TheGMS
The Gazette of Medical Sciences
https://www.thegms.co ISSN 2692-4374 DOI https://www.doi.org/10.46766/thegms

Neurology | Review

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

K. E. Thorp[1]*, James A. Thorp[2], Christiane Northrup[3], Elise M. Thorp[4], Sue E. Peters[5], Paul R. Walker[6]

[1]MD, Department of Radiology, Sparrow Health System, Lansing, MI.
[2]MD, Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Sisters of St. Mary's Health System, St. Louis, MO.
[3]MD, Former Assistant Professor Obstetrics and Gynecology, Vermont College of Medicine, Maine Medical Center, Yarmouth, ME 04096.
[4]BS FNTP. Williamston, MI.
[5]PhD, Research Fellow, Children's Health Defense, Franklin Lakes, NJ.
[6]BSME, MSEE.

Submitted: 29 June 2023
Approved: 19 July 2023
Published: 21 July 2023

Address for correspondence: K. E. Thorp, Department of Radiology, Sparrow Health System, Lansing, MI.

How to cite this article: Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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. Such advances, however, didn't come from expected quarters where scientists had focused much of their efforts but, instead, from outside the proverbial box, in areas that had been overlooked or rejected by the science horde.

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

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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 Alöis 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).

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

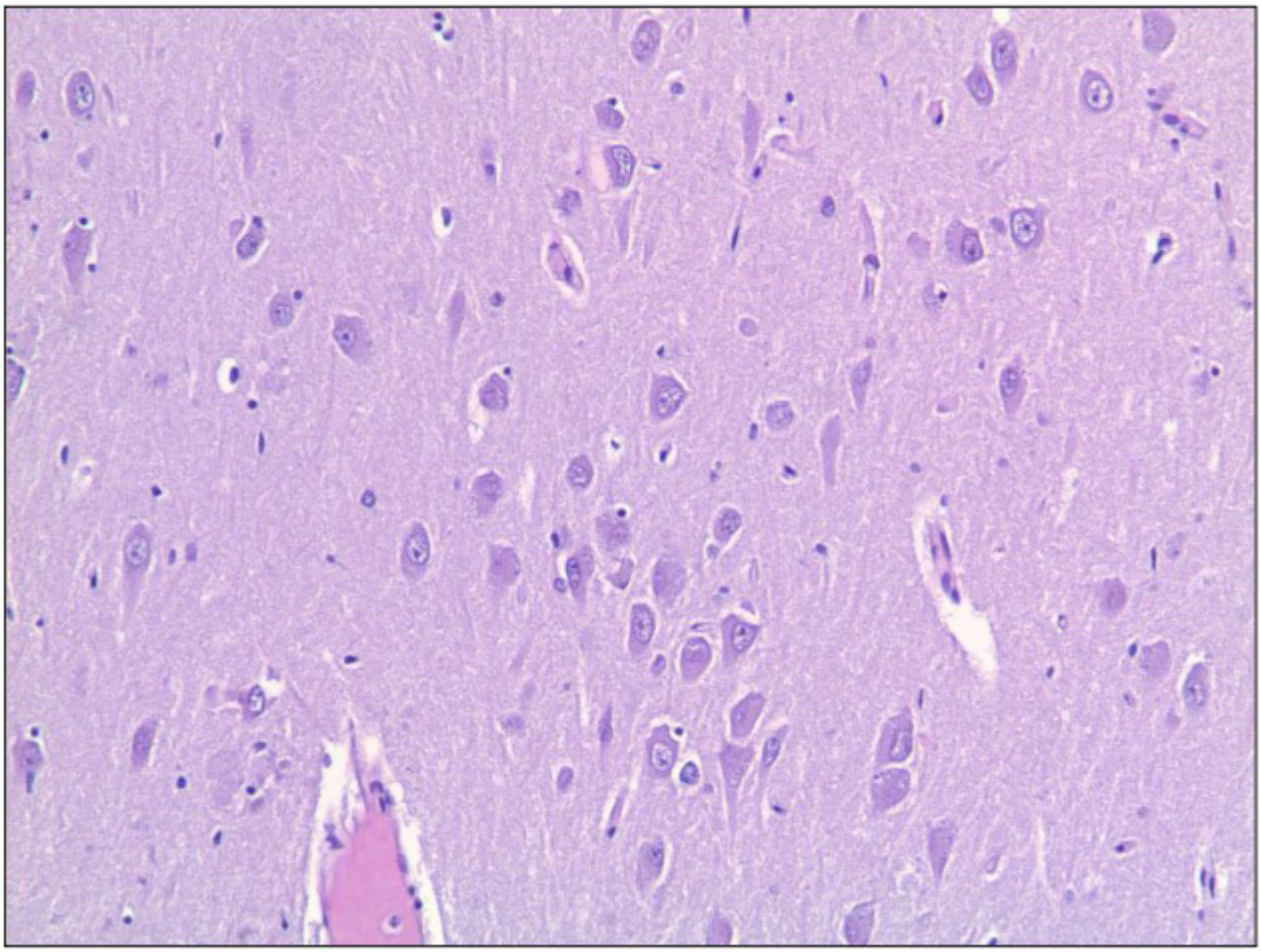

Figure 1: Hippocampal Aβ deposits in a 77 y/o man with Alzheimer's dementia. (Courtesy of Howard Chang, MD, PhD)

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).

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

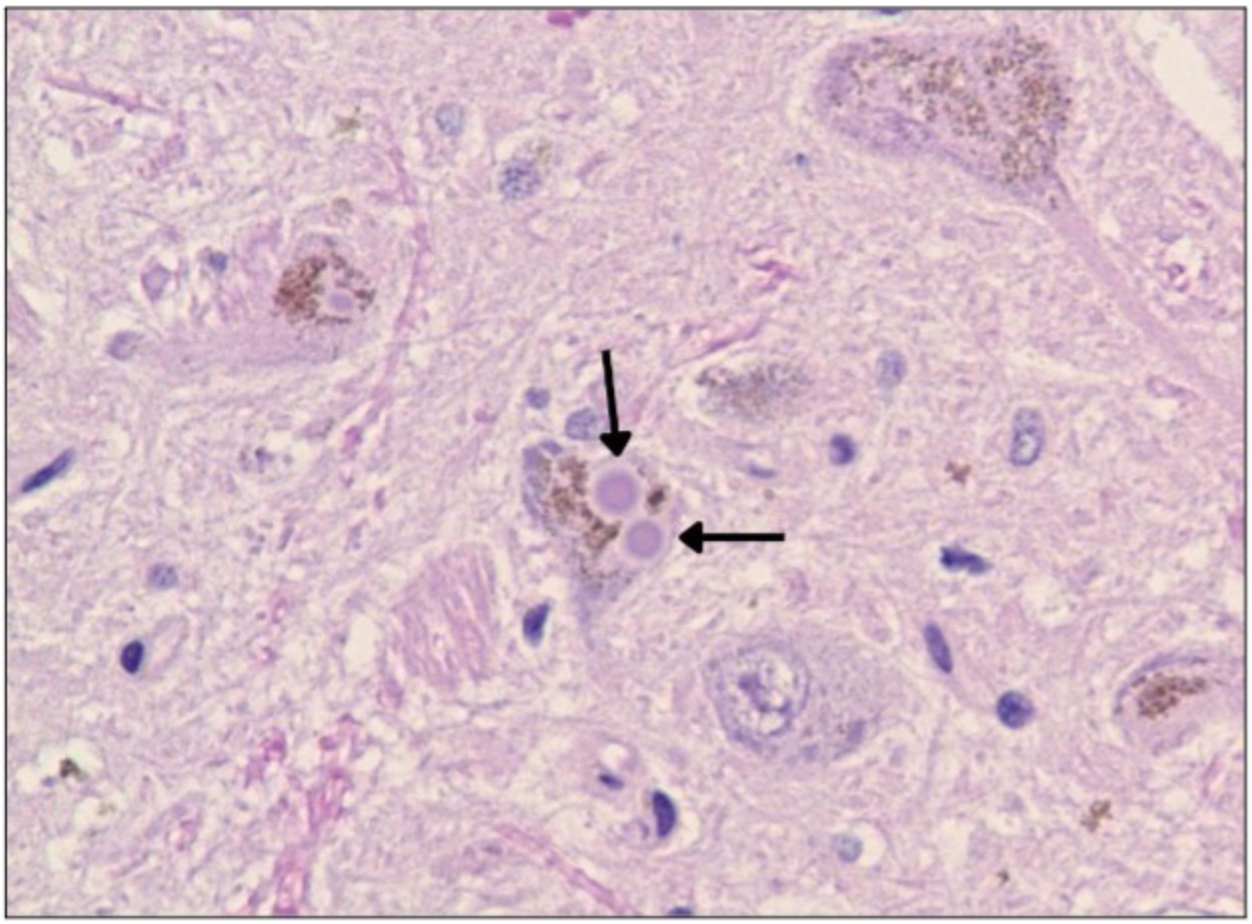

Figure 2: Lewy bodies in the substantia nigra in an 85 years-old female with Parkinson's Disease. (Courtesy of Howard Chang, MD, PhD)

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

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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 questionable 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 *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, Aβ plaques and neurofibrillary tangles, then became the subject of scrutiny [29]. Geneticist John Hardy advanced the amyloid hypothesis and asserted that Aβ plaques represent the primary pathology [30, 31]. He claimed that Aβ fibrils gradually coalesce into larger strands and thereby morph into the characteristic AD aggregates. Such Aβ 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 Aβ 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 *Nature,* science writer Simon Makin posed the question 'is it time to look beyond amyloid-β 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

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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 suctional force are even more striking.

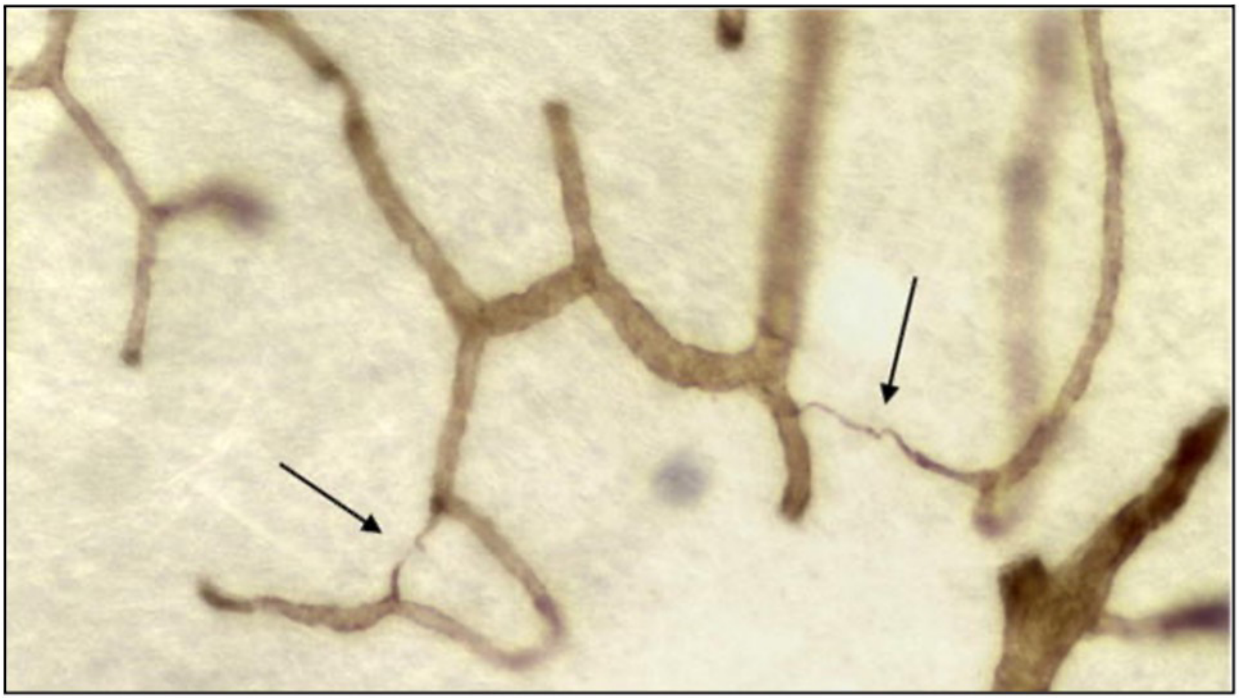

Figure 3: Vascular string vessels in neurodegenerative disease [95].

