure among others [21, 22]. To date scientists have no satisfying explanation for this clustering. The outward motion of the heart and arterial walls, on the other hand, can only be explained on the basis of a mechanical force.

During its cycles of contraction and dilation the heart generates a large magnetic field which is responsible for diastolic expansion. In a series of earlier articles, we describe mechanisms at play in this phenomenon [23-25]. For over a century it has been recognized that the heart and blood contain large iron stores and, while iron's role in various chemical reactions has been exhaustively detailed, there has been little discussion as to whether

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iron might play a broader role.

Equally the question arises as to the function served by nerves that course over the surface of the heart. Cardiologists claim these nerves cause the heart to contract but is this correct? As early as the 2nd century AD Roman physician Galen observed in animal experiments that when the heart was cut out and placed in fluid it continued to dilate and contract, what is called cardiac automaticity. By the same token, transplanted hearts continue to function in recipients even though nerve conduction has been interrupted.

What happens during systolic contraction of the ventricle is identical to what happens during the induction of an external magnetic field by electrification of ferrous objects. As the ventricle contracts and iron stores are brought into closer apposition iron nuclei in the heart muscle and blood align and precess synchronously on the basis of field interactions. The flow of electrical currents through nerves saturates the field and induces formation of an external three-dimensional magnetic field within the ventricular chamber causing its expansion. A similar mechanism is at play with magnetic resonance imaging (MRI) in which images are generated by saturation of a magnetic field with radiofrequency pulses.

It cannot be said that recognition of this organized energy field generated by the motions of the heart constitutes a new discovery. Such dynamics were first described by Roman physician Galen around 200 AD and accepted as fact by physicians for over 1500 years until chemically oriented scientists in the 17th and 18th centuries discarded the concept without ever disproving it. Galen's system of humoral medicine was premised on the existence of a blood-borne energy field that gave rise to all bodily functions [26]. Medicine, it seems, has come full circle back to its roots.

While medical scientists acknowledge the centrality of active dilation in cardiovascular dynamics, they advanced the concept of 'endothelial-dependent dilation' to explain such phenomena. They claim that intra-arterial pressure and blood flow induce synthesis and release of the free radical substance nitric oxide which is responsible for vascular dilation. While this may be factually correct it sidesteps the phenomenon of active energy generation, the most significant causal event in the economy of living bodies. To ascribe energy and mechanical forces to molecular causes is like trying to ascribe a thunderstorm to cloud formation: it is a necessary but not sufficient condition.

COVID-19 Energy Deficiency

One of the most unexpected revelations related to COVID-19 infection has been the degree to which the cardiovascular system is involved in its pathogenesis. Studies indicate that SARS-CoV-2 infects vascular endothelial cells early in the course of the illness leading to inflammation, i.e., endothelitis, which, in advanced cases, extends diffusely throughout the circulatory system. The inflammatory state, in turn, induces further diastolic dysfunction and impairment of energy generation. Some researchers have thus questioned whether the cardiovascular system plays the primary role in mediating the COVID-19 syndrome [27-34].

Endothelial cells form the boundary between blood and the vascular wall and orchestrate energy-dependent processes like smooth muscle contraction and elongation, vessel permeability, coagulation and fibrinolysis. Diastolic and endothelial dysfunction is widely believed to not only impair organ perfusion but augment the pro-thrombotic state resulting in formation of large and small clots throughout arterial and venous channels.

The ubiquitous distribution of the vascular system explains the diverse range of symptoms and functional disturbances from person to person with apparent random involvement of organs like the lungs, heart, kidneys and brain [35-46]. As indicated above, diastolic dysfunction is the common link among such diverse states as old age, obesity, hypertension, diabetes, chronic heart and kidney disease, all of which increase the risk for severe COVID-19 and mortality. This is to say that pre-existing diastolic dysfunction is the leading prognosticator for poor outcomes.

Diffuse endothelial inflammation in large and small vessels points to a more than coincidental relationship between inflammation and impaired energy-generation. Inflammation is an adaptive 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, accumulation of acidic by-products and altered voltage potentials across intracellular membranes [47-53].

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Reactive oxygen species cause structural damage by inducing denaturation of proteins, i.e., protein misfolding, as well as formation of the stress-related structure known as the NLRP3 inflammasome which initiates the cytokine storm that accompanies inflammation in COVID-19. Numerous studies link the cytokine storm to both COVID-19 severity and higher mortality rates [54-67]. Blood analysis of COVID-19-infected patients has shown increased TNF-α and pro-inflammatory cytokines including IL-1β, IL-2, IL-6, and IL-10 which amplify already existing endothelial dysfunction. There is not one but two storms, the cytokine storm and a primary, equally impactful reactive oxygen species storm, which inflicts widespread damage upon intracellular proteins [68-76].

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 [77-86]. In both cases pathologic events are associated with altered protein dynamics. The common link is seen in phenomena like autoantibodies (autoAbs), NLRP3 inflammasome formation and neutrophil extracellular traps (NETS).

COVID-19 patients have marked increases in autoAb levels compared with non-infected individuals. As with autoimmune disease, an array of autoAbs have been found directed against endogenous cytokines, chemokines, cell surface proteins as well as RNA and DNA. AutoAbs, depending on the type, may be found in 10%-50% of COVID-19 patients. Since the mid-20th century scientists have claimed that autoAbs were a result of spontaneous genetic mutations that gave rise to 'forbidden clones' of autoAb-producing lymphocytes but evidence surfacing during the pandemic challenges this notion. Studies find that autoAb levels track directly with rising levels of antibodies against SARS-CoV-2 and with disease severity suggesting they form spontaneously during the course of the illness. It is more likely that autoAbs result from protein misfolding related to energy deficiency which, in turn, leads to loss of antigenic specificity and cross-reactions with native structures [87-97].

The NLRP3 inflammasome is a complex protein aggregate that forms in the cytoplasm secondary to impaired energy generation by mitochondria. In response to oxidative stress the inflammasome releases pro-inflammatory cytokines into the extracellular fluid (ECF) space initiating the cytokine storm and, as a coup de grâce, activates cell death (apoptosis) pathways. The NLRP3 complex is found in a host of inflammatory states including autoimmune disorders, Alzheimer's disease, diabetes and atherosclerosis [98-105].

In further support of the energy hypothesis, studies indicate that inflammasome formation is directly related to diastolic and endothelial dysfunction [106-110]. Inflammasomes likely represent the energy-depleted state of a normally folded protein, much like the ventricle at the end of systolic contraction. In the case of the inflammasome, however, energy repletion (repolarization) cannot occur and, instead, the proteins undergo spontaneous aggregation with activation of cell death pathways [111].

Neutrophils (PMNs) are phagocytic cells capable of assimilating and digesting both endogenous and foreign materials. Under conditions of energy depletion, i.e., oxidative stress, the digestive capacity of phagocytic cells is impaired and, as a result, denatured biomolecules accumulate both in cells and in the ECF space. NET release typically occurs during PMN cell death. NETs are large web-like structures containing materials like DNA and a variety of proteins that have spilled into the ECF space following cell injury and death. NETs likely represent energy-depleted proteins that undergo spontaneous aggregation. NETs, found in a variety of autoimmune and inflammatory disorders, are abundant in COVID-19 patients [112-129].

