INTRODUCTION

In October 1923 renowned English physiologist Ernest Starling delivered an address at the annual Harveian Oration before the Royal College of Physicians entitled ‘The Wisdom of the Body’ [1]. Heaping lavish praise on William Harvey and his discovery of the circulation of the blood, Starling waxed eloquently on the integrative actions of the heart and its ‘marvelous power of adaptation’, referring to it, in Harvey’s words, as ‘the sun of the microcosm’ and ‘the foundation of life’.

But Harvey’s great gift to the world, Starling confided to his audience, wasn’t the discovery of the circulation of the blood but his method of formulating and solving problems. The true potential of the experimental method, he continued, was first realized by Harvey who encouraged his followers to 'study the secrets of Nature by way of experiment' and, through this endeavor, greatly expanded the domain of science and its power to shape the world.

‘When I compare our present knowledge of the workings of the body’, Starling effused rhapsodically, ‘and our powers of interfering with and of controlling those workings for the benefit of humanity . . . I feel that I have had the good fortune to see the sun rise on a darkened world, and . . . a new birth of man's powers over his environment and his destinies unparalleled in the whole history of mankind’.

Around the same time medical scientists embarked upon what would become a century long odyssey
in search of answers to the vexing enigma of dementia, which was being seen with increasing frequency. But fate was not so kind to scientists and they spent much of the 20th century wandering about in an intellectual desert chasing evidentiary trails that ultimately went nowhere. By the turn of the 21st century scientists knew little more about causes of the neurodegenerative disorders (NDs) than when they commenced their long-drawn-out pilgrimage.

And after more than a century of focused research on the central nervous system (CNS) scientists still can't seem to agree on simple questions like the function of the ventricles and cerebrospinal fluid even though such matters were accurately explained by Roman physician Galen 1800 years ago. And by the same token, the model of cardiac function advanced by Harvey and later Starling was shown to be erroneous. At every step, with each new discovery, the tenuous nature of scientific knowledge and the inability of scientists to make proper adjudications has taken center stage.

In recent decades, however, the pace of discovery has quickened and a series of conceptual breakthroughs has, for the first time, kindled hope that definitive answers – and perhaps effective therapies – may finally be on the horizon. At every step, with each new discovery, the tenuous nature of scientific knowledge and the inability of scientists to make proper adjudications has taken center stage.

The most important and determinative development has been discovery of an organized blood-borne electromagnetic field generated by the cyclical contraction and dilation of the heart. Energy currents, transmitted in the fluidic element of blood, exit arteries as a clear watery fluid, known as interstitial or extracellular fluid (ECF), that bathes all cells and tissues and engenders all bodily functions. The entire pathologic cascade of events surrounding dementia and the gamut of NDs is related to deterioration of this all-encompassing energy field.

In this paper we examine 20th century conceptual developments regarding dementia and the NDs, from the first recognition of their clinical and pathological characteristics, through recognition of their molecular and cellular attributes and, ultimately, to recognition of their dynamic and vascular origins. We introduce a new energy-based causal model of these disabling neurologic conditions that provides vital insights into their origins and necessary treatment. The term 'causal' implies that future treatment of these conditions necessarily entails recognition and correction of underlying energy deficits.

**CHASING SHADOWS**

The first issue concerns the nature of a handful of chronic, progressive, ultimately lethal and pathologically distinct NDs including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). These entities are now widely recognized to be related by a single pathogenic mechanism: misfolding of cellular proteins and the formation of intra- and extracellular aggregates that are said to cause cell injury and death. Scientists remain uncertain as to the cause of such misfolding and, moreover, cannot explain how or why chemically inert aggregates should exert toxic effects.

In each case the tissue pathology occurs in conjunction with a primary symptom complex – memory deficits and cognitive impairment in AD; tremor, rigidity, and slowing of movement in the case of PD; involuntary jerking and writhing movements along with cognitive and psychiatric deterioration in HD; progressive muscle atrophy and weakness in ALS – each of which involves
different nerve tracts in separate brain areas along with chemically distinct neurotransmitters. And yet in each case protein misfolding dynamics play a key role.

Dementia is a devastating problem among the elderly with a prevalence ranging from ~1-2% in the 60–65-year-old range and up to 35% by age 90. In the dementia spectrum of diseases, AD accounts for ~60%. PD, conversely, is the most common chronic movement disorder and, like AD, PD-associated neurological deficits increase with age, ultimately affecting over 1% of the population above 60 years. These common age-related disorders consume vast health care resources and impose a steep socioeconomic burden on industrialized societies [2-7].

While HD and ALS have neither the widespread recognition nor socioeconomic impact of the other two, each has played a significant role in the development of ideas concerning the nature of the NDs. Early on HD was recognized to have a strong genetic basis, being transmitted in an autosomal dominant fashion, which shaped 20th century notions about the hereditary nature of the NDs. The majority of NDs, it is now recognized, are spontaneous, i.e., non-hereditary, in origin.

ALS was the first disease in which the symptoms and clinical signs were linked to pathologic alterations in a particular anatomic locus. This, in turn, became the dominant biomedical paradigm for the study and classification of all other diseases not to mention serving as a justification for the century-long search for cellular and molecular causal mechanisms.

In 1817 English physician James Parkinson described a chronic, progressive nervous system disorder characterized by a combination of tremor, rigidity, and stooped posture which became known as paralysis agitans and later as PD [8]. An 1872 paper by physician George Huntington, 'On Chorea', appeared in the Medical and Surgical Reporter which described a hereditary form of chorea associated with mental deterioration that began in middle age and ran a relentlessly progressive course. His lucid account captured the attention of the medical community and soon became known as Huntington's chorea [9, 10].

The first systematic attempt to explain the movement disorders was begun in the 1870s by French neurologist Jean-Marie Charcot, regarded as the founder of modern neurology [11]. Charcot introduced the term amyotrophic lateral sclerosis to designate the pathologic changes in grey and white matter tracts of the spinal cord. Charcot claimed that ALS was the most thoroughly understood disease of the time and yet he could never explain how the characteristic lesions developed, where they began, or how they evolved. Nor could 20th century scientists.