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

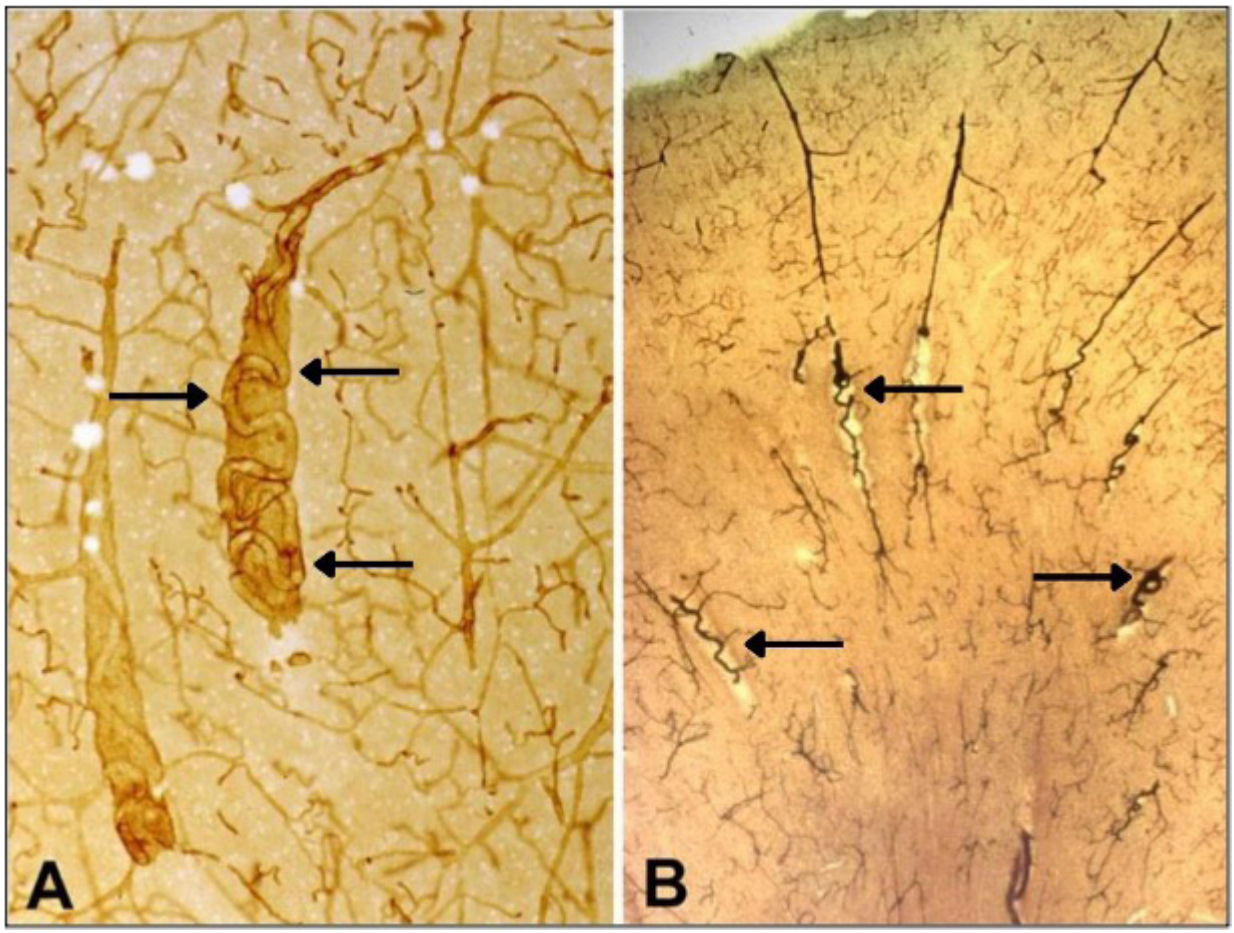

Figure 4: Tortuous arterioles in the white matter [98].

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].

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

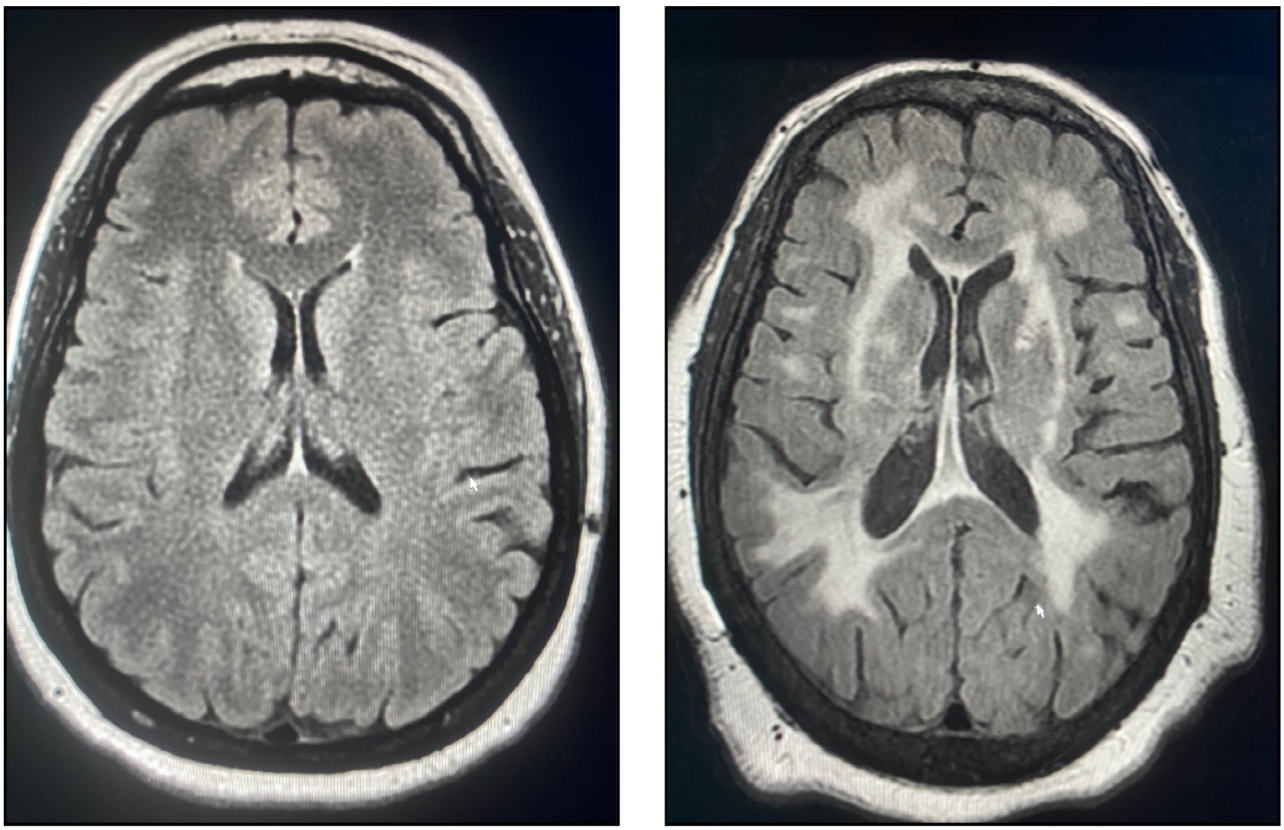

Figure 5: Axial T2-weighted MRI FLAIR images of the brain. Left image: normal-appearing brain in a cognitively intact 40yr female. Right image: extensive confluent white matter hyperintensities in the periventricular regions of a 79yr female with advanced dementia. (Courtesy of Simone Arrington, MD)

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].

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

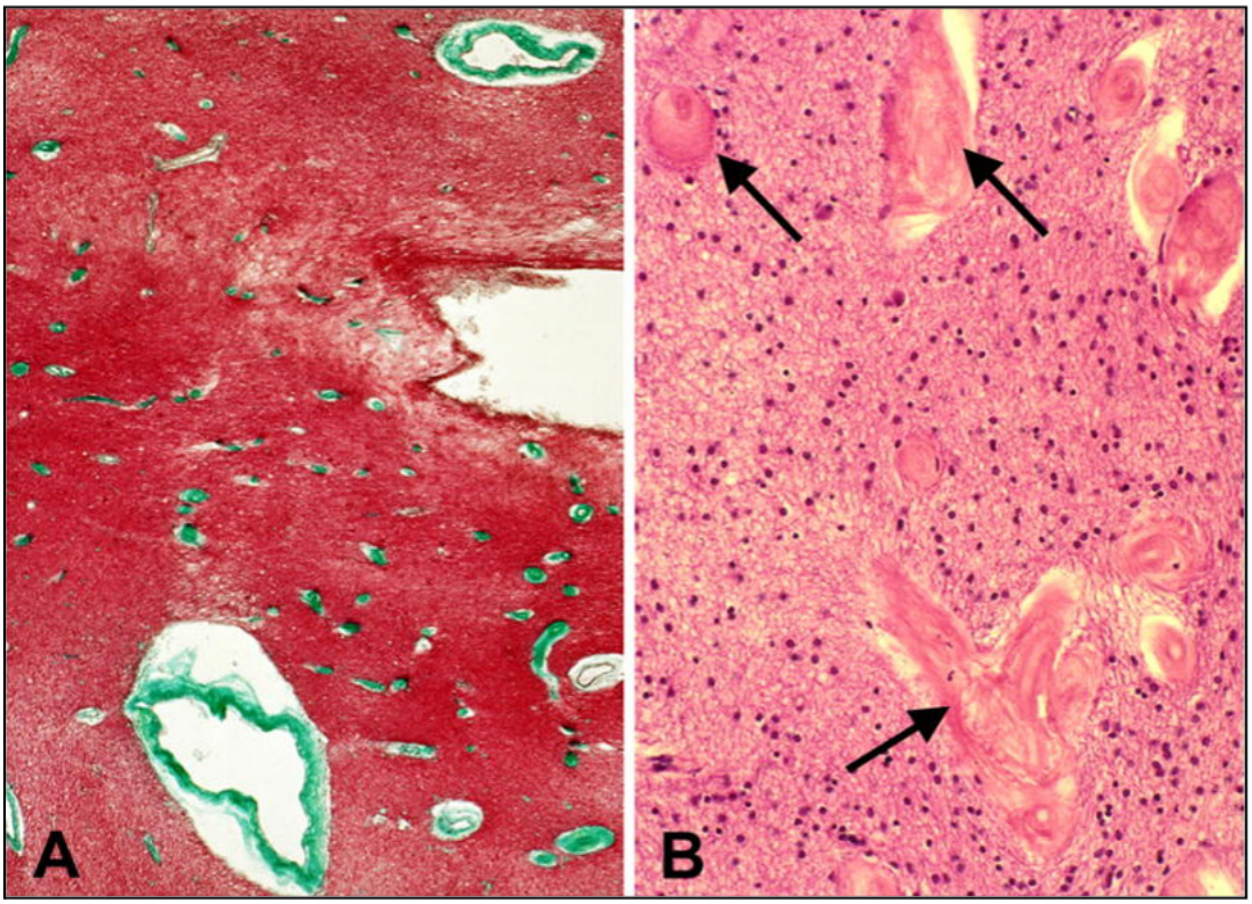

Figure 6: Marked venous wall thickening secondary to collagen deposition (collagenosis) in a subject with white matter hyperintensities (leukoariosis) [113].

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).