Some scientists claim the purpose of NETs is to trap extracellular materials like bacteria and viruses but this doesn't make sense. NETs, especially DNA, are highly pro-inflammatory and, instead, likely induce conformational change and aggregation of biomolecules in the ECF space. In addition to triggering autoAb formation, NETS serve as scaffolding for thrombus formation and their presence increases the risk for lung injury, multi-organ damage, and mortality in COVID-19 disease. Formation and accumulation of NETs appears to be primarily due to failure of clearance mechanisms by functionally impaired phagocytic cells.

In the early 1950s 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

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designate intracellular digestion [130, 131]. In autophagy acid is concentrated in lysosomes and catabolic enzymes activated not unlike that which occurs in the stomach. Now widely recognized as a function critical to cellular homeostasis, autophagy culls aging and damaged cell structures as well as generating energy through auxiliary pathways during periods of nutrient deficiency [132]. Such orchestrated body-wide autophagic activities constitute what we call the internal digestive system.

As concentration of acid within lysosomal membranes is energy-dependent, impaired mitochondrial function inevitably leads to lysosomal dysfunction and diminished breakdown of defunct cellular structures thus leading to accumulation of undigested material inside and outside of cells. While autophagy plays a key role in all cells, it forms the raison d'être for phagocytic cells of the immune system and thus during periods of energy depletion, such as in advanced COVID-19 infection, deterioration of phagocytic functions is common [133-138].

Evidence we have presented thus points to widespread disruptions in energy generation originating in the cardiovascular system as a hallmark of COVID-19 infection which, secondarily, impairs mitochondrial function and intracellular energy production. Intracellular energy deficits, in turn, induce disturbances in protein metabolism and function, namely, impaired conformational change, i.e., depolarization and repolarization- of normally folded proteins and/or misfolding in newly-synthesized proteins. A related aspect of energy depletion and inflammation, accumulation of intra- and extracellular deposits due to impaired autophagy, can also be ascribed to similar origins.

Proteomics

The discovery of intravascular amyloid in COVID-19 patients ties into one of the most protracted and circuitous scientific investigations in search of causality, one that stretches from the early years of the 20th century to the present, and still has yet to fully resolve. The Alzheimer's saga vividly capsulizes the shortcomings of the experimental method.

In 1907 Alöis Alzheimer reported the case of a 51-year-old demented woman at a local asylum in Frankfurt, Germany, constituting the first known description of the disease. Symptoms included loss of memory for recent events along with a cluster of verbal and visual impairments. After the woman died Alzheimer examined her brain microscopically and observed the typical amyloid deposits and neurofibrillary tangles [139]. Thereafter aggregates became the subject of on-again, off-again investigations but, from the onset, scientists were unable to agree on whether they were cause or effect. Much of the 20th century was spent chasing leads that went nowhere. And yet the solution to the dilemma had been articulated in the early decades of the 20th century but roundly ignored.

In 1984 pathologist George Glenner isolated amyloid-β (Aβ) and showed that it was derived from a cell membrane protein later called amyloid precursor protein (APP) [140]. With little additional evidence Glenner seized on the notion that Aβ was the cause of Alzheimer's disease (AD). In 1991 a mutation in the gene that codes for APP was discovered in individuals with the familial form of AD leading geneticist John Hardy to advance the amyloid hypothesis imputing that Aβ deposits represent the primary disease pathology [141]. He argued that Aβ fibrils gradually coalesce into larger strands which morph into the characteristic sheet-like plaques. Such plaques were claimed to trigger pathologic sequelae like synaptic dysfunction, neurofibrillary tangles, inflammation and cell death, all of which invariably progressed to dementia [142].

From the beginning the amyloid hypothesis was on thin ice. Not only did the presence of Aβ plaques not correlate well with cognitive impairment in AD but geneticists were left trying to explain the presence of plaques in the brains of cognitively normal elderly adults who had died from other causes. Equally problematic was how such aggregates produced cellular injury. Originally it was assumed that plaques were toxic but given that they are insoluble and non-reactive the basis for such toxicity was never established [143].

Most cases of AD are not familial but, instead, spontaneous and not associated with mutations involving APP [144-146]. Dozens of genetic markers have been associated with AD (as well as the other neurodegenerative diseases) but almost none involve precursor proteins to the characteristic deposits. Instead, gene analysis points squarely to impaired autophagy and associated protein degradation pathways [147-153]. Geneticists assumed that since genes code for protein synthesis all protein disorders must have a genetic origin. But protein folding and misfolding is a cytoplasmic function dependent on energy availability.

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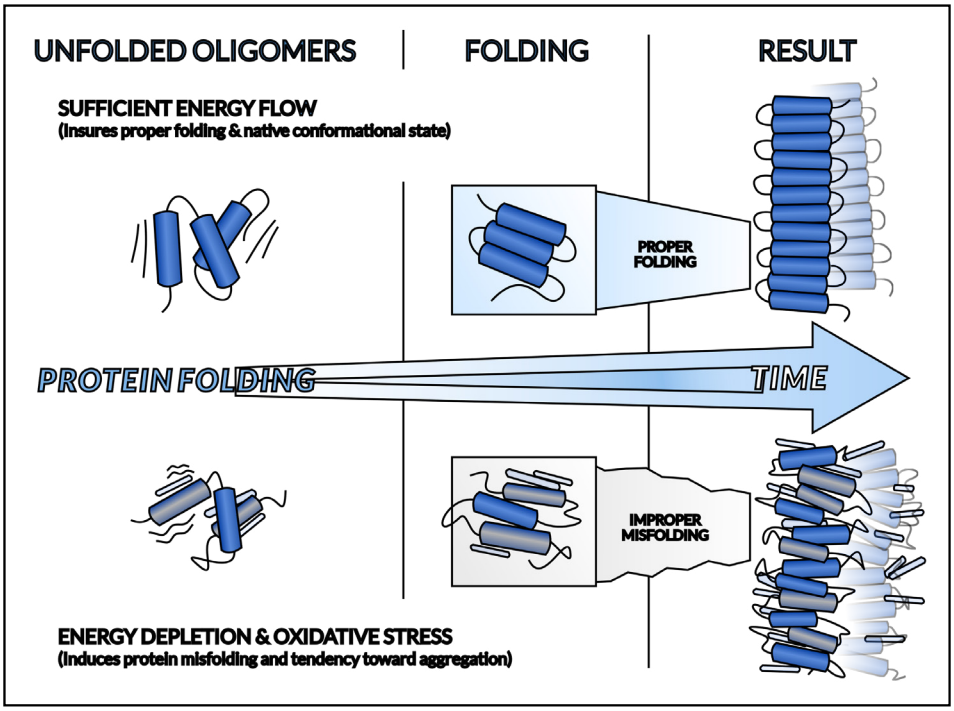
Proteins possess a complex three-dimensional arrangement. Primary structure, which is genetically coded, refers to the sequence of amino acids that forms the backbone of the chain. Secondary structure comprises a regularly repeating pattern such as the α-helix characteristic of DNA or the β-sheet form typical of amyloid. Such secondary attributes are generated by intermolecular forces like hydrogen bonds and dipole-dipole interactions. The tertiary structure represents the overall 3D conformation of the protein which also is stabilized by non-covalent intermolecular forces [154-157].