In 1907 German physician Alois Alzheimer reported the case of a 51-year-old demented woman constituting the first known description of AD. Symptoms included loss of memory for recent events along with a cluster of verbal and visual impairments. When the woman died Alzheimer microscopically examined the brain tissue and observed the typical amyloid-β (Aβ) plaques and neurofibrillary tangles in the condition which now bears his name [12] (Figure 1).
In short order histologic descriptions of other ND diseases followed. Dutch pathologist Jelgersma (1908) and Alzheimer (1911) described the characteristic insoluble aggregates of HD. In 1912 neurologist Friedrich Lewy, working in Alzheimer's laboratory, described small deposits in the substantia nigra of what is now recognized to be the α-synuclein protein in the brain cells of individuals with PD (Figure 2).
In 1919 Russian pathologist Tretiakoff reported the presence of cell death and degeneration in the substantia nigra in 16 cases of PD and argued for a necessary relation between the motor symptoms and nerve cell death. His hypothesis sparked heated debate over the next several decades but was eventually substantiated. Nonetheless the connection between the symptoms and pathology of PD remained controversial until well into the 1960s [13].

In the early 1960s a report described decreased levels of the neurotransmitter dopamine in the corpus striatum of the basal ganglia of PD subjects [14]. The significance between cell death and dopamine deficiency became more apparent after administration of levodopa produced dramatic (if only temporary) reversal of symptoms in PD subjects. Later studies found that electrical stimulation of nerve tracts exiting the substantia nigra induce dopamine release [15].

Based on such developments the notion that AD symptoms might be related to neurotransmitter deficiencies gained currency in the 1970s. Levels of the enzyme choline acetyltransferase, responsible for the synthesis of acetylcholine, were found to be reduced by 60-90% in the cortex and hippocampal region of subjects with AD compared with age-matched controls [16-18].

Statistically based studies found inverse correlations between accumulation of misfolded protein aggregates like Aβ and α-synuclein and depletion...
of the neurotransmitter substances acetylcholine and dopamine respectively [19-22]. Based on such evidence strategies were implemented to augment neurotransmitter availability, either through administration of substances like L-dopa in PD that promote neurotransmitter synthesis or, conversely, by substances like the cholinesterase inhibitors donepezil and rivastigmine in AD which impair degradation of acetylcholine. Such molecular approaches remain first line treatments for AD and PD [23, 24].

While placebo-controlled clinical studies report modest improvement in the treatment of the various NDs, effects are mostly short-lived, often on the order of 6-12 months, and side effects not uncommon. Although such treatments are said to slow progression of the underlying disease processes, a questioned assertion, the fact remains that once symptoms manifest the ND diseases progress relentlessly leading to death over a variable course of years.

In the 1980s linkage analysis studies established a relationship between HD and chromosome #4. By 1993 the \textit{HDD} gene, which codes for the huntingtin protein, was isolated [25]. This discovery rekindled interest in the genetic basis of the ND disorders. Proponents argued that establishing genetic links would provide not only a means for early detection but insights into potential therapies [26].

During the 1990s and early 2000s mutations on three separate genes were found in families with early-onset AD, i.e., onset before 60 years old. But familial forms are rare and account for only about 1-2% of all cases of AD. Up to 30 genes have so far been identified for sporadic forms of AD but their significance remains unknown [27]. Five genes associated with early-onset Parkinson's have been found but such familial forms account for less than 5% of cases. While over 20 genes have been linked to PD, in most instances the significance of the gene as well as the function of the involved gene products remain unknown [28].

The insoluble protein aggregates of AD, A\textsubscript{β} plaques and neurofibrillar tangles, then became the subject of scrutiny [29]. Geneticist John Hardy advanced the amyloid hypothesis and asserted that A\textsubscript{β} plaques represent the primary pathology [30, 31]. He claimed that A\textsubscript{β} fibrils gradually coalesce into larger strands and thereby morph into the characteristic AD aggregates. Such A\textsubscript{β} plaques were said to be toxic and to trigger a plethora of morbid events like synaptic dysfunction, neurofibrillary tangles, inflammation and cell death, all of which result in dementia.

For nearly three decades researchers chased the A\textsubscript{β} hypothesis only to come up empty-handed. In recent years the failure of the amyloid hypothesis to explain the debilitating events in AD has come under increasing scrutiny [32-34]. In a 2018 editorial in \textit{Nature}, science writer Simon Makin posed the question 'is it time to look beyond amyloid-\textbeta as the root cause of the condition?' Neuroscientist Michael Murphy commented, 'the time to cast a wider net is now—we need a bigger base of ideas' [35].

**VASCULAR DYNAMICS**

As researchers groped their way through the maze of cellular and molecular pathways in search of answers, one of the most crucial discoveries in 20th century medical science took place with barely a glimmer of awareness among neuroscientists.

The 20th century concept of the circulatory system, advanced by Harvey and uncritically accepted by Starling, held that the heart functioned in the manner of a mechanical pump, propelling blood forward through the arteries during the systolic phase of the cycle. Diastole, conversely, was said to be a period of relaxation. But there was a
problem with the Harvey-Starling formulation: for 350 years scientists were unable to explain how blood returned through veins to the right side of the heart.

Then, in the 1980s, negative intraventricular pressure, i.e., a suction force, was discovered during early diastole indicating it was not a period of passive relaxation but, instead, a time during which blood was actively drawn forward through the veins into the right ventricle [36-39]. Systole could not be the primary phase of the heart cycle as Harvey and Starling had claimed. It must instead be diastole. In order for ventricles to pump blood through arteries they must first contain blood.

This recognition has deep historical significance: 1500 years earlier Galen had claimed that diastole was the primary phase of the cardiac cycle and Harvey, in his seminal work On The Motions Of The Heart (1628) [40], seeking to overturn the Galenic framework, the dominant medical system of the time, used his observations on the motions of the heart to supposedly refute Galen's assertion. But evidence now affirms Galen's version of cardiac function. Harvey and Starling were wrong.

Evidence continued to accumulate: studies found spiral flow currents in arteries and veins which can only be explained on the basis of a suctional force [41-54]. During its cycles of contraction and dilation the heart generates an electromagnetic field which forms the energetic basis for diastolic expansion and the suctional force. Galen described it as an 'attractive' force and, invoking the lodestone analogy, imputed it was magnetic in nature [55]. He was not so far off.

What happens during systolic contraction of the ventricles is identical to what happens during the induction of an external magnetic field by electrification of ferrous objects. As the ventricles contract and iron stores are brought into closer apposition iron nuclei in the heart muscle and blood align and process synchronously on the basis of field interactions. Electrical potentials in the nerves saturate the field and induce formation of a 3D magnetic field leading to dilation of the heart and arteries. The physical expansion is effected by conformational change in blood proteins.