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

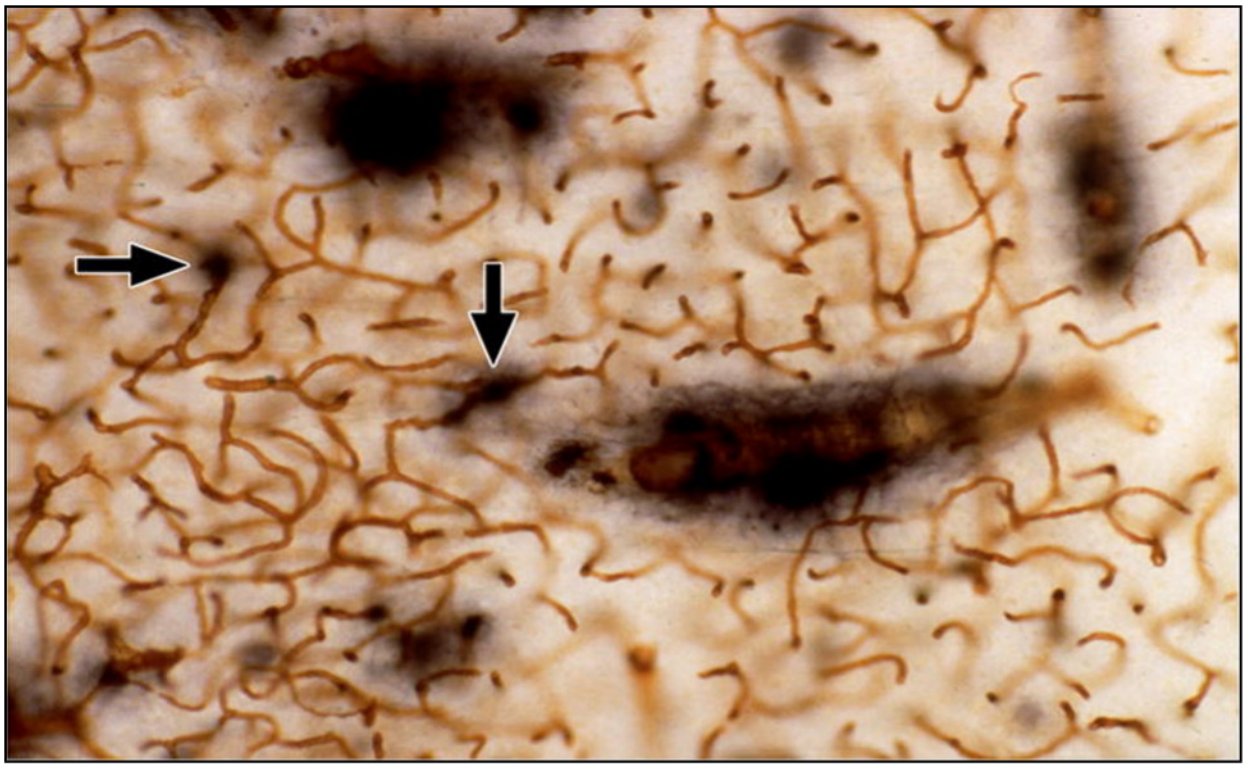

Figure 7: Aβ deposits in and around capillaries and larger blood vessels. Stained with antibodies to collagen and Aβ [141].

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 suctional 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

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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.

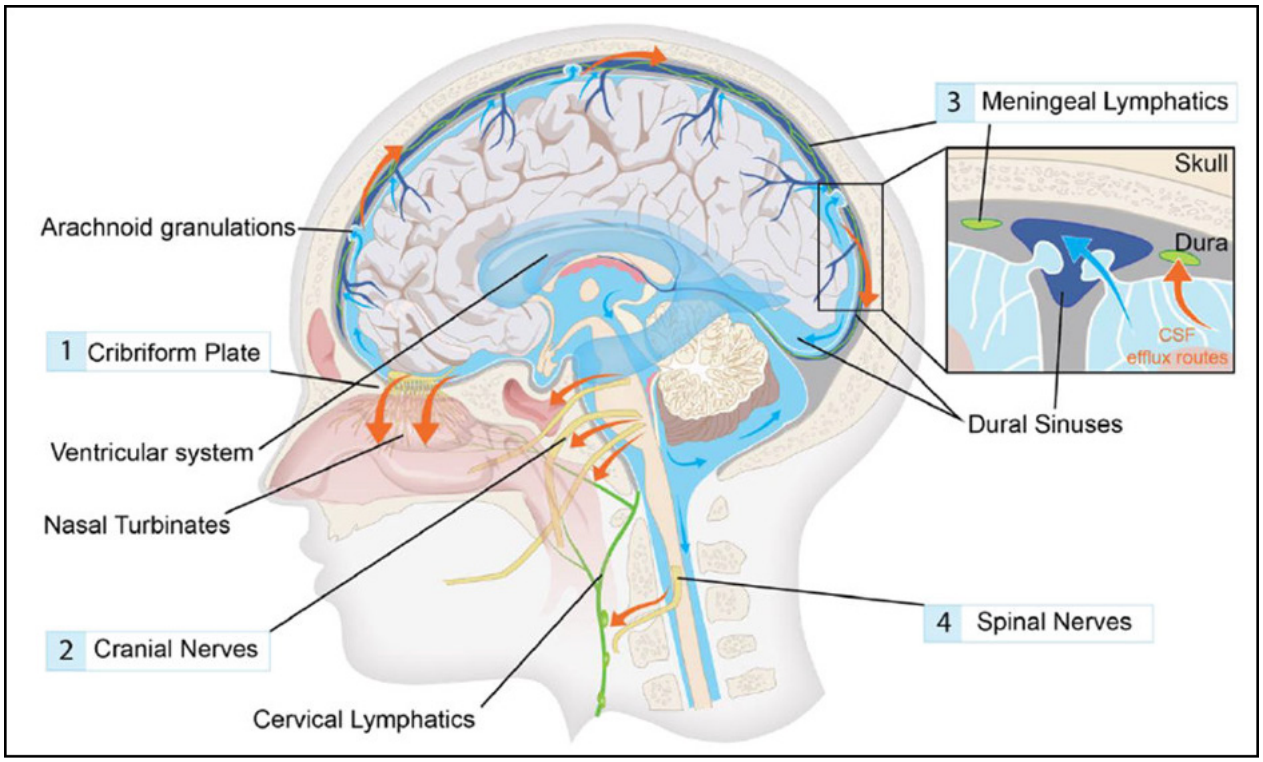

Figure 8: Cerebrospinal fluid flow in the human brain. Important sites of egress include the cribriform plate (1), cranial nerves (2), meningeal lymphatics (3), and Spinal nerves (4) [168].

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.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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?

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

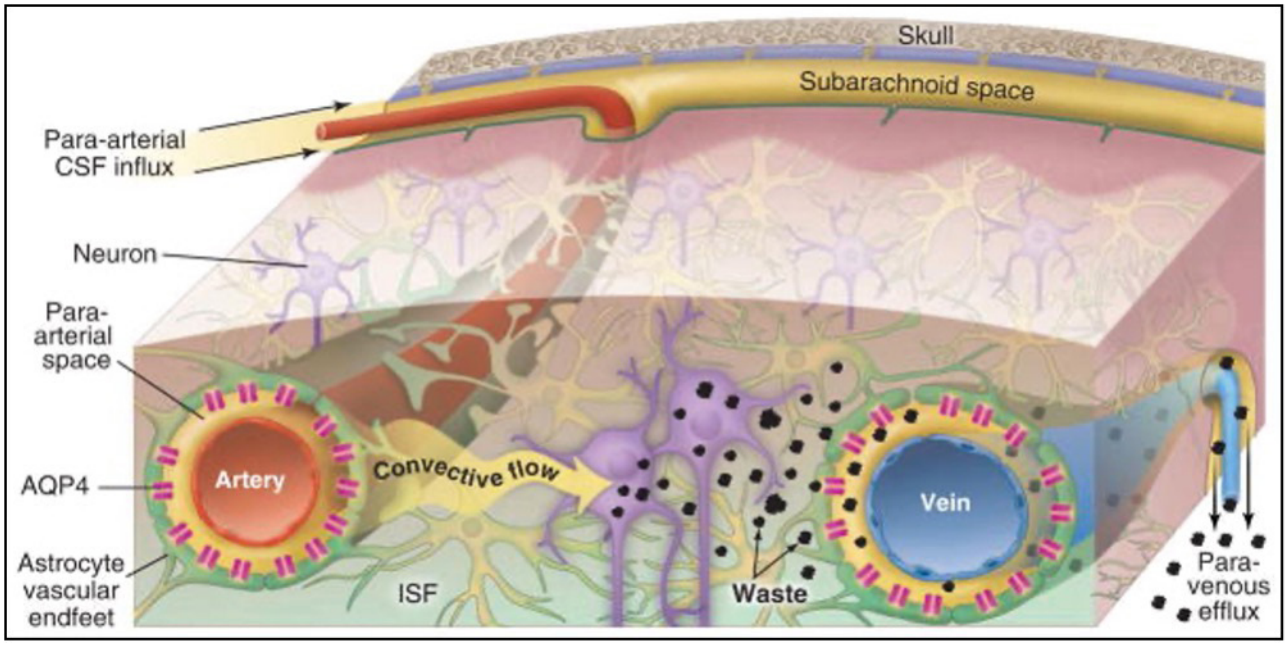

Figure 9: Relationships between the subarachnoid space, perivascular lymphatic system and cerebral vascular system. The perivascular space is continuous with the subarachnoid space. CSF is actively drawn into these channels by a suction force generated during right ventricular diastole. Fluid also moves 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

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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).

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

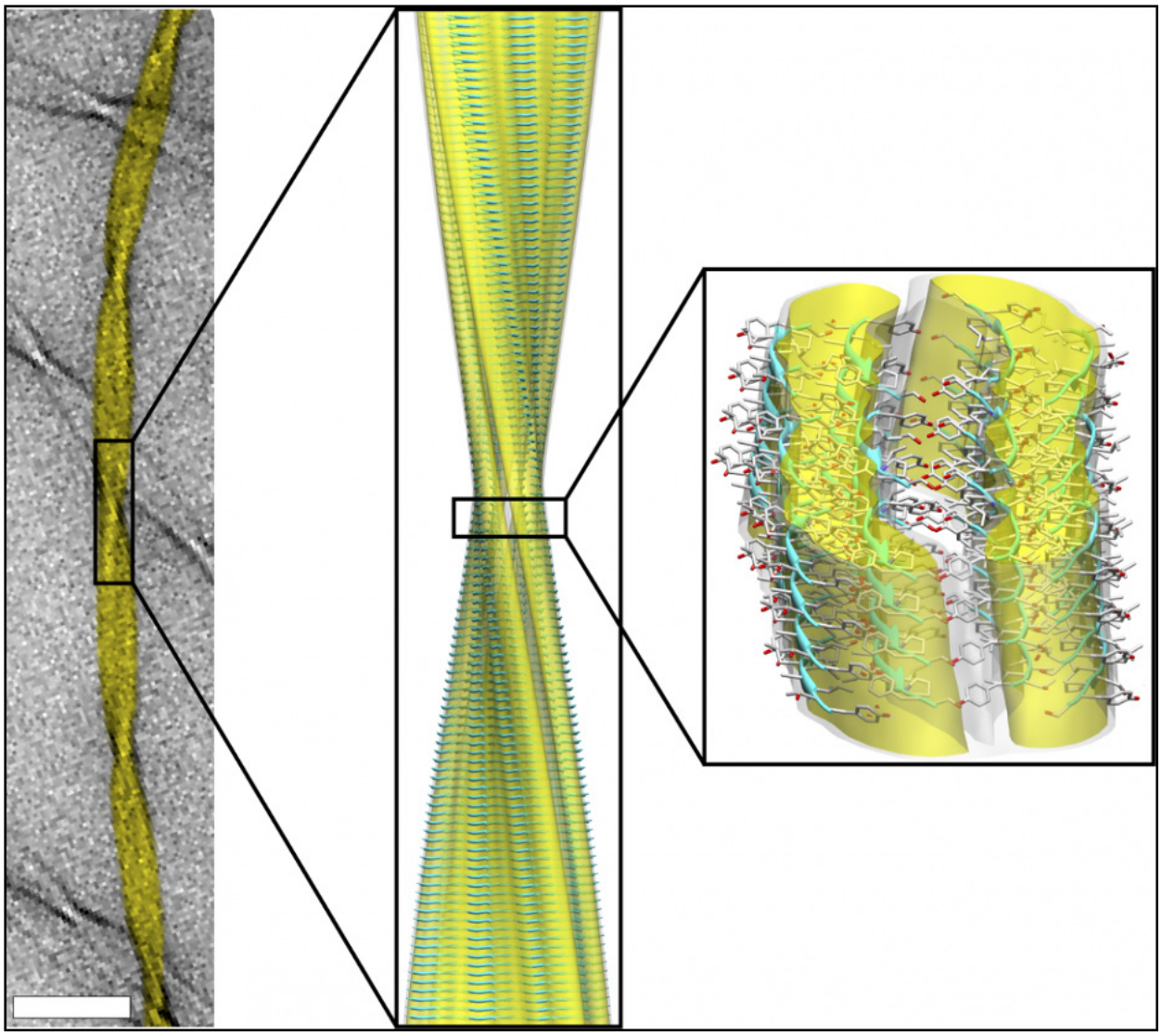

Figure 10: Pictorial representation of amyloid-β at varying degrees of magnification. Image on right, resolved to the atomic level, depicts the structural basis for the hierarchical organization of aggregates. The architecture of amyloid fibrils is not strongly dependent on sequence because constituent β-strands in the core of the fibril are linked by a vast array of hydrogen bonds which form the basis of secondary and tertiary protein structure [254].