Tertiary structure, known as the native fold, is responsible for the functional properties of a protein. While effecting their functions proteins continually undergo spatial rearrangement, alternating between related conformations as seen, for example, in contraction and dilation of heart muscle. Such changes represent transitions between discrete energy states. In the cardiac cycle, for example, systole represents a period of energy discharge (depolarization) while diastole represents the phase of energy repletion (repolarization).

During or after synthesis most proteins are converted into compactly folded 3D structures many of which are astonishingly complex. Living organisms possess elaborate mechanisms by which to ensure proper folding. Under certain conditions, as in the congelation of egg white by heat, for example, even normally folded proteins may revert to a misfolded state. By whatever mechanism misfolding occurs, such conformational alterations diminish function. Because of the import of maintaining native conformation, intracellular processes exist to either refold misfolded proteins or to break them into smaller parts for either reassembly or elimination.

The majority of proteins fold in the cytoplasm or endoplasmic reticulum. Both compartments provide not only a proper folding milieu but quality control mechanisms by which to maintain natively folded proteins. A specialized class of macromolecules. i.e., chaperones, discriminate between native and non-native conformations. If misfolded proteins cannot be properly refolded, they are earmarked for degradation, i.e., intracellular digestion, through a second set of processes known as the ubiquitin-proteasome system. During periods of energy depletion and oxidative stress coordination between various internal processes is impaired and misfolding more likely to occur. Once a critical concentration of misfolded protein is reached, they become prone to the kind of aggregate and inclusion body formation typical of the neurodegenerative disorders and now recognized to play a role in COVID-19 infection [158-162] (Figure 1).

Figure 1. Proper 3D conformation of a protein is dependent on available energy in the cellular milieu. Protein misfolding is more likely to occur during periods of impaired mitochondrial function and oxidative stress.



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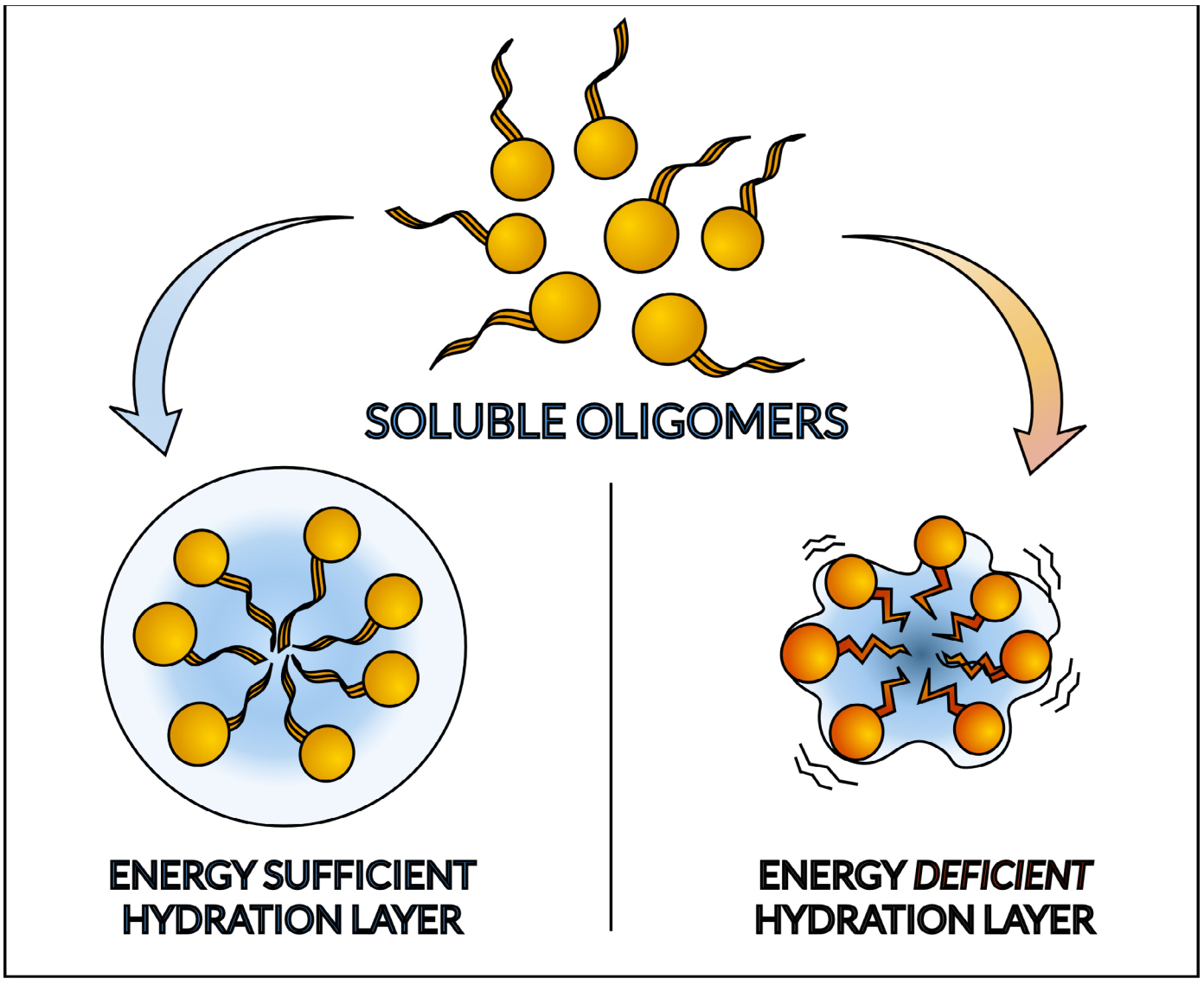
Based on unknown factors amyloid aggregates assume a common secondary structure, the β-sheet pattern, which likely represents a common energetically stable form accessible by a wide range of polypeptides independent of amino acid sequence. This provision is critical since most of the disease related proteins do not share obvious sequence homologies in their native state [163].

Whatever mechanism drives the formation of the β-sheet architecture it is clear that aggregates develop from a series of intermediates beginning with smaller chains, i.e., oligomers, that gradually self-assemble into larger units. A key feature in the aggregation process is the transition from water-soluble oligomers to insoluble deposits. In the late 1980s pathologists described a peripheral halo surrounding Aβ aggregates [164]. More recently such halos have been shown to contain soluble Aβ oligomers suggesting that aggregation bears resemblance to a crystallization process and is driven primarily by dynamics in the surrounding fluid medium [165] (Figure 2). Such recognition opens the door to an entirely new concept of energy flow in living bodies.

Figure 2. Proper 3D conformation is dependent on the expansionary magnetic component of the energy field which enables component domains and strands to repel one another. Oxidative stress, conversely, with its generation of acid by-products, impairs magnetic field strength and augments the contractionary force. This, in turn, leads to protein misfolding and aggregation of susceptible pathologic proteins and oligomers.



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Water Dynamics

As impactful as the revolution in proteomics has been it could not have occurred without an equally profound transformation in the conception of water. The recognition of dozens of anomalous properties of water not explainable on the basis of its chemical properties now challenges conventional notions as to its true nature. Emerging evidence substantiates ancient notions of water as a distinct element. Perhaps the most significant contributions have come from biologist Gerald Pollack whose work, *The Fourth Phase of Water*, has triggered yet another decisive paradigm shift [166].