By the late 1980s studies affirmed the primacy of diastole in the cardiac cycle and found, unexpectedly, that impaired outward movement of the ventricular and arterial walls, aka 'diastolic dysfunction', was the primary functional deficit in a wide range of chronic conditions like hypertension, diabetes, obesity, autoimmune diseases, and chronic organ failure syndromes like heart failure and chronic kidney disease [56, 57]. This is to say that all these conditions have as their primary basis an energy deficiency.

In an earlier review we show that microvascular dysfunction is the common underlying pathophysiology in all of these conditions [58]. On the arterial side of the circulation this leads to impaired energy generation in the blood and endothelial inflammation; on the venous side it results in weakening of the suction force, elevated central venous pressure (CVP), and impaired venous return of fluids to the right heart. Such small vessel dynamics form the basis of the NDs [59-66]. It is hardly surprising that all the traditional cardiovascular risk factors, i.e., hypertension, diabetes, obesity, hyperlipidemia and so on, are also risk factors for the dementias and NDs: microvascular dysfunction is systemic.

Evidence indicates that microvascular dysfunction and microcirculatory damage in the brain precedes the onset of symptoms in the various dementias and NDs. This has reshaped ideas about dementia and led to the concept of vascular dementia and so-called vascular cognitive impairment (VCI) [67-72]. The risk for dementia following stroke, for
example, increases in a linear manner, ranging from about 2-fold to 7-fold higher, depending on the severity, extent and number of stroke events [73-76]. Vascular causes of dementia are now second only to AD. And increasingly AD is being regarded as a vascular disorder [77].

Pathological changes in the dementias are well-described and point clearly to a vascular origin [78-83]. Due to cell death the number of arteries and veins in affected brain territories is sharply decreased [84-86]. Characteristic 'string vessels,' remnants of capillaries in which endothelial cells have died, are common features in the dementias in which oxidative stress and inflammation play a role [87, 88] (Figure 3). As a result of shrinkage of tissues, or perhaps due to increased venous back-pressure, small arterioles often appear tortuous and hyper-coiled [89-91] (Figure 4). Changes related to venous insufficiency and loss of the suctionsal force are even more striking.

Figure 3: Vascular string vessels in neurodegenerative disease [95].
For decades radiologists have observed on brain MRI scans what, originally, were called unidentified bright objects (UBOs) and are now known as white matter hyperintensities (WMHs), focal areas of increased signal in the white matter tracts surrounding the ventricles [92] (Figure 5). Called 'leukoaraiosis' by pathologists, such WMHs are seen both in cognitively normal and impaired adult persons, gradually progressing with age, from about 10-20% at 60 years-old to 80-90% at 80 years [93-97]. While largely asymptomatic they are not merely incidental milestones of aging. Instead, they denote microvascular dysfunction in the brain and their numbers increase in parallel with cognitive deterioration [98]. Altered venous dynamics play a key role in development of WMHs [99-101].
Figure 5: Axial T2-weighted MRI FLAIR images of the brain. Left image: normal-appearing brain in a cognitively intact 40yr female. Right image: extensive confluent white matter hyperintensities in the periventricular regions of a 79yr female with advanced dementia. (Courtesy of Simone Arrington, MD)

In the 1990s pathologists observed in histology specimens of WMH lesions increased venous wall thickness with accumulation of collagen and other proteins [102-105] (Figure 6). Calling it 'venous collagenosis' pathologists were quick to point out that the thickened walls might impair passage of fluids, solutes, and toxins into the veins but never made the connection with diastolic dysfunction. WMHs are associated with decreased cerebral arterial perfusion, small lacunar infarcts and microbleeds [106-111]. MRI studies later found increased diameter of veins draining these areas suggesting increased internal pressure and venous stasis [112-117].
Pathologists also described thickening of the basement membranes of arteries and veins, both in cognitively normal elderly and people with dementia, suggesting deposition and accumulation of proteinaceous material, a small vessel pathology known as cerebral amyloid angiopathy [118-126]. In this poorly defined, untreatable condition vessel walls are thickened and prone to rupture leading, once again, to small infarcts, microbleeds, and progressive cognitive decline [127-129].

While the etiology of amyloid angiopathy remains unclear, accumulation of amyloid secondary to disrupted venous drainage is believed to play a primary role [130-133]. Similar deposits are found in the interstitial fluid spaces of brain tissue [134]. While Aβ and neurofibrillary tangles are found in these deposits multiple other amyloid types are also present suggesting general impairment of fluid drainage and protein elimination [135, 136] (Figure 7).
Based on such evidence it is not surprising that elevated intravenous pressure and increased diameter of the jugular veins in the neck are associated with reduced cognitive function, dementia, progression of WMH lesions, loss of brain volume, disruption of the blood-brain-barrier and the whole spectrum of pathology [137-142].

On the venous side of the circulation diastolic dysfunction begins with impaired outward movement of the right ventricle and loss of the suctionsal force. Acute and chronic elevations in CVP are now recognized to be at play in a wide range of other pathological conditions including heart and kidney failure, pulmonary arterial hypertension, congestive hepatopathy, pancreatitis, and ascites [143-154]. Why should the brain be any different?

**CSF & GLYMPHATIC SYSTEM**

Nowhere is the dubious merit of the experimental method more apparent than in the centuries-long trek by scientists to discover the purpose, anatomy, and function of the brain's ventricular system and cerebrospinal fluid (CSF) pathways. Such phenomena were originally described by Galen in the 2nd century AD and form the basis for modern ideas on the subject.

Called the 'third circulation' by early 20th-century surgeon Harvey Cushing – in contradistinction to the blood and lymphatic channels – CSF is said to serve a protective function by cushioning the brain against injury and as a conduit for removal of wastes. But as to where CSF is produced, its circulatory pathways, or how it exits the CNS, scientists still haven't reached consensus [155-162]. And to date they have yet to even consider...
its most important function which, as we will see, is intimately tied to the origin and progression of the dementias and NDs.

Galen claimed that the primary purpose of the ventricles and CSF is to provide energy currents to brain tissue for its role in the mediation of consciousness functions. A secondary purpose includes removal of metabolic wastes. Galen, one of the foremost experimentalists in the ancient world, was a vocal proponent of an organized energy field originating in the blood. Central to his humoral system of medicine was the concept of pneuma, an energetic substance variably denoting spirit, movement, force, wind, breath, or consciousness [163].