Most significant among the so-called anomalous behaviors of water is its ability to undergo phase transitions between three distinct states—ice, liquid, and vapor—each reflective of its energy content. In experiments Pollack observed that water often underwent spontaneous reorganization and formed a clear zone of variable thickness along the surface of many objects with which it came into contact. Such behaviors had been described by other scientists as early as 1949 but never investigated further. Based on such properties Pollack called the clear layer 'exclusion zone' (EZ) water based upon its tendency to repel solute particles into the adjacent fluid which, in turn, he called 'bulk water'.

Pollack's team found that the EZ tended to form along hydrophilic surfaces and required a molecular template. This explains the peripheral halo researchers observed surrounding Aβ oligomers. Using microelectrodes Pollack et al found significant differences between EZ and bulk water: the EZ was negatively-charged, more alkaline, dense and viscous; bulk water was positively-charged, acidic, with pH often as low as 1-2 suggesting accumulation of protons. As the two phases of water formed, a charge separation took place. The presence of current flow suggested to Pollack that water functions like a battery to generate and conduct energy.

His team deduced that as the EZ acquired spatial order (and physical force) it pushed solute particles into the adjacent bulk water similar to how glaciers extrude rocks. Studies by physical scientists suggest that EZ water has a quasi-crystalline structure and arranges itself in stacked honeycomb sheets, hence the term 'structured water'. Pollack regards it as a distinct fourth phase beyond the traditional solid, liquid and vapor states. As the battery metaphor implies, structured water appears to play a central role in energy flow. Evidence suggests the fourth phase of water represents a resonant energy state.

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 of which substantiate the vital role water plays in proteomics [167-171]. To be biologically active proteins must acquire a so-called hydration shell consisting of multiple layers of water molecules sometimes extending up to 25Å from the protein surface. The hydration shell appears to be instrumental in determining not only 3D protein structure but the folding process itself.

The hydration shell, which surrounds hydrophilic domains of most intracellular proteins and membranes, spontaneously organizes into a complex hexagonal lattice-type arrangement, which researchers have compared to a semi-crystalline state. The protein-water complex spontaneously develops structure and assumes gel-like consistency. Hydration shell water surrounding proteins, like the EZ, has physical properties distinct from that of bulk water in the adjacent fluid spaces. Such changes in water state, both in the intracellular and extracellular fluid spaces, would seem to provide an ideal energy source for the many protein-mediated biological processes.

The conjoined role of proteins and water in the energy economy of the body formed a recurrent motif throughout the 20th century. Swedish physical chemist Svante Arrhenius published the first work on the electrical conductivity of ionic solutions, *Investigations on the Galvanic Conductivity of Electrolytes,* in 1894 [172]. He noted that salts dissolved in water split into electrically positive and negative ions that transmit electrical currents in the fluid medium. Based on its tendency to undergo polarization into two opposing species, we refer to this water-mediated energetic component as the dielectric field [173]. Arrhenius conducted studies showing the biological importance of electrolyte dynamics in the interactions between antigens and antibodies.

Arrhenius' work formed the basis for what became known as 'colloid theory' which, simply stated, asserted that ion-containing intracellular water interacts with cell proteins to produce complex three-dimensional structures which, under specific conditions, assume gel-like consistency. In

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that bound water conducts electrical currents, changes in energy flux through cells induce conformational changes in the colloid matrix resulting in 'work,' i.e., functional activities like muscle contraction or glandular secretion.

Viennese physician and immunologist Karl Landsteiner, discoverer of the ABO blood groups, was an early proponent of colloid theory. He argued that colloid dynamics and electrochemical forces mediated antigen-antibody interactions. It seems, he wrote, 'that this extraordinary type of reaction plays a particularly large part in living organisms; living substance is mostly made up of colloids' [174]. Landsteiner and co-workers found that charged acidic and basic colloids not only moved in opposite directions in electrolysis experiments but precipitated each other. Interactions were based less on chemical constitution than on physical phenomena like pH, solubility and temperature.

Beginning in the 1950s cell biologist Gilbert Ling emphasized the central role of water and colloid dynamics in all cell functions. The cytoplasm, Ling argued, is an integrated system of proteins, water, ions and molecules like ATP that drive all functional processes in the body. All structural elements are linked together by electromagnetic interactions, what he called 'ferromagnetic cooperativity' [175].

In 1962 Ling advanced the association-induction hypothesis based on the notion that electrical polarizations and depolarizations, i.e., induction, were at play in such conformational dynamics [94]. Close-contact interactions among protein chains link them into an organized nexus with secondary, tertiary and even quaternary structure. All colloids exist in open and closed states and undergo reversible transitions based on energy flux. In the years following introduction of his theory Ling's lab was forced to shut down due to inability to secure research grants from funding agencies like the National Institutes of Health.

A recurrent question concerns the nature of the processes that drive protein folding: do amino acid chains randomly generate secondary and tertiary conformations or are conformations determined by the energy state? In the late 1960s Christian Anfinsen called attention to the intricacies of protein folding, particularly the phenomenon of reversibility, which necessarily involves transitional kinetic states. Folding, he argued, is related more to the disposition of electromagnetic forces than to covalent chemical bonding [176].

Cyrus Levinthal pointed out the sheer improbability of protein chains searching randomly through an infinitely large pool of potential configurations to attain native fold [177]. The extreme rapidity with which such folding occurs, on the order of milliseconds, implicates preordained folding pathways related to specific energy states. In 1995 Bryngelson et al showed that in various protein families, like lysozyme for example, polypeptides fold into identical 3D conformations despite extreme disparities in amino acid sequence [178]. They argued in favor of a dynamic energy landscape in which proteins are 'funneled' into their functional energy states [179-183].

For much of the 20th century biological causation was held to be determined by processes originating at the molecular and cellular levels. These assertions are unfounded. Protein folding and misfolding, now widely recognized to drive all functional processes in the body, and to be a leading cause of disease including COVID-19 infection, demand the presence of an organized energy landscape.

Even mainstream medicine seems to be wavering in its century-long infatuation with molecular reductionism. Concerning the relationship between Aβ and AD science writer Simon Makin, in an influential 2018 Nature editorial, raises the critical question 'is it time to look beyond amyloid-β as the root cause of the condition'? Neuroscientist Michael Murphy comments, 'the time to cast a wider net is now—we need a bigger base of ideas' [184]. Another dramatic paradigm shift is underway.

The Prion Connection

Beyond an association between SARS-CoV-2 infection and amyloid deposition, studies emerging during the pandemic found striking similarities between patterns of COVID-19 propagation and that of classic neurodegenerative diseases like AD and Parkinson's (PD), now recognized to operate on the basis of prion-like mechanisms. Protein misfolding in the nervous system behaves entirely in line with principles we have just established.

The prion diseases are progressive, transmissible neurodegenerative disorders seen in higher vertebrate species: scrapie in sheep, chronic wasting disease in deer, mad cow disease in cattle, and in humans like kuru and Creutzfeldt-Jacob disease [185-187]. The causal agent is a neuronal protein that undergoes pathological misfolding and propagates along nerve tracts in cell-to-cell fashion [188, 189]. Beyond such pathologic descriptions, however,

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researchers have never explained exactly how they induce disease. The term prion, rather than denoting a particular disease entity, designates the means by which protein misfolding disorders propagate throughout the nervous system.

During the pandemic it was observed that patients with neurodegenerative disorders like AD and PD were not only more susceptible to severe COVID-19 infection but more likely to experience worsening of their underlying symptoms. Such trends are especially pronounced in AD with multiple reports describing rapid cognitive decline during COVID-19 infection. Moreover, spontaneous cases of AD and PD as well as Creutzfeld-Jacob disease have been described both after SARS-CoV-19 infection as well as COVID-19 vaccination [190-202]. Such phenomena have corollaries at the molecular level.

Injection of purified Aβ material into AD-prone mice induces accelerated deposition of Aβ and intracellular aggregation of tau-protein with neurofibrillary tangle formation in surrounding brain tissue of the mice [203-204]. Based on such behaviors it is suggested that Aβ possesses prion-like behaviors. By the same token, the presence of the SARS-CoV-2 protein in the serum has been found to enhance amyloid formation [205-206]. In laboratory studies the SARS-CoV-2 protein interacts with α-synuclein to induce Lewy body formation in PD-prone cell lines [207]. Other studies find that interactions between the SARS-CoV-2 protein and α-synuclein also accelerate amyloid formation [208]. Such intertwined phenomena constitute what researchers refer to as prion-like transmission.

To explain such behaviors on a cellular and molecular basis scientists describe four attributes of prion-like propagation: intracellular conversion of a natively-folded protein into a misfolded form; extrusion of misfolded protein into the ECF space with uptake by neighboring cells; the ability of misfolded species to induce misfolding in other similar proteins; and the tendency of misfolded proteins to induce misfolding at distant sites [209, 210]. Based on such spurious criteria, a misfolded protein must somehow exit one cell, travel through the ECF space, enter another cell and, by some vague 'template' mechanism, induce protein misfolding in other cells. This is pure science fiction. A far simpler explanation is that introduction of pathogenic protein material into the system places additional stress on degradation pathways with subsequent accumulation of aggregates.

From an energetic standpoint such physical mechanisms aren't necessary. Only three phenomena must be accounted for in all the related disorders: Why do proteins misfold? Why do they accumulate in cells or the ECF space? And, importantly, what is the basis for this tendency toward aggregation? The aggregation question will be addressed in the final section.

We have already established that deficient energy flow into cells and impaired mitochondrial function are responsible for all of the disturbances. The fact that proteins in nearby cells undergo subsequent misfolding and aggregation can only indicate an expanding energy debt. In that mitochondrial dysfunction and oxidative stress impair lysosomal function, the accumulation of Aβ oligomers, Lewy bodies, neurofibrillary tangles and other misfolded proteins can only be ascribed to deficient autophagy. Not only is direct contact between proteins not necessary to induce misfolding, there is no plausible mechanism by which this should even occur. Protein conformation is purely related to energy status. End of story. It is surprising that cell biologists have failed to reach consensus on such a critical issue.

It goes without saying that the brain and nervous system do not represent the primary route of infection for SARS-CoV-2. While CNS manifestations such as stroke, hemorrhage, or inflammation can be attributed to the vascular system, other manifestations take origin by a distinctly different route. Of great relevance to the spread of so-called prion disease in the nervous system is recognition of early functional disturbances which point with inerrant accuracy to where the pathogenic action unfolds.

Given the well-established oral route for propagation of various prion diseases, it is not surprising that in recent years both AD and PD have been linked to this mechanism. Early in the course of PD misfolded proteins accumulate in gut lymphoid tissue and spread to organs like the spleen, tonsils, appendix and the enteric nervous system [211-219]. A peripheral origin for PD is supported by the early appearance of autonomic dysfunction [220-224]. Subjects often develop symptoms like decreased saliva production, dysphagia, impaired gastric emptying or constipation. Of particular significance is the presence of disorders of smell in up to 90% of early-stage PD and 85% of early-stage AD patients [225-229]. Such symptoms usually precede the onset of motor disturbances, cognitive decline and dementia.

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Based on such evidence it has been suggested that misfolded proteins, acting in prion-like fashion, gain access to the CNS via two routes: one through the nose into the olfactory nerve, and the second through the intestinal mucosa and into the vagus nerve. The nasal route would account for the high percentage of PD subjects with olfactory symptoms and, in more advanced cases, pathology in the forebrain. Retrograde propagation of α-synuclein misfolding along the vagus nerve not only explains various autonomic dysfunctions but involvement of the dorsal motor nucleus in the medulla [230-232].

Surprisingly few reports have commented on the well-documented association between neurodegenerative disorders and autonomic dysfunction [233-236]. Autonomic dysfunction is a frequent accompaniment of all the dementias and includes postural hypotension, dizziness, gastrointestinal disturbances and urinary incontinence. Autonomic symptoms are associated with poorer disease outcomes. Such imbalances indicate altered nerve traffic patterns and trace directly to decreased energy flow in the ECF space which itself is secondary to diminished energy generation by the cardiovascular system.

The same early symptom patterns are observed in subjects with SARS-CoV-2 infection [237-244]. In various studies disorders of smell and taste range from 10% to as high as 85% with a mean in the 60% range. Such chemosensory dysfunction has also been reported following COVID-19 vaccination. Deficits may occur before or coincident with onset of other manifestations. Symptoms are generally self-limited and range from 3-4 days up to several months.

Autonomic dysfunction as detected by heart rate variability testing is a frequent accompaniment of COVID-19 infection. Of special interest is the recognition of widespread autonomic dysfunction in subjects with the long-COVID syndrome. Symptoms may include fatigue, palpitations, tachycardia, chest pain, shortness of breath, orthostatic hypotension, loss of smell and/or taste, exercise intolerance, headaches, 'brain fog' and difficulty concentrating, sleep disturbances as well as depression and/or anxiety [245-255]. The syndrome, believed to affect 10-20% of infected individuals, generally persists for weeks to months. How to reconcile the striking similarities between COVID-19 and early forms of the neurogenerative disorders?

To explain energy flow through nerves, early 20th century scientists posited that neurons functioned like tiny batteries and generated their own electrical currents. But this explanation doesn't fly in the face of dramatic events like sudden cardiac arrest in which there is immediate cessation of all neuronal functions and loss of consciousness the moment cardiac activity ceases. How to account for such a tight functional linkage between the two compartments?

Given the directionality of flow currents in nerves the question arises as to where peripheral sensory nerves, which course toward the brain and spinal axis, derive their currents. The unavoidable conclusion is that they originate in the ECF space just as Pollack's structured water concept would suggest. By the same token, given that the surface of the cerebral hemispheres is lined by dendrites, which convey currents directionally into the deeper brain structures, and which are in direct contact with cerebrospinal fluid, one must draw similar conclusions as to the origin of electrical currents in the hemispheres.

The flow of currents in the nervous system, necessarily, is driven by cardiac dynamics. Each systolic contraction of the heart creates a suctional force in nerves which draws currents forward into both peripheral sensory nerves and dendrites over the outer surface of the brain. When the heart dilates it moves fluids; when its contracts it moves energy currents. This substantiates the claim of Swedish radiologist Björn Nordenström in his pioneering (but overlooked) work Biologically Closed Electric Circuits (1983) that there is not one but two overlapping circulations, one consisting of the flow of fluids and the other of energy currents [256].

Such a model goes a long way in explaining early functional deficits such as loss of smell and taste as well as the plethora of autonomic imbalances that define both acute and long-haul COVID-19 syndromes as well as the early neurodegenerative disorders. It is axiomatic that therapeutic attempts must be aimed at restoration of energy deficits and correction of imbalances.