According to Galen, pneuma, drawn inwardly to the lungs through the breath, passes into the pulmonary veins and subsequently the left ventricle of the heart where it is transformed, i.e., energized, into pneuma zötikon (vital energy). This vital pneuma, in turn, is carried by arterial blood to all parts of the body. In the brain it is filtered by the choroid plexus, which lines the ventricular cavities, and secreted into the ventricles as pneuma psychikon, (cerebral pneuma). Cerebral pneuma, in turn, is distributed throughout the brain in the CSF where it provides the energetic basis for all functions.

Experimental scientists have largely avoided the question as to the origin of electrical currents that pass-through nerves. Since the early 20th century neurons have been conceived as tiny batteries that generate their own currents but this doesn’t fly in the face of dramatic events like sudden cardiac arrest in which there is immediate loss of consciousness and neuronal function at the moment cardiac activity ceases. How to explain the tight functional linkage between the two compartments?

Given the directionality of flow currents in nerves the question also arises as to where peripheral sensory nerves, which course toward the brain and spinal axis, derive their potentials. The unavoidable conclusion is that they originate in ECF and the interstitial fluid space. By the same token, given that the surface of the cerebral hemispheres is lined by dendrites, which lie in intimate relation to the CSF, and which convey currents directionally into deeper brain regions, one must draw similar conclusions as to the origin of electrical currents in the brain.

CSF is not simply a passive medium intended to cushion the brain against injury or transport waste materials. CSF, an ultrafiltrate of energy-rich arterial fluid, carries electromagnetic currents that pass-through voltage-gated ion channels of cell membranes and, ultimately, drive all cell functions. This will become apparent when we examine the protein misfolding problem associated with the NDs.

Scientists distinguish between CSF and ECF but, from a functional standpoint, they are one and the same and, in fact, freely admix throughout the CNS. In this sense the CSF and ventricular system must be regarded as an adaptive expansion of the interstitial fluid space for the purpose of delivering sufficient energy currents to meet the energetic needs of the brain. No other explanation makes sense.

In the early 20th century neurosurgeon Walter Dandy experimentally removed the choroid plexus of lab animals and, when CSF didn’t reaccumulate, claimed it ‘proved’ that the choroid plexus was the site of CSF production. This sparked a century-long debate among scientists as to the origins of CSF [164-166]. Experiments repeatedly suggested that CSF was secreted at other sites besides the choroid plexus and more recent evidence suggests it is produced throughout the brain [167]. Galen
claimed that while the choroid plexus was the primary source of CSF, cerebral pneuma also derived from small arteries that course over the surfaces of the hemispheres. It seems a foregone conclusion that arterioles and capillaries should secrete fluid in brain tissue just as they do in all other tissues of the body. It is now generally accepted that about 70-80% of the CSF is produced by the choroid plexus with the remainder generated diffusely throughout the brain.

Equally vexing is the question of CSF flow patterns and the pathways by which it exits the CNS. This circles back to the diastolic suction force. By mid-century it was widely accepted that CSF was produced at the choroid plexus, circulated through the ventricles into the subarachnoid space over the surface of the hemispheres and, finally, was reabsorbed into the venous system through so-called arachnoid granulations in the superior sagittal sinus (Figure 8). But there were problems with this concept.

![Cerebrospinal fluid flow in the human brain. Important sites of egress include the cribriform plate (1), cranial nerves (2), meningeal lymphatics (3), and Spinal nerves (4) [168].](image)

When dyes and tracer substances were introduced into the CSF they were often found in other venous structures as well as in lymphatic channels. Other studies found the cribriform plate above the nasal cavity was a major site of exit from the CNS. And drainage patterns changed according to how, where and what kind of tracer was introduced. Galen claimed CSF exited through the cribriform plate. Multiple egress pathways are now recognized including veins, lymphatics, cribriform plate and the sheathes of spinal nerves [169-181]. More important than where CSF is reabsorbed is how it happens. And once again our friend Ernest Starling plays a role.
Because 20th century scientists had no recourse to physical forces other than the propulsive systolic force generated by ventricular contraction, they were at a loss to explain the movement of fluids, electrolytes and other substances across membranes and barriers. Based on experiments Starling advanced two key concepts, called osmotic and hydrostatic pressure, that gained wide currency among 20th-century scientists [182, 183].

The idea is simple: when ions or molecular substances are in higher concentration, or water pressure higher, on one side of a biological membrane than on the other, forming a so-called gradient, directional flow is created leading to equilibration between the two compartments. This concept was used, for example, to explain the flow of fluids back into the veins from the interstitial fluid space: higher osmotic pressure inside veins 'pulled' ECF water back into the vascular compartment. Some called into question the notion of osmotically driven fluid flows [184, 185]. So-called osmotic phenomena are readily explainable on the basis of the suction force or equilibration of voltage potentials. There were other problems with Starling’s model.

Throughout the 20th century evidence kept pointing toward some kind of diffusely orchestrated movement of fluids, what researchers called 'bulk flow', that occurred over shorter time frames, greater distances, and possessed a directional or vectorial component, what is now called 'convective flow' [186-188]. Earlier in the century several researchers had reported negative pressures inside the sagittal sinus compared to the adjacent subarachnoid space but didn’t fully consider the implications of this finding [189].

Galen observed that brain pulsations and CSF movement coincided with arterial pulsations. And after the heart stopped so too did the movement of CSF. But because he regarded the arteries and veins as separate circulations, he was unable to explain the significance of this observation. More recent experiments confirm synchronicity between cardiac pulsations and CSF flow [190-193]. Convective flow movements can only be explained on the basis of the diastolic suction force in the venous system. This leads us to consider the discovery of the glymphatic system.

In an ingenious study reported in 2012, Iliff et al. introduced a fluorescent tracer into the CSF and observed its sequential passage through a system of pathways: from the subarachnoid space tracer moved rapidly into the brain along perivascular spaces surrounding small arteries and, minutes later, entered the interstitial fluid compartment, freely mixing with ECF, and, finally, accumulated in perivascular spaces surrounding the venous side of the circulation [194].

This linchpin study is the first to convincingly demonstrate convective flow of CSF/ECF along organized channels and, ultimately, its egress into lymphatic and/or venous conduits for return to the right heart. The possibility of this system had been raised in multiple earlier studies dating back to the 1980s but never developed further [195-203].

Based on such evidence researchers posited the presence of an organized system of flow channels surrounding cerebral arteries and veins they called the glial-lymphatic or 'glymphatic' system (Figure 9). The system, donut-shaped in cross-section, is bounded internally by the outer basement membrane of arteries or veins and, externally, by a membrane formed by foot-processes of astrocytes. This outer astrocyte barrier is lined with what are called aquaporin-4 (AQP-4) channels that shuttle water from the perivascular space into the interstitial fluid space. So where does all this lead?
Figure 9: Relationships between the subarachnoid space, perivascular lymphatic system and cerebral vascular system. The perivascular space is continuous with the subarachnoid space. CSF is actively drawn into these channels by a suction force generated during right ventricular diastole. Fluid also moves from the arterial lumen, across the blood-brain barrier in the vessel wall, and freely admixes with CSF. Astrocytes form the boundary between the perivascular space and the interstitial fluid space (ISF). Fluid movement between these two compartments is mediated by aquaporin-4 (AQP-4) channels in astrocytic endfeet. Fluid flow through the interstitial space and back into veins is convective in nature and, once again, mediated by dilation of the right ventricle. Perivenous spaces (right side of image) are confluent with periarterial and subarachnoid spaces thereby creating a continuous system of channels that drain into progressively larger veins and lymphatics, all driven by cardiovascular and respiratory dynamics [204].

Recognition of bulk fluid movement by Iliff et al. represents indisputable evidence that the diastolic suction force of the right ventricle orchestrates the convective flow of CSF throughout the brain including passage of ECF through the interstitial fluid space. The so-called glymphatic pathway constitutes the primary elimination route for metabolic wastes from the brain and, by implication, must play a role in the genesis and progression of the dementias and NDs.

In the same set of experiments Iliff et al introduced fluorescent-tagged Aβ into the CSF of lab animals and found that it tracked along these same pathways. In a strain of AQP4 genetically-deficient mice (with impaired fluid movement into the interstitial space) they observed a 70% reduction in clearance of Aβ affirming the role of the glymphatic system as a drainage pathway and suggesting its impairment played a role in accumulation of misfolded proteins. In another study they found dramatic decreases – up to 40% – in the efficiency of the glymphatic system in old versus young mice along with a 27% reduction in arterial pulsatility [205]. Dozens of subsequent studies support these findings [206-228].

In recent years researchers have employed an MRI technique known as diffusion tensor imaging (DTI) to assess the strength and directionality of water flow along perivascular routes in the brain [229]. Called the ALPS-index, higher values signal...
stronger, more coherent convective flow while low values suggest glymphatic dysfunction. Various clinical studies found 'remarkable differences' in the ALPS-index between cognitively normal and cognitively impaired individuals. Lower ALPS values predict severity of white matter hyperintensities, lacunar infarcts, microbleeds, and enlargement of perivascular glymphatic channels. The ALPS-index strongly correlates with cognitive impairment as well as attention and memory deficits [230-240]. All roads lead back to diastolic dysfunction.

Based on strength of evidence numerous scientists have come out in support of the glymphatic system and its pivotal role in the elimination of metabolic wastes and misfolded proteins [241-248]. But curiously, to date, we have yet to find a single report tying this organized convective flow system into right ventricular diastolic function. Instead neuroscientists continue to invoke 'Starling forces' to account for its function. How ironic, in light of perceptions of the experimental method as a gold standard for adjudicating matters pertaining to fact-based knowledge, not to mention correcting flawed assumptions of the past, that contemporary scientists cannot even explain the basis of their own experimental findings. Scientists, it appears, 'see' only what their conceptual framework allows them to see.

THE MISFOLDING PROBLEM

In the late 1990s the Aβ issue took on a new layer of complexity. Decades earlier researchers had discovered that cataracts, the accumulation of cloudy opaque material in the lens of the eye, resulted from misfolding of proteins [249]. Then, in the mid-90s, researcher Stanley Prusiner discovered that prions, the suspected cause of a transmissible and invariably fatal form of neurodegeneration in animals and humans, were also misfolded proteins. This led researchers to reconsider not only the genesis of the NDs but the nature of Aβ.

Amyloid aggregates, aka 'plaques,' typically found in the ECF space in tissues throughout the body, are composed of fragments of numerous – perhaps as many as 20-30 – different proteins. For reasons we will discover, normal synthesis, folding and degradation pathways in cells become impaired and, in consequence, protein fragments accumulate in cells and in the interstitial fluid compartment. Amyloid aggregates gradually develop from small fragments, called oligomers, that self-assemble into larger fibrillar complexes. Although oligomers share little similarity in terms of amino acid sequence, during aggregation they organize into a common architecture called the pleated β-sheet configuration [250-253] (Figure 10).
A defining step in the Aβ aggregation process is transition from water-soluble oligomers to insoluble deposits. In the 1980s pathologists described a peripheral 'halo' surrounding Aβ aggregates which was later found to be mainly water [255]. More recently such halos were found to contain soluble Aβ oligomers suggesting that aggregation dynamics bear resemblance to a crystallization process and are driven primarily by energy content in the surrounding fluid medium [256-260].

It appears that, as the β-sheet structure continues to expand and elongate, it absorbs energy from the surrounding fluid milieu. This would explain scientists' claim that Aβ aggregates exhibit a 'toxic gain of function' [261-264]. But the so-called
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Toxicity lies not in the inert Aβ plaques themselves but in the fact that their transition to an insoluble state diverts energy away from other cell functions.

Proteins possess a complex 3D arrangement. Primary structure, which is genetically coded, refers to the sequence of amino acids that form 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 not by covalent bonding but by intermolecular forces like hydrogen bonds and dipole-dipole interactions. Folding takes place in the cytoplasm and is energy-dependent. The tertiary structure represents the overall 3D conformation of the protein which is also a result of non-covalent intermolecular forces [265-272].

Tertiary structure, known as 'native fold', is responsible for the functional properties of a protein. When carrying out 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 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). The very same events take place in the CNS, for example, during transmission of electrical impulses through nerves.