Aggregation Dynamics

So, we return to the point at which our deliberations began: deposition of amyloid aggregates in the vascular compartment. It is established that accumulation of amyloid fibrils is the end result of mitochondrial

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dysfunction and impaired intracellular digestion of misfolded proteins. But another question looms large: why are pathologic species prone to aggregation? What dynamics are in play that would precipitate such events?

Recently, scientists discovered that fibrinogen, precursor to the clot-forming protein fibrin, can, under certain circumstances, transform into a misfolded form of fibrin not unlike the β-sheet rich amyloids and prions [257-259]. This pathologic isoform propagates intravascularly forming micro-clots which, in turn, entrap other proteins and propagate to form larger clots. Such thrombi persist in the vascular system indefinitely and, eventually, may occlude small and large arteries and veins with predictable consequences. It was further observed that such atypical clots are highly resistant to standard anticoagulant therapy and may require prolonged treatment with multiple agents if they first don't cause irreversible organ injury or death.

By the same token, in lab experiments when the SARS-CoV-2 protein was added to the blood it resulted in structural changes not only to fibrinogen but other blood proteins like prothrombin and complement [260-264]. The spike protein binds to a host of aggregation-prone proteins like heparin, the heparin binding proteins, Aβ, α-synuclein, tau and others to accelerate aggregation of pathological amyloid proteins. Reports describe multiple amyloidogenic and prion-like domains in the spike protein. How can such phenomena be explained? Examination of the prion protein provides further insight.

The prion protein exists in two stable energy-dependent isoforms, i.e., natively folded and misfolded states. The functional domain of the protein consists of three α-helix and two β-sheet regions. In its natively-folded conformation α-helix-rich regions predominate while the pathogenic misfolded state is characterized by β-sheet dominance. This pathologically folded protein, considered 'toxic' by researchers, gives rise to the observed pathology. Breakdown of the misfolded prion protein generates Aβ oligomers. Like other misfolded proteins the prion protein tends to aggregate not only with itself but also other proteins [265-273].

It seems likely that when aggregation prone proteins undergo misfolding they revert to stable conformations like the β-sheet-dominant form which cannot expand fully into their 3D conformations. Such misfolding induces compaction of constituent chains and inability to repel nearby proteins. This mechanism has received increased attention in recent years [274-278]. Crowded physiological environments, both intra- and extracellular, favor protein aggregation by promoting conformational instability, inhibiting breakdown of oligomers, accelerating seeding of amyloids, and promoting prion-like replication. Such events, in turn, translate into pathological changes in the blood.

During the pandemic studies found that SARS-CoV-2 infected individuals had higher blood viscosity than non-infected persons and, among the infected, higher viscosity measurements translated into higher mortality [279-281]. Higher blood viscosity is associated with diastolic dysfunction, blood flow disturbances, increased shear stress, increased tendency for platelet and red blood cell aggregation, and, finally, increased blood coagulation. Energy deficiency, protein misfolding and water dynamics come full circle in the blood and must be explained on an entirely different basis than simply molecular factors.

In an experiment intended to demonstrate the effects of electric fields in water Nordenström packed a U-shaped glass tube with cotton wool in its lower curved portion to simulate capillary resistance [282] **(Figure 3).** Both limbs of the tube were filled with water and metallic electrodes connected to a DC power source were placed on each side. After a variable period of time, depending on the size of the tube and strength of the battery, one observes differential water levels in the two limbs with the left (cathodic) side higher than the right (anodic) pole. What is happening here?

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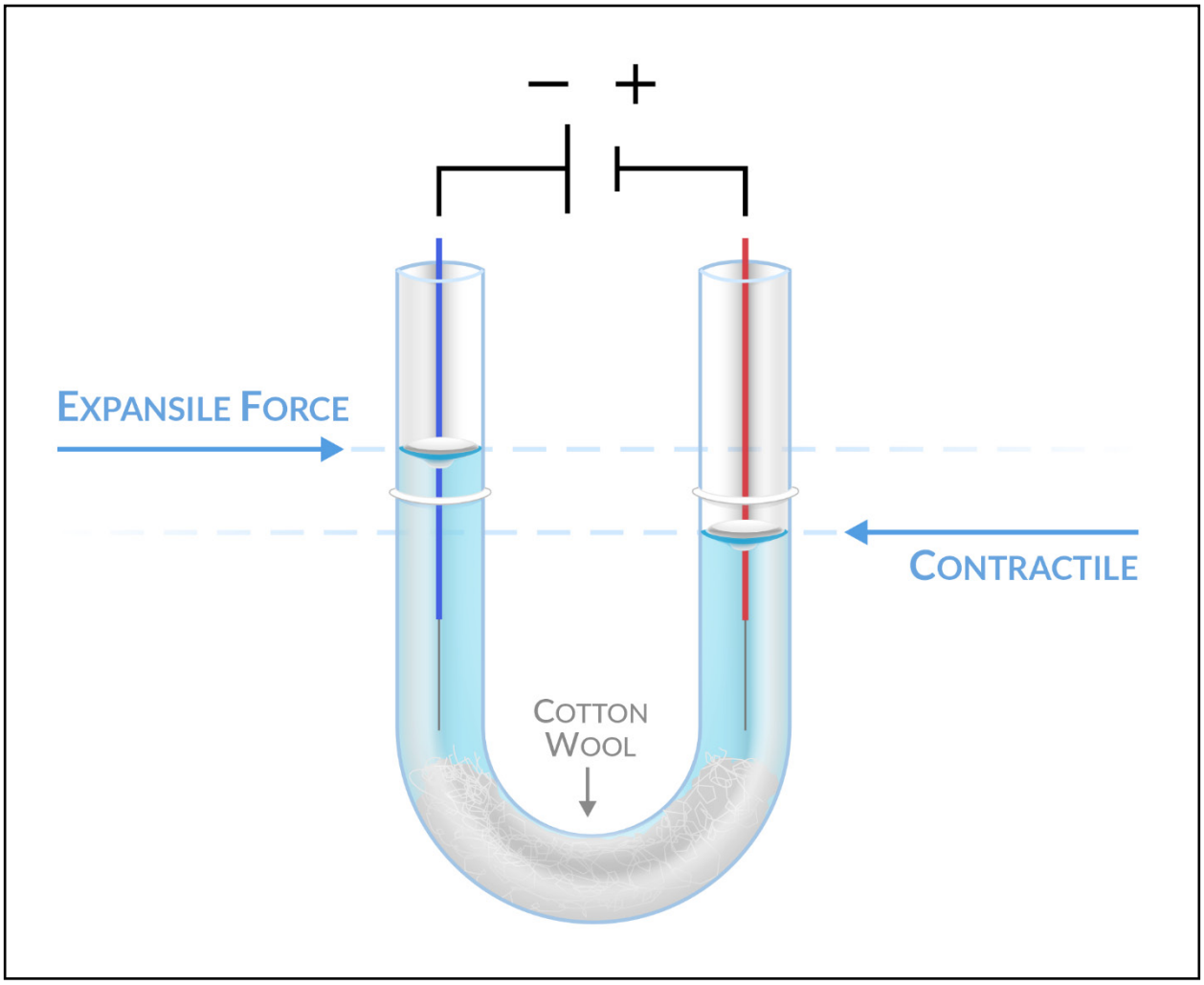
Figure 3. A U-shaped glass tube is packed with cotton wool in its lower curved portion and filled with water. Metallic electrodes connected to a DC power source are introduced on each side. After a variable period of time one observes differential water levels in the two limbs with the cathodic side higher than the anodic pole, illustrating the conjoined expansionary and contractionary forces within the dielectric field of the water medium.