In recent decades an explosion of research in the physical sciences using x-ray scattering, NMR spectroscopy, and x-ray crystallography has examined protein structure and folding dynamics [273-282]. All the various methods affirm the role that tissue water plays in protein-related dynamics. To be biologically active proteins must acquire a so-called hydration shell which consists of multiple layers of water molecules. The hydration shell appears to be instrumental in determining not only 3D 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 likened to a semi-crystalline state. The protein-water complex becomes structured and assumes gel-like consistency. Hydration shell water surrounding proteins has physical properties distinct from water in the adjacent fluid spaces including net (−) charge, higher pH, and increased density, as detailed by biologist Gerald Pollack in his groundbreaking work *The Fourth Phase of Water* (2013) [283]. Changes in water state, both in the intracellular and extracellular fluid compartments, would seem to provide an ideal energy source for many protein-mediated biological processes. A dramatic example of such structured water is the zona pellucida, the translucent protein-water matrix surrounding the outer membrane of the ovum.

To explain altered protein functions researchers introduced the concept of 'intrinsically disordered proteins' (IDPs), proteins that do not have a stable native 3D conformation and are prone to spontaneously self-aggregate. A characteristic feature of IDPs is 'conformational plasticity' and lack of a proper 'folding code', which is to say they cannot assume native configuration [284-287]. A prime example is auto-antibodies in which impaired folding dynamics leads to cross-reactivity with normal cellular structures. IDPs have altered binding affinities for water and hydrogen bonding capacity compared with natively-folded proteins [288-291]. IDPs represent the link between the NDs and prion disease.

The prion diseases are progressive, transmissible NDs seen in higher vertebrate species: scrapie in sheep, chronic wasting disease in deer, mad cow...
disease in cattle, and kuru and Creutzfeldt-Jacob disease in humans. The 'causal' agent is said to be a neuronal protein that undergoes pathological misfolding and propagates along nerve tracts in cell-to-cell fashion [292-300]. Alzheimer's and Parkinson's have many similarities with the prion diseases and are now recognized to spread in 'prion-like' fashion [301-306]. In this sense, the term prion, rather than denoting a particular disease entity, designates the means by which protein misfolding disorders propagate and spread throughout the nervous system. To wit: Injection of purified Aβ material into AD-prone mice accelerates deposition of Aβ and intracellular neurofibrillary tangle formation in surrounding brain tissue of the mice [307-311]. Similar phenomena were observed during the pandemic: the presence of the SARS-CoV-2 protein in the serum was found to enhance amyloid formation [312-316]. In lab studies the SARS-CoV-2 protein induced Lewy body formation in PD-prone cell lines. Other studies found that interactions between the SARS-CoV-2 protein and α-synuclein accelerated Aβ formation. Such phenomena constitute what researchers now increasingly refer to as prion-like transmission.

Once pathologic fibrillization pathways become established misfolded species continue to spontaneously self-assemble and propagate at the expense of normal cell functions. And given that, in many cases, they are located in the interstitial fluid space, they have access to ECF-borne energy currents before they reach the cell membrane which is to say that aggregation phenomena are capable of inducing a self-amplifying spiral of deterioration. Conversely, a primary decline of energy pathways as seen, for example, in normal aging may also predispose to misfolding leading to Aβ accumulation along drainage pathways. The strong association between the NDs and aging is well established [317,318].

The conjoined role of proteins and water in the energy economy of the body formed a central motif in early 20th century research. Swedish physical chemist Svante Arrhenius published the first work on electrical conductivity of ionic solutions, Investigations on the Galvanic Conductivity of Electrolytes, in 1894 [319]. He noted that salts dissolved in water split into electrically positive and negative ions that transmit electrical currents in the fluid medium.

Arrhenius' work formed the basis for what became known as 'colloid theory' which, simply stated, held that ion-containing intracellular water interacts with cell proteins to produce complex 3D structures which, under physiologic conditions, assume gel-like consistency. In 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 mediate a wide range of bodily processes. 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' [320]. Interactions are based less on chemical constitution than on physical phenomena like pH, solubility and temperature.

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 that drive all functional processes. Structural elements are linked by electromagnetic interactions, what he called 'ferromagnetic cooperativity' [321]. In 1962 Ling advanced his 'association-induction' hypothesis claiming that
electrical polarizations and depolarizations, i.e., induction, were at play in such conformational dynamics. (94) Colloids exist in open and closed states and undergo reversible transitions based on energy flux [322]. More recently, in *Cells, Gels and the Engines of Life* (2001) Pollack ties cell functions into a tidy unifying framework on the basis of colloid dynamics [323].

But, once again, the science community failed to incorporate such evidence into its conceptual framework and continued, instead, to chase shadows based on flawed cellular, genetic, and chemical theories of causation. It is even accurate to say that research which ran contrary to their encrusted dogma was actively squelched: 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. In hot pursuit of its one-sided agenda 20th century medical science must shoulder a large burden of responsibility for the unfolding epidemic of chronic disease that now spreads unchecked across the globe.

**INTRACELLULAR ENERGY PATHWAYS**

We have established that water-borne energy dynamics drive conformational change in normally functioning proteins as well as inducing their folding into the native 3D configuration. All aspects of protein metabolism and function, including synthesis, folding, and degradation, are intimately bound into the body's energy economy.

On the venous side of the circulation diastolic dysfunction manifests as weakening of the suctional force with diminished return of fluid and metabolic wastes into the veins. On the arterial side the problem is quite different and is driven by deficient energy currents in the ECF space resulting in chronic inflammation along with progressive functional deterioration of cells and organs. The pathologic cascade configures around one primary disturbance: microvascular dysfunction and impaired energy generation in the blood.

Microvascular dysfunction was first recognized in the 1970s in people with angina pectoris who, paradoxically, had normal appearing coronary arteries by angiography. Called cardiac syndrome X, it was originally believed to be a benign condition that involved only coronary vessels but this proved to be wrong on both counts. It is now recognized to involve the entire microcirculation and adversely impact the function of multiple organs including the brain and kidneys [324-332]. People with coronary microvascular dysfunction often have abnormal brain perfusion and are at higher risk for neurologic problems like the NDs and stroke. Microvascular dysfunction is an invariant accompaniment of chronic systemic conditions like obesity, diabetes, and hypertension.

The first clue that cellular disturbances in the NDs are secondary to impaired energy flow into the cell is seen in the increasingly recognized phenomenon of ion-channel dysfunction [333-335]. So-called ion channels are formed by proteins in the cell membrane that connect the ECF space with the interior of the cell. They may or may not be actual openings but, instead, likely function on the basis of conformational changes that shuttle water, ions, or energy between the two compartments. More than 100 different ion channels have been described. A single neuron may contain 10-20 different kinds of channel proteins [336].

While channel activity is driven by various stimuli, we are interested in a particular class known as voltage-gated channels which function on the basis of energy gradients across the two sides of a membrane. The term 'gated' implies that such channels are not always open but, rather, alternate between open and closed states, which one would expect from a protein-mediated (and...
energy-dependent) process. Such voltage-gated channels are said to induce current flux through nerves, electrical excitation of muscle tissue and are likely to be involved in intracellular protein folding and conformational change.

A key feature of ion channels is selective permeability: each allows preferential passage of a particular kind, i.e., Na⁺, K⁺, Ca²⁺, Mg²⁺, or Cl⁻, into the adjacent fluid space. The ability to regulate ion flux across membranes is essential for maintaining an optimal milieu inside cells. When channels 'open' they permit rapid flow of ions along their electrochemical gradients, i.e., from high to low concentrations, just as Starling's concept of osmotic pressure would suggest. But when one inspects the dynamics more closely it isn't quite as simple as Starling implied.

Potassium (K⁺), for example, is the major intracellular cation, with 98% of the total pool located inside cells at a concentration of ~130-150 mmol/L compared to ~3.5-5 mmol/L in the ECF space [337, 338]. This amounts to roughly a 30-40:1 ratio between the two compartments. When a neuron transmits its impulses channels open and K⁺ surges out of the cell into the ECF space along the gradient. But for this to happen continuously K⁺ must be repeatedly pumped back into the cell to reestablish the gradient. Neuronal transmission is highly energy-intensive. From where does this energy derive if not the ECF/CSF?

The critical import of voltage gradients and the ECF/CSF compartment is even more apparent in the case of Ca²⁺. In the ECF space Ca²⁺ concentration is ~2-5 mmol/L while intracellularly it is ~100-300 nanomols/L equating to roughly a 10,000:1 gradient. Elevated intracellular Ca²⁺ levels are associated with oxidative stress, inflammation, defective neurotransmitter release, elevation of pro-inflammatory cytokines and cell death [339-343]. Increased intracellular calcium promotes progression of AD by inducing Aβ and neurofibrillary tangle formation [344-349]. Given such detrimental effects the critical role of protein channels in maintaining Ca²⁺ gradients is obvious. Yet another energy intensive process.

In recent decades an increasing number of diseases have been linked to ion channel dysfunction and constitute a broad category of conditions known as the 'channelopathies' that now include Alzheimer's, Parkinson's, Huntington's, ALS, and the vascular dementias [350-352]. Channelopathy is but another name for altered colloid dynamics. Characteristic symptoms of the various NDs have been traced to ion channel dysfunction: ALS, for example, involving cortical and spinal motor neuron tracts, is associated with impaired Na⁺ and K⁺ ion channel function causing membrane hyperexcitability with fasciculations and cramping [353-358].

The tremors, altered muscle tone and gait disturbances of PD are related to K⁺ channel dysfunction which alters membrane excitability, depolarization frequency and neurotransmitter release in affected neuronal territories [359-364]. Huntington's chorea, characterized by hyperexcitability and sustained muscle contractions, is associated with K⁺ and Cl⁻ channel dysfunction [365-371]. Voltage-gated Na⁺ channels are recognized to play a key role in AD [372-376]. And Ca²⁺ channel dysfunction has been described in most of the NDs [377-385]. Energy deficits in the dementias and NDs begin at the cell membrane and point unambiguously to deficient current flow from the ECF/CSF compartment into the cell.

The influence of ion channels is not restricted to the outer cell membrane. All the key cellular organelles – mitochondria, lysosomes, endoplasmic reticulum, and nucleus – possess ion channels that induce function. Recognition of such channels would seem to demand existence of an organized system.
of pathways inside cells based on voltage gradients and ion conductances. Altered channel dynamics underlie the nest of disturbances associated with inflammation, protein misfolding and, ultimately, cell death.

A rash of intracellular abnormalities are found in all the NDs: endoplasmic reticular, lysosomal and mitochondrial dysfunctions, diminished energy substrates like ATP, accumulation of reactive oxygen species and other toxic by-products, lowering of cellular pH, and defects in processes responsible for protein folding as well as the degradation and elimination of misfolded proteins [386-395]. The laundry list of cellular abnormalities in the NDs once again implicates a global energy deficit. Scientists seek to explain such phenomena on cellular and molecular mechanisms but they should be looking elsewhere for answers.

Most proteins fold in the endoplasmic reticulum which provides a conducive milieu and quality control mechanisms by which to maintain native fold. Voltage-gated Ca\(^{2+}\) and K\(^{+}\) ion channels in the membrane are essential to this function [396-400]. A specialized class of proteins called 'chaperones' discriminates between native and non-native (IDP) conformations. If misfolded proteins cannot be refolded, they are earmarked for degradation through a second set of processes known as the 'ubiquitin-proteasome pathway'. In oxidative stress coordination between such processes is disrupted and misfolding more likely to occur. Once a critical concentration of misfolded protein or soluble oligomers is reached, they become irreversibly prone to form aggregates which, once again, diverts energy away from normal cell functions and compounds the energy debt [401-409].

By the same token the main degradative pathway in cells, autophagy, which occurs in lysosomes, is energy dependent [410-414]. Misfolded proteins and damaged organelles are engulfed in membrane-bound vesicles and transported to lysosomes where they are exposed to highly acidic conditions (pH<5) and up to 60 different acid-activated proteolytic enzymes that degrade and digest the defective macromolecules. A variety of ion channels in the membrane, including voltage-gated 'two-pore' channels, actively mediate the flux not only of protons (H\(^{+}\)) into the lysosome but differential movement of ions like Ca\(^{2+}\), Na\(^{+}\), K\(^{+}\), and Cl\(^{-}\) [415-420]. Defective autophagy is a primary feature of all the NDs.

Mitochondrial dysfunction also plays a key role in all the NDs. Impaired voltage-gated ion channel function leads to disruption of ionic gradients in mitochondrial membranes, reduced energy generation, and formation of toxic reactive oxygen species [421-428]. This, in turn, induces oxidative damage in macromolecules like RNA and DNA as well as promoting misfolding of proteins and aggregate formation. Reduced energy availability impairs lysosomal concentration of acid adversely impacting autophagy and secondarily leading to cellular acidification. Equally, mitochondrial dysfunction affects neurotransmitter release and generation of action potentials in neurons [429-441]. Even cell death is mediated by ion channel pathways.