Scientists would ascribe such results to electrically-induced migration of charged species, including water, with differential accumulation at the two poles. Such differential levels are no more explainable on the basis of water and ion movement than are the oceanic tides. The spatial reorganization of water is purely a field-mediated effect. Real forces produce differential fluid levels and the migration of ion species.

Electrical currents streaming through the electrode at the cathode generate a magnetic field around the wire which causes expansion of water. By the same token, currents drawn out by the anode induce contraction of the surrounding water which causes its level in the tube to drop. The dielectric field is composed of two opposing forces, the expansionary magnetic and a contractionary or counter spatial force. When we say water is polarizable, we mean that electrical currents cause the two components of the dielectric field to separate and assert their opposing effects. And as with an automotive battery aggregates tend to precipitate out at the anodic pole where the contractionary force is strongest.

We can thus say with certainty that protein misfolding and aggregation reflect the energy content of the milieu in which they reside. In the cardiovascular system, as we have shown, the outward movement of the ventricular and arterial walls is related to generation of a magnetic force. Magnetism is the only energy form possessing 3D spatiality. As the field weakens, as in diastolic dysfunction, the contractionary force gains strength thereby altering fluid dynamics within both in the

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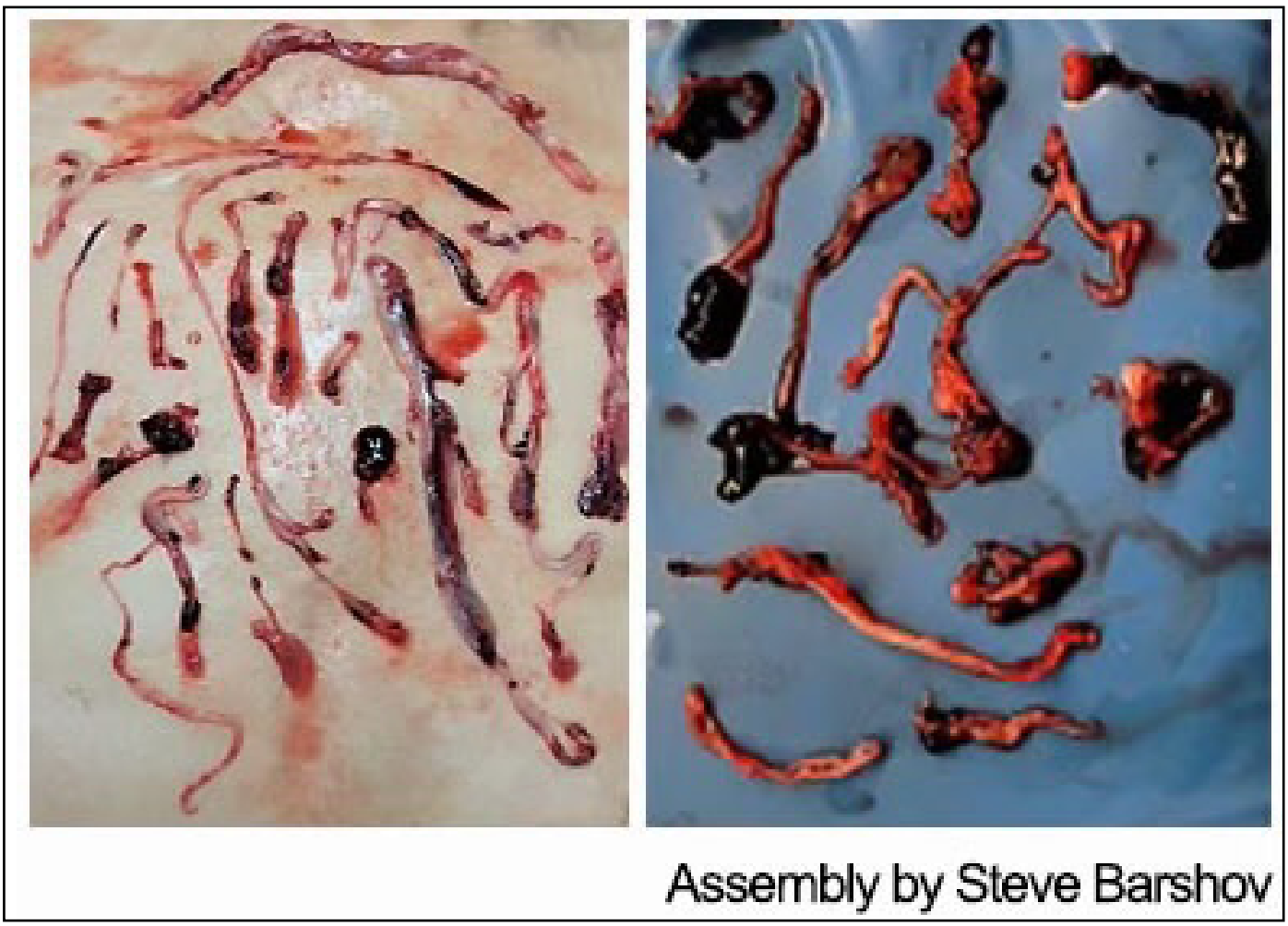
intravascular compartment and ECF giving rise to downstream pathologic carnage. As Galen's functionally based humoral system of medicine asserts, *quae incipit in sanguine:* everything begins in the blood.

Without a doubt such dynamics are in play during COVID-19 infections and account not only for protein misfolding and aggregation in the blood, resulting in atypical thrombi resistant to anticoagulant therapy, but in the peripheral nervous system giving rise to symptoms associated with autonomic dysfunction. Increasing evidence links such phenomena to the rising tide of long-COVID-19 cases [283-285]. Misfolding dynamics also explain *in toto* the proliferation of autoantibodies associated with primary SARS-CoV-2 infection as well as the COVID-19 vaccines, as seen in the well-described vaccine induced thrombotic thrombocytopenia (VITT) syndrome. None of the therapies currently employed by medical science effectively addresses a single one of these energy-related disturbances. As we pointed out in a previous piece, 80-90% of the COVID-19 pandemic-related deaths were preventable had appropriate measures been implemented.

We spoke with an embalmer, one who preserves bodies for ceremonial burial practices, who claims that since introduction of the vaccines he has encountered mortuarial phenomena he had never seen before in his career. After the COVID-19 pandemic and introduction of mRNA vaccines he began to encounter many cases with extensive arterial and venous clot formation. Other embalmers in the US and Europe describe similar phenomena. He sent pictures of clots he extracted from decedents **(Figure 4).**

Figure 4. Variegated post-mortem clots typical of those embalmers have encountered with increasing frequency in the COVID-19 era. (Courtesy of Richard Hirschman)



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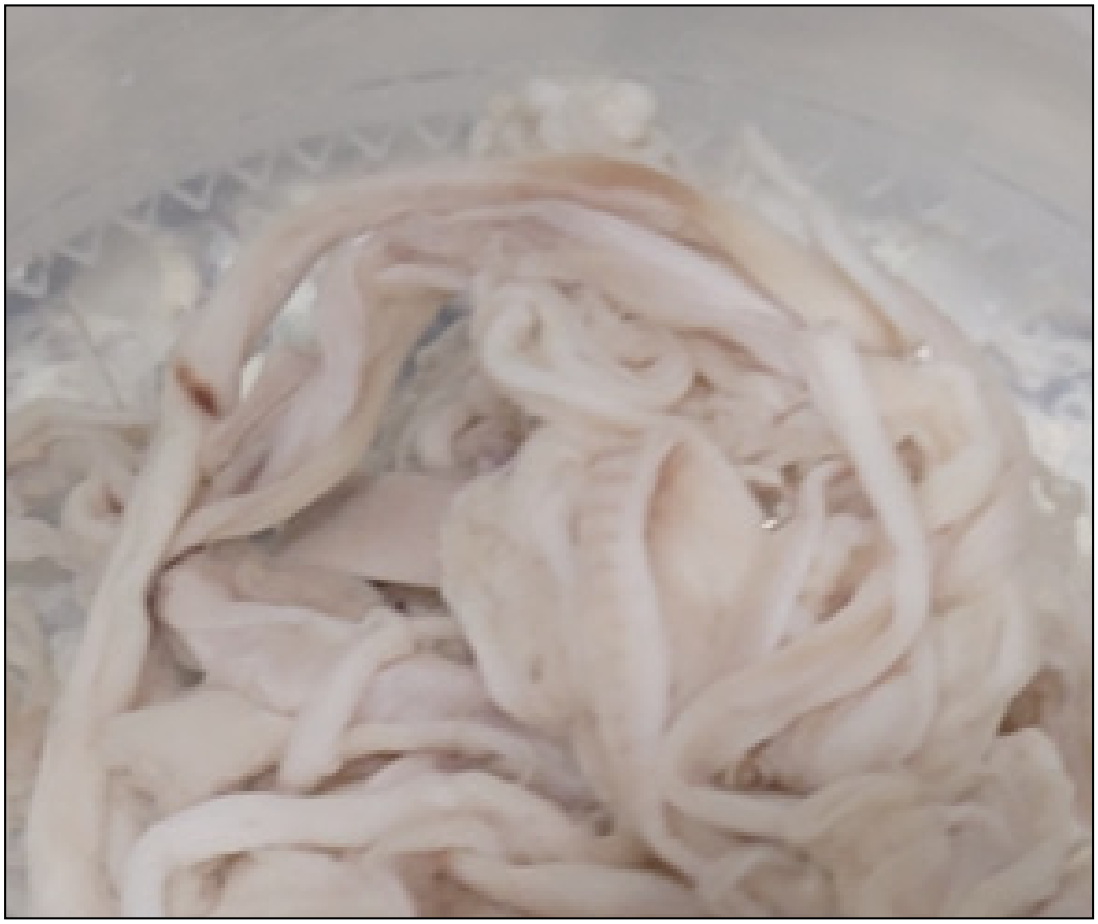

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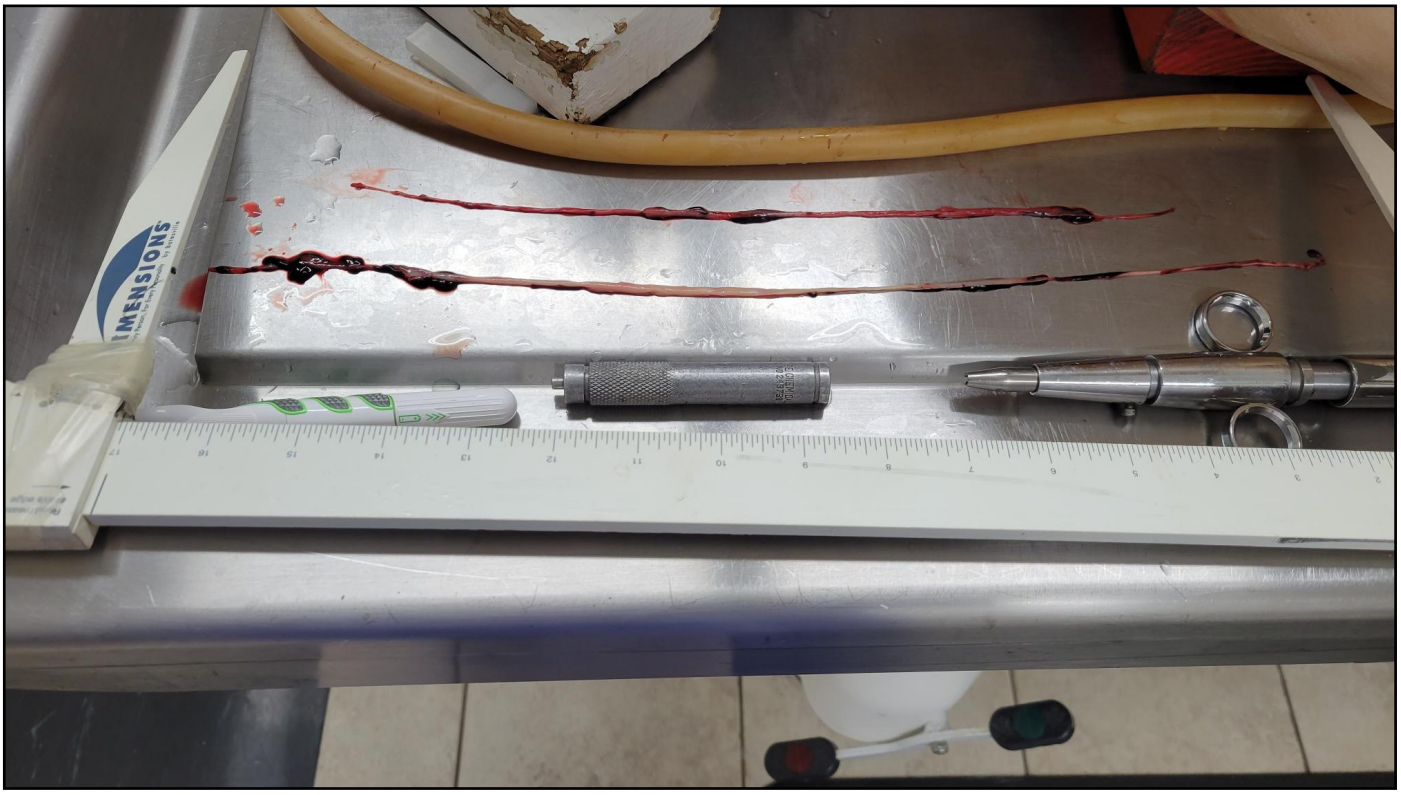

A colleague of ours who is in robust health received two doses of the Pfizer vaccine in April 2021. Five months later, for no apparent reason, he developed extensive lower extremity deep vein thrombosis. After months of anticoagulant treatment, he continued to experience intermittent swelling and pain. How many latent arterial and venous thromboses, autoimmune phenomena, and chronic conditions like AD and PD are insidiously propagating in post-COVID-19-infected subjects or in those who received the vaccine? This looming catastrophe is all the more disturbing given that medical scientists mishandled the pandemic from the onset and have only magnified its detrimental impact.

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