When oxidative stress and reactive oxygen species reach critical thresholds a class of membrane protein known as 'transient receptor potential' (TRP) channels is activated [442-450]. Mainly located in the outer cell membrane, they function as 'sensors' that undergo conformational change in response to deteriorating intracellular conditions. The TRPM2 channel in neurons is a 'non-selective,' 'non-voltage-dependent' Ca\(^{2+}\)-permeable channel, which is to say a default pathway, that induces broad cellular depolarization. The resultant surge of Ca\(^{2+}\) into cells induces NLRP3 inflammasome activation, release of pro-inflammatory cytokines and apoptotic cell death [451-459]. Ion channels
and energy flow drive all cell functions. So how does water play into such dynamics?

In an experiment intended to demonstrate the effects of electric fields in water Swedish radiologist Bjorn Nordenström packed a U-shaped glass tube with cotton wool in its lower curved portion to simulate capillary resistance [460] (Figure 11). 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?

Figure 11: Nordenström's galvanic experiment. DC currents induce differential fluid levels in the limbs of the glass tubes surrounding the cathodic and anodic elements. Elevated water levels around the cathode are mediated by the 3D expansile force of the magnetic field. Lowered water levels around the anodic element are secondary to the contractile/densification field.

Scientists ascribe such results to electrically-induced migration of charged species, including water, with differential accumulation at the two poles but this doesn’t make sense. The differential levels are no more explainable by bulk movement of water and ions than are oceanic tides. Such spatial reorganization of water is purely field-mediated. Currents on the cathodic side generate a magnetic field around the wire that induces local expansion of water. By the same token, currents pulled out at the anode induce contraction of surrounding water which causes its level to drop. Real forces produce...
differential fluid levels and local accumulation of ion species.

In an earlier work we describe the unique energetic properties of water and its role in mediation of what 19th century physicist Michael Faraday originally called the 'dielectric field' [461-463]. The dielectric field is composed of two opposing forces, the expansionary magnetic and a contractionary (or densification) force. It is no coincidence that water has one of the highest dielectric constants, i.e., polarizability, of any substance. When electrical currents pass through water, they cause the two fields to repel each other and assert their opposing effects around the cathode and anode. It is precisely this dynamic which is at play in the NDs. As in automotive battery aggregates tend to precipitate out at the anodic pole where the contractionary force is strongest. Accumulating evidence points clearly in this direction.

In the past decade scientists have drawn increasing attention to the problem of 'macromolecular crowding' and the impact of confined environments on protein folding and conformational change. Studies indicate such conditions influence protein structure, folding, shape, conformational stability, functional activity, and interactions with other substances. Intracellular crowding is more prone to result in intrinsically disordered proteins and pathologic aggregation [464-483]. Scientists have no compelling explanation for this cell-wide phenomenon.

Protein misfolding and aggregation reflect the energy content and disposition of forces of the milieu in which they reside. In the cardiovascular system, as we have seen, the outward movement of the ventricular and arterial walls is related to generation of a magnetic force. Magnetism is the only primary energy form possessing 3D spatiality. It is not surprising that arterial stiffness, which indicates dominance of the contractile force, is associated with so many chronic disease conditions including the NDs [484-493]. With progressive weakening of the magnetic field, as seen with diastolic dysfunction, the contractionary force gains proportional strength thereby altering water dynamics in the vascular system, ECF and intracellular compartments giving rise to widespread downstream pathologic carnage. As Galen claimed, *omnia incipit in sanguine*, everything begins in the blood.

**SUMMARY**

One hundred years after Starling's delusional 1923 Wisdom of the Body oration we are afforded quite a different view of science and the experimental method. Starling's sentiments typify the monumental hubris (and naiveté) of the 20th century science community which professed unwavering belief in the power of experiment and infallibility of scientific knowledge.

But as science philosopher Karl Popper points out in *The Logic of Scientific Discovery*, all scientific knowledge is tenuous and provisional [494]. There is no such thing as 'proof' in science. While experiment can verify the factuality of observed phenomena, explaining their significance is a quite a different matter. As the primary basis of experimentation involves isolation of variables from their natural circumstances, or simply comparing one set of conditions to another, it would seem inevitable that this approach would predispose to creation of a fragmented and abstract form of knowledge lacking in proper context.

Throughout the 20th century the experimental method was touted as a gold standard for knowledge generation and scientists issued definitive proclamations on the nature of phenomena without ever understanding the context of facts they propounded. Over decades this fledgling work-in-progress became elevated to
a voice of authority which, in turn, morphed into an authoritarian voice that sought to dominate the intellectual strata of societies. By the end of the century science had devolved into scientism, a collectively shared delusion that had less to do with objectivity than an irrational belief in its own power to adjudicate and issue binding proclamations.

Medical scientists purported to establish an ironclad science based on experimental analysis at the cellular and molecular levels but completely overlooked the existence of an organized energy economy. With recognition of the causal potency of the blood-borne energy field their cell- and molecular-based theories become irrelevant, which is to say they have little bearing on the proper treatment and cure of disease conditions.

By the same token, medical science has been in steep decline in recent decades with few conceptual advances and even fewer new effective treatments. It is questionable whether cellular and molecular science has any further contributions to make in the realm of therapeutics. Given the abysmal mismanagement of the recent pandemic by medical scientists its long-term future looks bleak. The entire history of medicine consists of warring medical factions that come and go with striking regularity. Galen's humoral medicine is the only system that has ever had any legs.

A new energy-based, functionally-oriented medicine is emerging at a grassroots level across the planet and will undoubtedly assume greater importance in coming decades as deterioration of organized healthcare continues. This transition represents a necessary conceptual advance while, at the same time, circling back to the very roots of medicine. But there are daunting challenges.

Undoubtedly the most pressing issue concerns the ever-widening arc of chronic disease and, by necessity, the new functional medicine must confront the glaring failures of the current system. The first imperative, which we hope to address in this ongoing series of papers, is to advance a unitary evidence-based dynamic framework that will allow common recognition and establishment of therapeutic principles. In our next piece we examine the autoimmune disorders.

**REFERENCES**


Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm