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

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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 pellucidum, 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

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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^+ Ca^{2+}, Mg^{2+}, 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 Ca^{2+}. In the ECF space Ca^{2+} concentration is ~2-5 mmol/L while intracellularly it is ~100-300 nanomols/L equating to roughly a 10,000:1 gradient. Elevated intracellular Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} 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

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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?

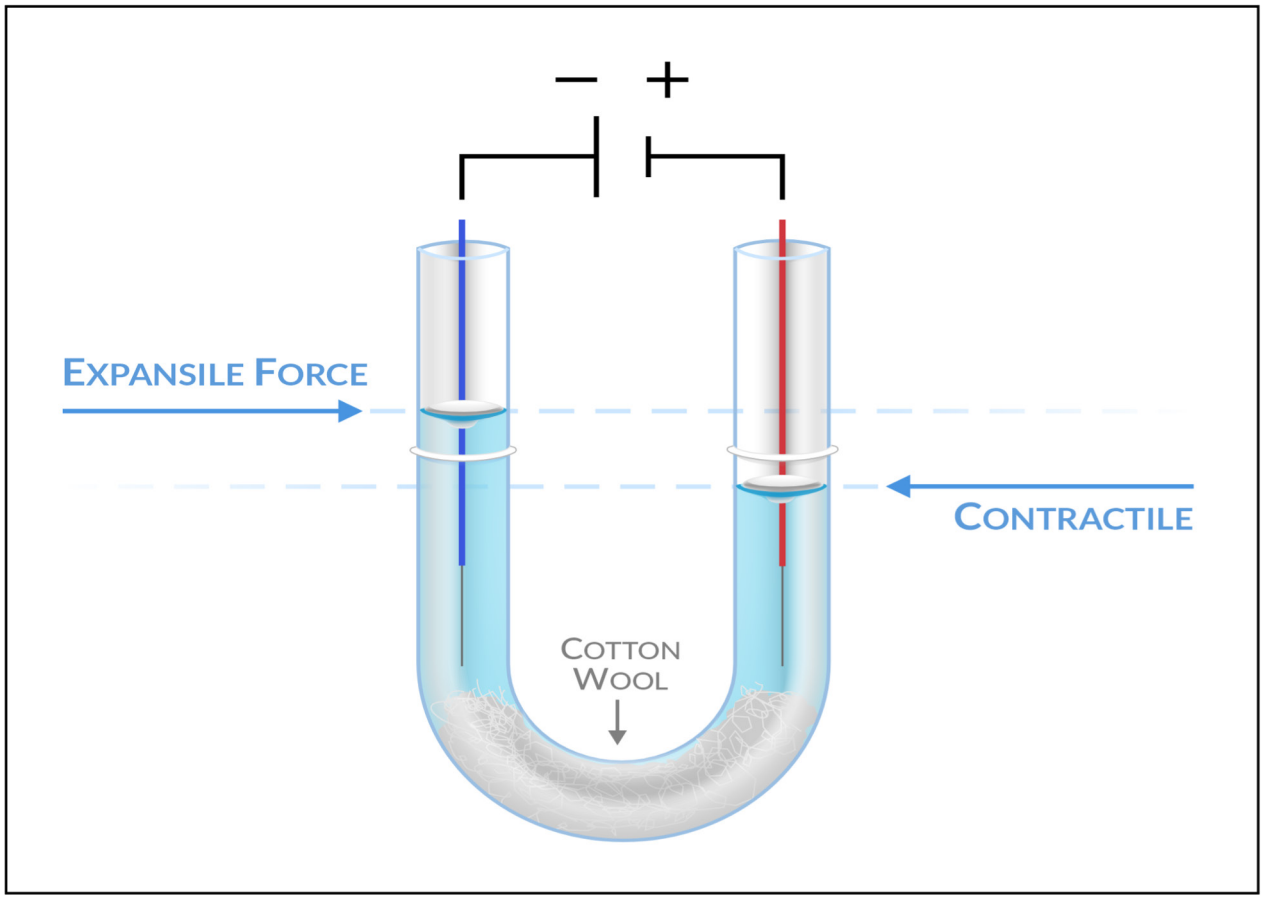

Figure 11: Nordenström's galvanic experiment. DC currents induce differential fluid levels in the limbs of the glass tubes surrounding the cathodic and anodic elements. Elevated water levels around the cathode are mediated by the 3D expansile force of the magnetic field. Lowered water levels around the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

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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 naïveté) 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

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

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

1. The Wisdom of the Body. The Harveian Oration. Starling EH. *British Med J.* 1923 Oct; 2(3277):685-90.

2. Alzheimer's disease and Parkinson's disease. Nussbaum RL, Ellis CE. *NEJM.* 2003 Apr 3;348(14):1356-64.

3. Parkinson's disease: A review. Beitz JM. *Front Biosci (Schol Ed).* 2014 Jan 1;6:65-74.

4. Alzheimer's disease. Scheltens P, Blennow K, Breteler MM, et al. *Lancet.* 2016 Jul; 388(10043):505-17.

5. Global prevalence of dementia: A Delphi consensus study. Ferri CP, Prince M, et al. *Lancet.* 2005 Dec 17;366(9503):2112-7.

6. Epidemiology of Parkinson's disease. Tysnes OB, Storstein A. *J Neural Transm (Vienna).* 2017 Aug;124(8):901-905.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

7. The prevalence of Parkinson's disease: A systematic review and meta-analysis. Pringsheim T, Jette N, Frolkis A. *Mov Disord.* 2014 Nov;29(13):1583-90.

8. Parkinson J. An essay on the shaking palsy. London, 1817.

9. Huntington's chorea: A centenary review. Heathfield KWG. *Postgrad Med J.* 1973 Jan;49(567):32-45.

10. Chorea: A Journey through History. Vale TC, Cardoso F. *Tremor Other Hyperkinetic Mov (NY).* 2015 May 28;5. pii: tre-5-296.

11. Amyotrophic Lateral Sclerosis: Early Contributions of Jean-Martin Charcot. Goetz CG. *Muscle & Nerve.* 2000: pp336-343.

12. Alzheimer's Disease: Past, Present, and Future. Bondi MW, Edmonds EC, Salmon DP. *J Int Neuropsychol Soc.* 2017 Oct;23(9-10):818-831.

13. Neuropathology of Parkinson's disease. Forno LS *J Neuropathol Exp Neurol.* 1996 Mar;55(3):259-72.

14. Demonstration and mapping out of nigro-neostriatal dopamine neurons. Anden NE, Carlsson A, Dahlstroem A, et al. *Life Sci.* 1964 Jun;3:523-30.

15. Stimulation of the subthalamic nucleus enhances the release of dopamine in the rat substantia nigra. Mintz I, Hammond C, Guibert B, Leviel V. *Brain Res.* 1986 Jun 25;376(2):406-8.

16. Selective loss of central cholinergic neurons in Alzheimer's disease. Davies P, Maloney AJ. *Lancet.* 1976 Dec 25;2(8000):1403.

17. Neocortical cholinergic neurons in elderly people. White P, Hiley CR, Goodhardt MJ, et al. *Lancet.* 1977 Mar 26;1(8013):668-71.

18. Necropsy evidence of central cholinergic deficits in senile dementia. Perry EK, Perry RH, Blessed G, et al. *Lancet.* 1977 Jan 22;1(8004):189.

19. The discovery of dopamine deficiency in the parkinsonian brain. Hornykiewicz O. *J Neural Transm Suppl.* 2006;(70):9-15.

20. Biochemistry of postmortem brains in Parkinson's disease: historical overview and future prospects. Nagatsu T, Sawada M. *J Neural Transm Suppl.* 2007;(72):113-20.

21. Alzheimer's disease: A disorder of cortical cholinergic innervation. Coyle JT, Price DL, DeLong MR. *Science.* 1983 Mar 11;219(4589):1184-90.

22. Cholinergic dysfunction in Alzheimer disease: Cause or effect? Plotkin DA, Jarvik LF. *Prog Brain Res.* 1986; 65:91-103.

23. Current and experimental treatments of Parkinson disease: A guide for neuroscientists. Oertel W, Schulz JB. *J Neurochem.* 2016 Oct;139 Suppl 1:325-337.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

24. Current and future treatments for Alzheimer's disease. Yiannopoulou KG, Papageorgiou SG. *Ther Adv Neurol Disord.* 2013 Jan;6(1):19-33.

25. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. *Cell.* 1993 Mar 26;72(6):971-83.

26. The molecular genetics of Huntington's disease. Goldberg YP, Telenius H, Hayden MR. *Curr Opin Neurol.* 1994 Aug;7(4):325-32.

27. The Role of Genetics in Advancing Precision Medicine for Alzheimer's Disease-A Narrative Review. Freudenberg-Hua Y, Li W, Davies P. *Front Med (Lausanne).* 2018 Apr 24;5:108.

28. The genetic architecture of Parkinson's disease. Blauwendraat C, Nalls MA, Singleton AB. *Lancet Neurol.* Sep 11. pii: S1474-4422(19)30287-X.

29. Alzheimer's disease: Initial report of the purification and characterization of a novel cerebrovascular amyloid protein. Glenner GG, Wong CW. *Biochem Biophys Res Commun.* 1984 May 16;120(3):885-90.

30. Amyloid precursor protein gene mutation in early-onset Alzheimer's disease. van Duijn CM, Hendriks L, Cruts M, Hardy JA, Hofman A, Van Broeckhoven C. *Lancet.* 1991 Apr 20;337(8747):978.

31. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Hardy J, Allsop D. *Trends Pharmacol Sci.* 1991 Oct;12(10):383-8.

32. Inconsistencies and controversies surrounding the amyloid hypothesis of Alzheimer's disease. Morris GP, Clark IA, Vissel B. *Acta Neuropathol Commun.* 2014 Sep 18;2:135.

33. The amyloid hypothesis, time to move on: Amyloid is the downstream result, not cause, of Alzheimer's disease. Drachman DA. *Alzheimer's Dement*. 2014 May;10(3):372-80.

34. A critical analysis of the 'amyloid cascade hypothesis'. Armstrong RA. *Folia Neuropathol.* 2014;52(3):211-25.

35. The amyloid hypothesis on trial. Makin S. *Nature.* 2018 (559); July 2018:S4-S7.

36. Negative intraventricular diastolic pressure in patients with mitral stenosis: Evidence of left ventricular diastolic suction. Sabbah HN, Anbe DT, Stein PD. *Am J Cardiol.* 1980; 45(3):pp 562-66.

37. Left ventricular diastolic suction as a mechanism of ventricular filling. Hori M, Yellin EL, Sonnenblick EH. *Jpn Circ J.* 46(1): pp 124-129;1982.

38. The heart as a suction pump. Robinson TF, Factor SM, Sonnenblick EH. *Scientific American.* 254(6):pp 84-91;1986.

39. The heart is not a pump: a refutation of the pressure propulsion premise of heart function. Marinelli R, Fürst B, van der Zee H, McGinn H, Marinelli W. *Frontier Perspectives.* 5(1): pp 15-24; Fall-Winter 1995.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

40. *Anatomical Studies on the Motion of the Heart and Blood* (1628). William Harvey Leake. translation; Charles Thomas Publisher, Springfield Illinois, 1958.

41. Spiral laminar flow in arteries? Stonebridge PA, Brophy CM. *Lancet.* 338(8779): pp 1360-61; 1991.

42. Spiral laminar flow in vivo. Stonebridge PA, Hoskins PR, Allan PL, Belck JF. *Clin Sci (Lond).* 91(1):pp 17-21;1996.

43. Helical and retrograde secondary flow patterns in the aortic arch studied by three-directional magnetic resonance velocity mapping. Kilner PJ, Yang GZ, Mohiaddin RH, et al. *Circulation.* 88(5):pp 2235-47;1993.

44. Physiological significance of helical flow in the arterial system and its potential clinical applications. Liu X, Sun A, Fan Y, Deng X. *Ann Biomed Engineer.* 43(1):pp 3-15;2015.

45. Three-dimensional blood flow dynamics: spiral/helical laminar flow. Stonebridge PA. *Methodist Debakey Cardiovasc J.* 2011;7(1):21-26.

46. Spiral laminar flow: A survey of a three-dimensional arterial flow pattern in a group of volunteers. Stonebridge PA, Suttie SA, Ross R, Dick J. *Eur J Vasc Endovasc Surg.* 2016;52(5):674-80.

47. Patterns of flow in the left coronary artery. Sabbah HN, Walburn FJ, Stein PD. *J Biomech Engin.*1984;106(3): 272-79.

48. Flow visualization study of spiral flow in the aorta-renal bifurcation. Fulker D, Javadzadegan A, Li Z, Barber T. *Comput Meth Biomech Biomed Engin.*2017;20(13):1438-41.

49. The mechanics of spiral flow: enhanced washout and transport. Huang Zhang P, Tkatch C, Newman R, Grimme W, et al. *Artif Organs.* 2019;43(12):1144-53.

50. Parallel and spiral flow patterns of vertebral artery contributions to the basilar artery. Smith AS, Belton JR. *Am J Neuroradiol.* 1995;16(8):272-79.

51. Flow patterns in the human carotid artery bifurcation. Motomiya M, Karino T. *Stroke* 1984;15(1): 50-56.

52. Spiral systolic blood flow in the ascending aorta and aortic arch analyzed by echodynamography. Tanaka M, Sakamoto T, Sugawara S, Nakajima H, et al. *J Cardiol.* 2010;56(1): 97-110.

53. Flow patterns in dog aortic arch under a steady flow condition simulating mid-systole. Endo S, Sohara Y, Karino T. *Heart Vessels.* 1996;11(4):180-91.

54. Blood flow analysis of the aortic arch using computational fluid dynamics. Numata S, Itatani K, Kanda K, Doi K, et al. *Eur J Cardiothorac Surg.* 2016;49(6):1578-85.

55. *Galen's System of Physiology and Medicine.* Rudolph E. Siegel publ. S. Karger, 1968.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

56. Diastolic Dysfunction. Little WC, Cheng CP. *Cardiol Rev.* 6(4):pp 231-239;1988.

57. State of the art: 'Diastology' research 1998. Oki T. *J Med Invest.* 45(1-4): pp 9-25;1998.

58. Energy dynamics in chronic heart failure, chronic kidney disease & the cardiorenal syndrome: A new causal paradigm. Thorp KE, Thorp JA, Northrup C, et al. *G Med Sci.* 2023 May;4(1):290-347.

59. Cerebral microvascular dysfunction and neurodegeneration in dementia. Han F. *Stroke Vasc Neurol.* 2019 Jun;4(2):105-07.

60. Association of white matter hyperintensities and cardiovascular disease: The importance of microcirculatory disease. Moroni F, Ammirati E, Hainsworth AH, et al. *Circ Cardiovasc Imaging.* 2020 Aug;13(8):e01046.

61. Microcirculatory dysfunction in the heart and brain. Mejía-Rentería H, Matias-Guiu JA, Lauri F, et al. *Minerva Cardioangiol.* 2019 Aug;67(4):318-329.

62. Cerebral small vessel disease: A review. Chojdak-Łukasiewicz J, Dziadkowiak E, Zimny A, et al. *Adv Clin Exp Med.* 2021 Mar;30(3):349-56.

63. Cerebral small vessel disease. Litak J, Mazurek M, Kulesza B, et al. *Int J Mol Sci.* 2020 Dec;21(24):9729.

64. Cerebral small vessel disease. Li Q, Yang Y, Reis C, et al. *Cell Transplant.* 2018 Dec;27(12):1711-22.

65. Cerebral small vessel disease: A glymphopathy? Benveniste H, Nedergaard M. *Curr Opin Neurobiol.* 2022 Feb;72:15-21.

66. Cerebral small vessel disease. Rost NS, Etherton M. *Continuum.* 2020 Apr;26(2):332-352.ial

67. Epidemiology of vascular dementia. Wolters FJ, Ikram MA. *Arterioscler Thromb Vasc Biol*. 2019 Aug;39(8):1542-49.

68. Inflammation, apoptosis and autophagy as critical players in vascular dementia. Wang XX, Zhang B, Xia R, et al. *Eur Rev Med Pharmacol Sci.* 2020 Sep;24(18):9601-14.

69. Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Gorelick PB, Scuteri A, Black SE, et al. *Stroke.* 2011 Sep;42(9):2672-713.

70. Functional vascular contributions to cognitive impairment and dementia mechanisms and consequences of cerebral autoregulatory dysfunction, endothelial impairment, and neurovascular uncoupling in aging. Toth P, Tarantini S, Csiszar A, et al. *Am J Physiol Heart Circ Physiol.* 2017 Jan;312(1):H1-H20.

71. Vascular cognitive impairment and dementia. Chang Wong E, Chang Chui H. *Continuum (Minneap)* 2022 Jun;28(3):750-80.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

72. Dementia, stroke, and vascular risk factors: A review. Sahathevan R, Brodtmann A, Donnan GA. *Stroke.* 2012 Jan;7(1):61-73.

73. Association of ischemic stroke incidence, severity, and recurrence with dementia in the Atherosclerosis Risk in Communities Cohort Study. Koton S, Pike JR, Johansen M, et al. *JAMA Neurol.* 2022 Mar;79(3):271-80.

74. Poststroke dementia in the elderly. Mackowiak-Cordoliani MA, Bombois S, Memin A, et al. *Aging.* 2005;22(6):483-93.

75. Post-stroke dementia – A comprehensive review. Mijajlović MD, Pavlović A, Brainin M, et al. *BMC Med.* 2017 Jan;15(1):11.

76. Cognitive impairment and stroke in elderly patients. *Vasc Health Risk Manag.* 2016 Mar;12:105-16.

77. Neurovascular dysfunction and vascular amyloid accumulation as early events in Alzheimer's disease. Apátiga-Pérez R, Soto-Rojas LO, Campa-Córdoba BB, et al. *Metab Brain Dis.* 2022 Jan;37(1):39-50.

78. Review: Cerebral microvascular pathology in ageing and neurodegeneration. Brown WR, Thore CR. *Neuropathol Appl Neurobiol.* 2011 Feb;37(1):56-74.

79. Vascular changes in the human senile brain. Ravens JR. *Adv Neurol.* 1978;20:487–501.

80. A study on the microvasculature of the cerebral cortex. Fundamental architecture and its senile change in the frontal cortex. Akima M, Nonaka H, Kagesawa M, et al. *Lab Invest.* 1986;55:482–489.

81. Vascular changes in senile brains. A micro-angiographic study. Hassler O. *Acta Neuropathol.* 1965; 5:40–53.

82. Altered angioarchitecture in selected areas of brains with Alzheimer's disease. Fischer VW, Siddiqi A, Yusufaly Y. *Acta Neuropathol.* 1990;79:672–679.

83. Cerebral arterial deformities in relation to senile deterioration. Beskow J, Hassler O, Ottosson JO. *Acta Psychiatr Scand Suppl.* 1971;221:111–119.

84. Differential degeneration of the cerebral microvasculature in Alzheimer's disease. Kalaria RN, Hedera P. *Neuroreport.* 1995;6:477–480.

85. Vascular dementia in leukoaraiosis may be a consequence of capillary loss not only in the lesions, but in normal-appearing white matter and cortex as well. Brown WR, Moody DM, Thore CR, et al. *J Neurol Sci.* 2007; 257:62–66.

86. Quantification of afferent vessels shows reduced brain vascular density in subjects with leukoaraiosis. Moody DM, Thore CR, Anstrom JA, et al. *Radiology.* 2004;233:883–890.

87. A review of string vessels or collapsed, empty basement membrane tubes. Brown WR. *J Alzheimer's Dis.* 2010;21(3):725-39.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

88. A three-dimensional study of brain string vessels using celloidin sections stained with anti-collagen antibodies. Challa VR, Thore CR, Moody DM, et al. *J Neurol Sci.* 2002; 203–204:165–167.

89. Review: Cerebral microvascular pathology in ageing and neurodegeneration. Brown WR, Thore CR. *Neuropathol Appl Neurobiol.* 2011 Feb;37(1):56–74.

90. Does tortuosity in cerebral arterioles impair downautoregulation in hypertensives and elderly normotensives? A hypothesis and computer model. Moody DM, Santamore WP, Bell MA. *Clin Neurosurg.* 1991;37:372–387.

91. Morphometric analysis of arteriolar tortuosity in human cerebral white matter of preterm, young, and aged subjects. Thore CR, Anstrom JA, Moody DM, et al. *J Neuropathol Exp Neurol.* 2007;66:337–345.

92. Venous collagenosis and arteriolar tortuosity in leukoaraiosis. Brown WR, Moody DM, Challa VR, et al. *J Neurol Sci.* 2002;203–204:159–163.

93. Pathogenesis of leukoaraiosis: A review. Pantoni L, Garcia JH. *Stroke.* 1997;28:652–659.

94. Association of white matter hyperintensity volume with decreased cognitive functioning: The Framingham Heart Study. Au R, Massaro JM, Wolf PA, et al. *Arch Neurol.* 2006;63:246–250.

95. Decline in intelligence is associated with progression in white matter hyperintensity volume. Garde E, Lykke ME, Rostrup E, et al. *J Neurol Neurosurg Psychiatry.* 2005;76:1289–1291.

96. Risk of rapid global functional decline in elderly patients with severe cerebral age-related white matter changes: The LADIS study. Inzitari D, Simoni M, Pracucci G, et al. *Arch Intern Med.* 2007;167:81–88.

97. Progression of leukoaraiosis and cognition. Schmidt R, Petrovic K, Ropele S, et al. *Stroke.* 2007;38:2619–2625.

98. Periventricular white matter changes and dementia. Clinical, neuropsychological, radiological, and pathological correlation. Gupta SR, Naheedy MH, Young JC, et al. *Arch Neurol.* 1988;45:637–641.

99. Markers of endothelial dysfunction in lacunar infarction and ischaemic leukoaraiosis. Hassan A, Hunt BJ, O'Sullivan M, et al. *Brain.* 2003;126:424–432.

100. Potential mechanisms of venous system for leukoaraiosis: From post-mortem to in vivo research. Nan D, Cheng Y, Feng L, et al. *Neurodegen Dis.* 2019;19(3-4):101-08.

101. Pathogenesis of leukoaraiosis: Role of jugular venous reflux. Chung CP, Hu HH. *Med Hypotheses.* 2010 Jul;75(1):85-90.

102. Venous dysfunction plays a critical role in 'normal' white matter disease of aging. Kapadia A, Dmytriw AA. *Med Hypotheses.* 2021 Jan;146:110457.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

103. Collagenosis of the deep medullary veins: An underrecognized pathologic correlate of white matter hyperintensities and periventricular infarction? Keith J, Gao FQ, Noor R, et al. *J Neuropathol Exp Neurol.* 2017 Apr;76(4):299-312.

104. Venous collagenosis of pathogenesis of white matter hyperintensity. Lahna D, Schwartz DL, Woltjer R, et al. *Ann Neurol.* 2022 Dec;92(6):992-1000.

105. Periventricular venous collagenosis: Association with leukoaraiosis. Moody DM, Brown WR, Challa VR, et al. Radiology. 1995 Feb;194(2):469-76.

106. Venous collagenosis and arteriolar tortuosity in leukoaraiosis. Brown WR, Moody DM, Challa VR, et al. *J Neurol Sci.* 2002;203–204:159–163.

107. Microvascular changes in the white matter in dementia. Brown WR, Moody DM, Thore CR, et al. *J Neurol Sci.* 2009 Aug;283(1-2):28-31.

108. Understanding white matter disease: Imaging-pathological correlations in vascular cognitive impairment. Black S, Gao F, Bilbao J. *Brain.* 2009 Mar;40(3 Suppl):S48-52.

109. White matter degeneration in vascular and other ageing-related dementias. Hase Y, Horsburgh K, Ihara M, et al. *J Neurochem.* 2018 Mar;144(5):617-33.

110. Cerebral venous congestion promotes blood-brain barrier disruption and neuroinflammation, impairing cognitive function in mice. Fulop GA, Ahire C, Csipo T, et al. *Geroscience.* 2019 Oct;41(5):575-589.

111. Cerebral venous congestion exacerbates cerebral microhemorrhages in mice. Nyul-Toth A, Fulop GA, Tarantini S, et al. *Geroscience.* 2022 Apr;44(2):805-816.

112. Role of deep medullary veins in pathogenesis of lacunes: Longitudinal observations from the CIRCLE study. Zhou Y, Li Q, Zhang R, et al. *J Cereb Blood Flow Metab.* 2020 Sep;40(9):1797-1805.

113. Increased Diameters of the Internal Cerebral Veins and the Basal Veins of Rosenthal Are Associated with White Matter Hyperintensity Volume. Houck AL, Gutierrez J, Gao F, et al. *Am J Neuroradiol.* 2019 Oct;40(10):1712-18.

114. Increased internal cerebral vein diameter is associated with age. Huang Z, Tu X, Lin Q, et al. *Clin Imaging.* 2021 Oct;78:187-93.

115. Increased visibility of deep medullary veins in leukoaraiosis: A 3-T MRI study. Yan S, Wan J, Zhang X, et al. *Front Aging Neurosci.* 2014 Jun;6:144.

116. Association of deep medullary veins with the neuroimaging burden of cerebral small vessel disease. Yin X, Han Y, Cao X, et al. *Quant Imaging Med Surg.* 2023 Jan;13(1):27-36.

117. A novel imaging biomarker for cerebral small vessel disease associated with cognitive impairment. The deep-medullary-veins score. Xu Z, Li F, Xing D, et al. *Front Aging Neurosci.* 2021 Oct;13:720481.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

118. The cerebrovascular basement membrane: Role in the clearance of β-amyloid and cerebral amyloid angiopathy. Morris AW, Carare RO, Schreiber S, et al. *Front Aging Neurosci.* 2014 Sep;6:251.

119. Ultrastructural features of cerebral amyloid angiopathy. Okoye MI, Watanabe I. *Hum Pathol.* 1982 Dec;13(12):1127-32.

120. The role of basement membranes in cerebral amyloid angiopathy. Howe MD, McCullough LD, Urayama A. *Front Physiol.* 2020 Nov;11:601320.

121. Beta-amyloid fibrils of Alzheimer's disease: Pathology altered, basement membrane-associated microfibrils? Inoue S, Kisilevsky R. *Anat Embryol.* 2001;106(2 Suppl 1):93-102.

122. Cerebral amyloid angiopathy and dementia. Tian J, Shi J, Mann DM. *Panminerva Med.* 2004 Dec;46(4):253-64.

123. Thickening of the basement membrane of cortical capillaries in Alzheimer's disease. Mancardi GL, Perdelli F, Rivano C, et al. *Acta Neuropathol.* 1980;49:79–83.

124. Increased collagen content of cerebral microvessels in Alzheimer's disease. Kalaria RN, Pax AB. *Brain Res.* 1995;705:349–352.

125. Cerebral amyloid angiopathy and blood-brain barrier dysfunction. Gireud-Goss M, Mack AF, McCullough LD, et al. *Neuroscientist.* 2021 Dec;27(6):668-84.

126. Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. Bell RD, Zlokovic BV. *Acta Neuropathol.* 2009 Jul;118(1):103-13.

127. Microbleed and microinfarct detection in amyloid angiopathy: A high-resolution MRI-histopathology study. van Veluw SJ, Charidimou A, van der Kouwe AJ, et al. *Brain.* 2016 Dec;139(Pt 12):3151-62.

128. The amyloid-tau-neuroinflammatory axis in the context of cerebral amyloid angiopathy. Cisternas P, Taylor X, Lasagna-Reeves CA. *Int J Mol Sci.* 2019 Dec;20(24);6319.

129. Emerging concepts in sporadic cerebral amyloid angiopathy. Charidimou A, Boulouis G, Gurol ME, et al. *Brain* 2017 Jul;140(7):1829-50.

130. Failure of perivascular drainage of β-amyloid in cerebral amyloid angiopathy. Hawkes CA, Jayakody N, Johnston DA, et al. *Brain Pathol.* 2014 Jul;24(4):396-403.

131. Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer's disease. Weller RO, Subash M, Preston SD, et al. *Brain Pathol.* 2008 Apr;18(2):253-66.

132. Perivascular drainage of solutes is impaired in the ageing mouse brain and in the presence of cerebral amyloid angiopathy. Hawkes CA, Härtig W, Kacza J, et al. *Acta Neuropathol.* 2011 Apr;121(4):431-43.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

133. Deposition of amyloid β in the walls of human leptomeningeal arteries in relation to perivascular drainage pathways in cerebral amyloid angiopathy. Keable A, Fenna K, Yuen HM, et al. *Biochim Biophys Acta.* 2016 May;1862(5):1037-46.

134. Cerebral amyloid angiopathy: amyloid beta accumulates in putative interstitial fluid drainage pathways in Alzheimer's disease. Weller RO, Massey A, Newman TA, et al. *Am J Pathol.* 1998;153:725–733.

135. Amyloid angiopathy in Alzheimer's disease. Bergeron C, Ranalli PJ, Miceli PN. *Can J Neurol Sci.* 1987 Nov;14(4):564-69.

136. Cerebrovascular pathology in Alzheimer's disease and leukoaraiosis. Brown WR, Moody DM, Thore CR, et al. *Ann N Y Acad Sci.* 2000; 903:39–45.

137. More severe white matter changes in the elderly with jugular venous reflux. Chung CP, Wang PN, Wu YH, et al. *Ann Neurol.* 2011 Mar;69(3):553-59.

138. Jugular venous reflux and white matter abnormalities in Alzheimer's disease: A pilot study. Chung CP, Beggs C, Wang PN, et al. *J Alheimers Dis.* 2014;39(3):601-09.

139. Jugular venous reflux and brain parenchyma volumes in elderly patients with mild cognitive impairment and Alzheimer's disease. Beggs C, Chung CP, Bergsland N, et al. *BMC Neurol.* 2013 Oct;13:157.

140. Cognitive functions and jugular venous reflux in severe mitral regurgitation: A pilot study. Sung SH, Lee CW, Wang PN, et al. *PLoS One.* 2019 Feb;14(2):e0207832.

141. The aging venous system: from varicosities to vascular cognitive impairment. Molnár AÁ, Nádasy GL, Dörnyei G, et al. *Geroscience.* 2021 Dec;43(6):2761-84.

142. Role of age-related alterations of the cerebral venous circulation in the pathogenesis of vascular cognitive impairment. Fulop GA, Tarantini S, Yabluchanskiy A, et al. *Am J Physiol Heart Circ Physiol.* 2019 May;316(5):H1124-H1140.

143. Cardiorenal interactions: Insights from the ESCAPE trial. Nohria A, Hasselblad V, Stebbins A, et al. J Am Coll Cardiol. 51(13):pp 1268-74;2008.

144. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. Mullens W, Abrahams Z, Francis GS, et al. *J Am Coll Cardiol* 2009 Feb 17;53(7):589-96.

145. Cardiorenal syndrome in acute heart failure: Revisiting paradigms. Núñez J, Miñana G, Santas E, et al. *Rev Esp Cardiol.* 2015 May;68(5):426-35.

146. Right heart failure in cardiorenal syndrome. Kramer T, Brinkkoetter P, Rosenkranz S. *Curr Heart Fail Rep.* 2022 Dec;19(6):386-99.

147. Abnormal liver function in relation to hemodynamic profile in heart failure patients. Van Deursen VM, Damman K, Hillege HL, et al. *Card Fail.* 2010 Jan;16(1):84-90.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

148. Pulmonary hypertension: a brief guide for clinicians. Mandras SA, Mehta HS, Vaidya A. *Mayo Clin Proc.* 2020 Sep;95(9):1978-88.

149. Congestive nephropathy: A neglected entity? Proposal for diagnostic criteria and future perspectives. Husain-Syed F, Gröne HJ, Assmus B, et al. *ESC Heart Fail.* 2021 Feb;8(1):183-203.

150. Congestive Hepatopathy. Fortea JI, Puente Á, Cuadrado A, et al. *Int J Mol Sci.* 2020 Dec; 21(24):9420.

151. Intra-abdominal hypertension and abdominal compartment syndrome in pancreatitis, paediatrics and trauma. De Waele JJ, Ejike JC, Leppäniemi A, et al. *Anaesthesiol Intensive Ther.* 2015;47(3):219-27.

152. Intra-abdominal hypertension and abdominal compartment syndrome: An underappreciated cause of acute kidney injury. Patel DM, Connor MJ. *Adv Chronic Kidney Dis.* 2016 May;23(3):160-66.

153. Abdominal compartment syndrome and intra-abdominal hypertension. Pereira BM. *Curr Opin Crit Care.* 2019 Dec;25(6):688-96.

154. Intra-abdominal hypertension and abdominal compartment syndrome: A current review. Kimball EJ. *Curr Opin Crit Care.* 2021 Apr;27(2):164-68.

155. The third circulation revisited. Milhorat TH. *J Neurosurg.* 1975 Jun;42(6):628-45.

156. The historical significance of the cerebrospinal fluid. Woollam DH. *Med Hist.* 1957;1(2):91–114.

157. The formation of cerebrospinal fluid: nearly a hundred years of interpretations and misinterpretations. Oreskovic D, Klarica M. *Brain Res Rev.* 2010 Sep;64(2):241-62.

158. Afferent and efferent immunological pathways of the brain. Anatomy, function and failure. Carare RO, Hawkes CA, Weller RO. *Brain Behav Immun.* 2014 Feb;36:9-14.

159. The mechanism of drainage of the cerebrospinal fluid. Davson H, Hollingsworth G, Segal MB. *Brain.* 1970; 93(4):665–678.

160. A new look at cerebrospinal fluid circulation. Brinker T, Stopa E, Morrison J, Klinge P. *Fluids Barriers CNS.* 2014 May;11:10.

161. A proposed model of cerebrospinal fluid circulation: Observations with radionuclide cisternography. Greitz D, Hannerz J. *AJNR.* 1996;17:431–438.

162. Reassessing cerebrospinal fluid (CSF) hydrodynamics: A literature review presenting a novel hypothesis for CSF physiology. Chikly B, Quaghebeur J J. *Bodyw Mov Ther.* 2013 Jul;17(3):344-54.

163. *Galen's System of Physiology and Medicine.* Rudolph E. Siegel publ. S. Karger, 1968.

164. Recent research into the nature of cerebrospinal fluid formation and absorption. McComb JG. *J Neurosurg.* 1983;59:369–383.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

165. Mechanisms of fluid movement into, through and out of the brain: Evaluation of the evidence. Hladky SB, Barrand MA. *Fluids Barriers CNS.* 2014 Dec; 11(1):26.

166. Recent insights into a new hydrodynamics of the cerebrospinal fluid. Bulat M, Klarica M. *Brain Res Rev.* 2011 Jan;65(2):99-112.

167. Anatomical relationships of the pia mater to cerebral blood vessels in man. Hutchings M, Weller RO. *J Neurosurg.* 1986;65:316–325.

168. The glymphatic pathway in neurological disorders. Rasmussen MK, Mestre H, Nedergaard M. *Lancet Neurol.* 2018 Nov;17(11):1016-24.

169. Cerebrospinal fluid outflow: A review of the historical and contemporary evidence for arachnoid villi, perineural routes, and dural lymphatics. Proulx ST. *Cell Mol Life Sci.* 2021 Mar;78(6):2429-57173.

170. The function and structure of the cerebrospinal fluid outflow system. Pollay M. *Cerebrospinal Fluid Res.* 2010 Jun;7:9.

171. Evidence of connections between cerebrospinal fluid and nasal lymphatic vessels in humans, non-human primates and other mammalian species. Johnston M, Zakharov A, Papaiconomou C, et al. *Cerebrospinal Fluid Res.* 2004 Dec;1(1):2.

172. Outflow of cerebrospinal fluid is predominantly through lymphatic vessels and is reduced in aged mice. Kress BT, Iliff JJ, Xia M, et al. *Nature Commun.* 2017 Nov;8(1):1434.

173. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. Aspelund A, Antila S, Proulx ST, et al. *J Exp Med.* 2015 Jun;212(7):991-99.

174. Cerebrospinal fluid is drained primarily via the spinal canal and olfactory route in young and aged spontaneously hypertensive rats. Murtha LA, Yang Q, Parsons MW, et al. *Fluids Barriers CNS.* 2014 Jun;11:12.

175. Cerebrospinal fluid drainage as influenced by ventricular pressure in the rabbit. McComb JG, Davson H, Hyman S, et al. *J Neurosurg.* 1982; 56(6):790–797.

176. The effects of raised ICP on lymph flow in the cervical lymphatic trunks in cats. Love JA, Leslie RA. *J Neurosurg.* 1984;60(3):577–581.

177. Passage of lipid insoluble substances from cerebrospinal fluid to blood. Prockop LD, Schanker LS, Brodie BB. J *Pharmacol Exp Ther.* 1962;135:266–270.

178. Drainage of brain extracellular fluid into blood and deep cervical lymph and its immunological significance. Cserr HF, Harling-Berg CJ, et al. *Brain Pathol.* 1992;2:269–276.

179. Compartments and perivascular arrangement of the meninges covering the cerebral cortex of the rat. Krisch B, Leonhardt H, Oksche A. *Cell Tissue Res.* 1984;238:459–474.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

180. Transventricular and transpial absorption of cerebrospinal fluid into cerebral microvessels. Bulat M, Lupret V, Oreskovic D, et al. *Coll Antropol.* 2008;32(Suppl 1):43–50.

181. Development of hydrocephalus and classical hypothesis of cerebrospinal fluid hydrodynamics: Facts and illusions. Orešković D, Klarica M. *Prog Neurobiol.* 2011 Aug;94(3):238-58.

182. On the absorption of fluids from the connective tissue spaces. Starling EH. *J Physiol.* 1896;19:312–326.

183. Microvascular fluid exchange and the revised Starling principle. Levick JR, Michel CC. *Cardiovasc Res.* 2010;87:198–210.

184. *Physiology of the ocular and cerebrospinal fluids.* Davson H publ. Churchill, London (1956).

185. The mechanism of drainage of the cerebrospinal fluid. Davson H, Hollingsworth G, Segal MB. *Brain.* 1970; 93(4):665–678.

186. Forces concerned in the absorption of the cerebrospinal fluid. Weed LH. *Am J Physiol.* 1935; 114(1):40–45.

187. Bulk flow and diffusion in the cerebrospinal fluid system of the goat. Heisey SR, Held D, Pappenheimer JR. *Am J Physiol.* 1962;203:775–781.

188. Directional and compartmentalized drainage of interstitial fluid and cerebrospinal-fluid from the rat-brain. Zhang ET, Richards HK, Kida S, et al. *Acta Neuropathol.* 1992;83:233–239.

189. Systemic effects of the intravenous injection of solutions of various concentrations with especial reference to the cerebrospinal fluid. Weed LH, Hughson W. *Am J Physiol.* 1921;58(1):53–84.

190. Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine brain. Iliff JJ, Wang M, Zeppenfeld DM, et al. *J Neurosci.* 2013;33(46):18190–18199.

191. Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. Mestre H, Tithof J, Du T, et al. *Nature Commun.* 2018;9(1):4878.

192. Cerebrospinal fluid flow driven by arterial pulsations in axisymmetric perivascular spaces: Analogy with Taylor's swimming sheet. Yokoyama N, Takeishi N, Wada S. *J Theor Biol.* 2021 Aug; 523:110709.

193. Brain cerebrospinal fluid flow. Kelley DH. *Phys Rev Fluids.* 2021 Jul;6(7):070501.

194. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Iliff JJ, Wang M, Liao Y, et al. *Sci Transl Med.* 2012;4(147):147ra111.

195. Brain stem penetration by horseradish peroxidase from the cerebrospinal fluid spaces in the cat. Borison HL, Borison R, McCarthy LE. *Exp Neurol.* 1980;69:271–289.

196. Evidence for a paravascular fluid circulation in the mammalian central nervous system, provided by the rapid distribution of tracer protein throughout the brain from the subarachnoid space. Rennels ML, Gregory TF, Blaumanis OR, et al. *Brain Res.* 1985;326:47–63.

197. Rapid solute transport throughout the brain via paravascular fluid pathways. Rennels ML, Blaumanis OR, Grady PA. *Adv Neurol.* 1990;52:431–439.

198. Distribution of extracellular tracers in perivascular spaces of the rat brain. Ichimura T, Fraser PA, Cserr HF. *Brain Res.* 1991;545:103–113.

199. Evidence for a 'paravascular' fluid circulation in the mammalian central nervous system, provided by the rapid distribution of tracer protein throughout the brain from the subarachnoid space. Rennels ML, Gregory TF, Blaumanis OR, et al. *Brain Res.* 1985;326:47–63.

200. Compartments and perivascular arrangement of the meninges covering the cerebral cortex of the rat. Krisch B, Leonhardt H, Oksche A. *Cell Tissue Res.* 1984;238:459–474.

201. Directional and compartmentalized drainage of interstitial fluid and cerebrospinal-fluid from the rat-brain. Zhang ET, Richards HK, Kida S, et al. *Acta Neuropathol.* 1992;83:233–239.

202. Cerebral amyloid angiopathy: Amyloid beta accumulates in putative interstitial fluid drainage pathways in Alzheimer's disease. Weller RO, Massey A, Newman TA, et al. *Am J Pathol.* 1998 Sep;153(3):725-33.

203. A proposed model of cerebrospinal fluid circulation: Observations with radionuclide cisternography. Greitz D, Hannerz J. *AJNR.* 1996;17:431–438.

204. Garbage truck of the brain. Nedergaard M. *Science.* 2013;340(6140):1529-30.

205. Impairment of paravascular clearance pathways in the aging brain. Kress BT, Iliff JJ, Xia M, et al. *Ann Neurol.* 2014 Dec;76(6):845-61.

206. Is there a cerebral lymphatic system? Iliff JJ, Nedergaard M. *Stroke.* 2013 Jun;44(601):S93-S95.

207. Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. Iliff JJ, Lee H, Yu M, et al. *J Clin Invest.* 2013;123(3):1299–1309.

208. Glymphatic dysfunction mediates the influence of white matter hyperintensities on episodic memory in cerebral small vessel disease. Ke Z, Mo Y, Li J, et al. *Brain Sci.* 2022 Nov;12(12):1611.

209. The association between glymphatic system dysfunction and cognitive impairment in cerebral small vessel disease. Tang J, Zhang M, Liu N, et al. *Front Aging Neurosci.* 2022 Jun;14:916633.

210. Glymphatic clearance function in patients with cerebral small vessel disease. Zhang W, Zhou Y, Wang J, et al. *Neuroimage.* 2021 Sep;238:118257.

211. Glymphatic dysfunction correlates with severity of small vessel disease and cognitive impairment in cerebral amyloid angiopathy. Xu J, Su Y, Fu J, et al. *Eur J Neurol.* 2022 Oct;29(10): 2895-2904.

212. Deposition of amyloid-β in the walls of human leptomeningeal arteries in relation to perivascular drainage pathways in cerebral amyloid angiopathy. Keable A, Fenna K, Yuen HM, et al. *Biochim Biophys Acta.* 2016 May;1862(5):1037-46.

213. Capillary and arterial cerebral amyloid angiopathy in Alzheimer's disease: Defining the perivascular route for elimination of amyloid beta from the human brain. Preston SD, Steart PV, Wilkinson A, et al. *Neuropathol Appl Neurobiol.* 2003 Apr;29(2):106-17.

214. Failure of perivascular drainage of β-amyloid in cerebral amyloid angiopathy. Hawkes CA, Jayakody N, Johnston DA, et al. *Brain Pathol.* 2014 Jul; 24(4):396-403.

215. Regional differences in the morphological and functional effects of aging on cerebral basement membranes and perivascular drainage of amyloid-β from the mouse brain. Hawkes CA, Gatherer M, Sharp MM, et al. *Aging Cell.* 2013 Apr;12(2):224-36.

216. Perivascular drainage of solutes is impaired in the ageing mouse brain and in the presence of cerebral amyloid angiopathy. Hawkes CA, Härtig W, Kacza J, et al. *Acta Neuropathol.* 2011 Apr; 121(4):431-43.

217. Cerebral amyloid angiopathy: amyloid beta accumulates in putative interstitial fluid drainage pathways in Alzheimer's disease. Weller RO, Massey A, Newman TA, et al. *Am J Pathol*. 1998 Sep;153(3):725-33.

218. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Iliff JJ, Wang M, Liao Y, et al. *Sci Transl Med.* 2012;4(147):147ra111.

219. Clearance systems in the brain-implications for Alzheimer disease. Tarasoff-Conway JM, Carara RO, Osorio RS, et al. *Nat Rev Neurol.* 2015 Aug;11(8):457-70.

220. Lymphatic clearance of the brain: Perivascular, paravascular and significance for neurodegenerative diseases. Bakker EN, Bacskai BJ, Arbel-Ornath M, et al. *Cell Mol Neurobiol.* 2016 Mar;36(2):181-94.

221. Perivascular drainage drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer's disease. Weller RO, Subash M, Preston SD, et al. *Brain Pathol.* 2008 Apr;18(2):253-66.

222. Failure of perivascular drainage of β-amyloid in cerebral amyloid angiopathy. Hawkes CA, Jayakody N, Johnston DA, et al. *Brain Pathol.* 2014 Jul;24(4):396-403.

223. Interstitial fluid drainage is impaired in ischemic stroke and Alzheimer’s disease mouse models. Arbel-Ornath M, Hudry E, Eikermann-Haerter K, et al. *Acta Neuropathol.* 2013;126:353–364.

224. Impaired glymphatic function and clearance of tau in Alzheimer's disease model. Harrison IF, Ismail O, Machhada A, et al. *Brain.* 2020 Aug;143(8):2576-93.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

225. Glymphatic system clears extracellular tau and protects from tau aggregation and neurodegeneration. Ishida K, Yamada K, Nishiyama R, et al. *J Exp Med.* 2022 Mar;219(3):e20211275.

226. Solutes, but not cells, drain from the brain parenchyma along basement membranes of capillaries and arteries: Significance for cerebral amyloid angiopathy and neuroimmunology. Carare RO, Bernardes-Silva M, Newman TA, et al. *Neuropathol Appl Neurobiol.* 2008 Apr;34(2):131-44.

227. Glymphatic dysfunction mediates the influence of white matter hyperintensities on episodic memory in cerebral small vessel disease. Ke Z, Mo Y, Li J, et al. *Brain Sci.* 2022 Nov;12(12):1611.

228. The association between glymphatic system dysfunction and cognitive impairment in cerebral small vessel disease. Tang J, Zhang M, Liu N, et al. *Front Aging Neurosci.* 2022 Jun;14:916633.

229. Diffusion tensor imaging. Ranzenberger LR, Snyder T. 2022 Jul; *StatPearls [Internet].* Treasure Island (FL): StatPearls Publishing; 2023 Jan.

230. Evaluation of glymphatic system activity with the diffusion MR technique: Diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease. Taoka T, Masutani Y, Kawai H, et al. *Jpn J Radiol.* 2017 Apr;35(4):172-78.

231. Assessment of the DTI-ALPS parameter along the perivascular space in older adults at risk of dementia. Steward CE, Venkatraman VK, Lui E, et al. *J Neuroimaging.* 2021 May;31(3):569-78.

232. Association between white matter alterations and domain-specific cognitive impairment in cerebral small vessel disease: A meta-analysis of diffusion tensor imaging. Xie Y, Xie L, Kang F, et al. *Front Aging Neurosci.* 2022 Nov;14:1019088.

233. Assessment of enlarged perivascular spaces and their relation to target organ damage and mild cognitive impairment in patients with hypertension. Riba-Llena I, Nafría C, Mundet X, et al. *Eur J Neurol.* 2016 Jun;23(6):1044-50.

234. Diffusion along perivascular spaces as marker for impairment of glymphatic system in Parkinson's disease. Shen T, Yue Y, Ba F, et al. *NPJ Parkinson's Dis.* 2022 Dec;8(1):174.

235. Associations among cognitive functions, plasma DNA, and diffusion tensor image along the perivascular space (DTI-ALPS) in patients with Parkinson's disease. Chen HL, Chen PC, Lu CH, et al. *Oxid Med Cell Longev.* 2021 Feb;2021:4034509.

236. Noninvasive neuroimaging provides evidence for deterioration of glymphatic system in Parkinson's disease relative to essential tremor. Gu L, Dai S, Guo T, et al. *Parkinsonism Relat Disord.* 2023 Feb;107:105254.

237. Diffusion along perivascular spaces reveals evidence supportive of glymphatic function impairment in Parkinson Disease. McKnight CD, Trujillo P, Lopez AM, et al. *Parkinsonism Relat Disord.* 2021 Aug;89:98-104.

238. Magnetic resonance images implicate that glymphatic alterations mediate cognitive dysfunction in Alzheimer disease. Hsu JL, Wei YC, Toh CH, et al. *Ann Neurol.* 2023 Jan;93(1):164-74.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

239. Relationship between the deposition of amyloid-β and tau protein and glymphatic system activity in Alzheimer's disease: Diffusion tensor image study. Hsu JL, Wei YC, Toh CH, et al. *Alzheimers Dis.* 2022;90(1):295-303.

240. Diffusion tensor imaging along the perivascular space index in different stages of Parkinson's disease. Ma X, Li S, Li C, et al. *Front Aging Neurosci.* 2021 Nov;13:773951.

241. Glymphatic failure as a final common pathway to dementia. Nedergaard M, Goldman SA. *Science.* 2020 Oct;370(6512):50-56.

242. The glymphatic system: A beginner's guide. Jessen NA, Munk AS, Lundgaard I, et al. *Neurochem Res.* 2015 Dec;40(12)2583-99.

243. The glymphatic system and waste clearance with brain aging: A review. Benveniste H, Liu X, Koundal S, et al. *Gerontol.* 2019:65(2):106-19.

244. Physiology of glymphatic solute transport and waste clearance from the brain. Zhao L, Tannenbaum A, Bakker ENTP, et al. *Physiology (Bethesda).* 2022 Nov;37(6):0.

245. Clearance systems in the brain-implications for Alzheimer disease. Tarasoff-Conway JM, Carara RO, Osorio RS, et al. *Nat Rev Neurol.* 2015 Aug;11(8):457-70.

246. A new look at cerebrospinal fluid circulation. Brinker T, Stopa E, Morrison J, Klinge P. *Fluids Barriers CNS.* 2014 May;11:10.

247. Garbage truck of the brain. Nedergaard M. *Science.* 2013;340(6140):1529-30.

248. Mechanisms of fluid movement into, through and out of the brain: Evaluation of the evidence. Hladky SB, Barrand MA. *Fluids Barriers CNS.* 2014 Dec;11(1):26.

249. Cataract, Alzheimer's disease, and other conformational diseases. Harding JJ. *Curr Opin Ophthalmol.* 1998 Feb;9(1):10-13.

250. Amyloidosis. Pepys MB. *Annu Rev Med.* 2006; 57:121304.131243.
Amyloid beta: Structure, biology and structure-based therapeutic development. Chen GF, Xu TH, Yan Y, et al. *Acta Pharmacol Sin.* 2017 Sep;38(9):1205-35.

251. Beta-amyloid protein aggregation: its implication in the physiopathology of Alzheimer's disease. Dumery L, Bourdel F, Soussan Y, et al. *Pathol Biol (Paris).* 2001 Feb;49(1):72-85.

252. Aggregation and structure of amyloid β-protein. Ono K, Watanabe-Nakayama T. *Neurochem Int.* 2021 Dec;151:105208.

253. The protofilament substructure of amyloid fibrils. Serpell LC, Sunde M, Benson MD, et al. *J Mol Biol.* 2000 Jul;300(5):1033-39.

254. Atomic structure and hierarchical assembly of a cross-β amyloid fibril. Fitzpatrick AWP, Debelouchina GT, Bayro MJ, et al. *Proc Natl Acad Sci USA.* 2013 Apr;110(14):468-73.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

255. Comparison of four staining methods on the detection of neuritic plaques. Wisniewski HM, Wen GY, Kim KS. *Acta Neuropathol.* 1989;78(1):22-7.

256. Oligomeric amyloid beta associates with postsynaptic densities and correlates with excitatory synapse loss near senile plaques. Koffie RM, Meyer-Luehmann M, Hashimoto T, et al. *Proc Natl Acad Sci USA.* 2009 Mar;106(10):4012-17.

257. The role of water in amyloid aggregation kinetics. Stephens AD, Kaminski Schierle GS. *Curr Opin Struct Biol.* 2019 Oct;58:115-123.

258. The Impact of water on the ambivalent behavior and paradoxical phenomenon of the amyloid-β fibril protein. Vajda T, Perczel A. *Biomol Concepts.* 2017 Dec;8(5-6):213-20.

259. Role of water in protein aggregation and amyloid polymorphism. Thirumalai D, Reddy G, Straub JE. *Acc Chem Res.* 2012 Jan;45(1):83-92.

260. Direct observation of protein structural transitions through entire amyloid aggregation processes in water using 2D-IR spectroscopy. Chun SY, Son MK, Park CR, et al. *Chem Soc.* 2022 Mar;13(16):4482-89.

261. Towards an understanding of amyloid-β oligomers. Lee SJ, Nam E, Lee HJ, et al. *Chem Soc Rev.* 2017 Jan;46(2):310-23.

262. Amyloid-like aggregating proteins cause lysosomal defects in neurons via gain-of-function toxicity. Riera-Tur I, Schäfer T, Hornburg D, et al. *Life Sci Alliance.* 2021 Dec;5(3): e202101185.

263. Cytotoxic species in amyloid-associated diseases: Oligomers or mature fibrils. Siddiqi MK, Malik S, Majid N, et al. *Adv Protein Chem Struct Biol.* 2019;118:333-69.

264. Mechanism of amyloid plaque formation suggests an intracellular basis of abeta pathogenicity. Friedrich RP, Tepper K, Rönicke R, et al. *Proc Natl Acad Sci USA.* 2010 Feb;107(5):1942-47.

265. Folding proteins in fatal ways. Selkoe DJ. *Nature.* 2003 Dec 18;426(6968):900-4.

266. Protein Misfolding Diseases. Hartl FU. *Annu Rev Biochem.* 2017 Jun 20;86:21-26.

267. Protein folding and misfolding: A paradigm of self-assembly and regulation in complex biological systems. Vendruscolo M, Zurdo J, MacPhee CE, Dobson CM. *Philos Trans A Math Phys Eng Sci.* 2003 Jun 15;361(1807):1205-22.

268. Principles of protein folding, misfolding and aggregation. Dobson CM. *Semin Cell Dev Biol.* 2004 Feb;15(1):3-16.

269. Unraveling the mysteries of protein folding and misfolding. Ecroyd H, Carver JA. *IUBMB Life.* 2008 Dec;60(12):769-74.

270. Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases. Soto C, Pritzkow S. *Neurosci.* 2018 Oct; 21(10):1332-40.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

271. Misfolding of membrane proteins in health and disease: The lady or the tiger? Sanders CR, Nagy JK. *Curr Opin Struct Biol.* 2000 Aug;10(4):438-42.

272. Protein misfolding, evolution and disease. Dobson CM. *Trends Biochem Sci.* 1999 Sep;24(9): 329-32.

273. Water structure and interactions with protein surfaces. Raschke TM. *Curr Opin Struct Biol.* 2006 Apr;16(2):152-9.

274. Water determines the structure and dynamics of proteins. Bellissent-Funel MC, Hassanali A, Havenith M, et al. *Chem Rev.* 2016 Jul;116(13):7673-97.

275. Water mediation in protein folding and molecular recognition. Levy Y, Onuchic JN. *Annu Rev Biophys Biomol Struct.* 2006;35:389-415.

276. Dynamics of hydration water in proteins. Teixeira J. *Gen Physiol Biophys.* 2009;28(2):168-73.

277. Sub-terahertz spectroscopy reveals that proteins influence the properties of water at greater distances than previously detected. Sushko O, Dubrovka R, Donnan RS. *J Chem Phys.* 2015 Feb 7;142(5):055101.

278. Water dynamics clue to key residues in protein folding. Gao M, Zhu H, Yao X-Q, She Z-S. *Biochem Biophys Res Commun.* 2010 Jan;392(1):95-99.

279. Mapping hydration dynamics around a protein surface. Zhang L, Wang L, Kao YT, et al. *Proc Nat Acad Sci USA.* 2007 Nov;104(47):18461-66.

280. Structural properties of hydration shell around various conformations of simple polypeptides. Czapiewski D, Zielkiewicz J. *J Phys Chem.* 2010 Apr;114(13):4536-50.

281. Protein solvent shell structure provides rapid analysis of hydration dynamics. Dahanayake JN, Shahryari E, Roberts KM, et al. *J Chem Inf Model.* 2019 May;59(5):2407-22.

282. Length-scale dependence of protein hydration-shell density. Biswas AD, Barone V, Amadei A, et al. *Phys Chem Chem Phys.* 2020 Apr;22(14):7340-47.

283. *The Fourth Phase of Water: Beyond Solid, Liquid, Vapor.* Gerald H Pollack. Ebner & Sons Publishers, 2013.

284. Intrinsically disordered proteins in chronic diseases. Kulkarni P, Uversky VN. *Biomolecules.* 2019 Apr;9(4):147.

285. Templated folding of intrinsically disordered proteins. Toto A, Malagrinò F, Visconti L, et al. *Biol Chem.* 2020 May;295(19):6586-93.

286. Features of molecular recognition of intrinsically disordered proteins via coupled folding and binding. Yang J, Gao M, Xiong J, et al. *Protein Sci.* 2019 Nov;28(11):1952-65.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

287. Intrinsically disordered proteins: An overview. Trivedi R, Nagarajaram HA. *Int J Mol Sci.* 2022 Nov;23(22):14050.

288. Local structure and dynamics of hydration water in intrinsically disordered proteins. Rani P, Biswas P. *J Phys Chem B.* 2015 Aug;119(34):10858-67.

289. Interaction with surrounding water plays a key role in determining the aggregation propensity of proteins. Chong SH, Ham S. *Angew Chem Int Ed Engl.* 2014 Apr:53(15):1961-4.

290. Protein structural and surface water rearrangement constitute major events in the earliest aggregation stages of tau. Pavlova A, Cheng CY, Kinnebrew M, Lew J, Dahlquist FW, Han S. *Proc Natl Sci USA.* 2016 Jan;113(2):E127-36.

291. The role of water in amyloid aggregation kinetics. Stephens AD, Kaminski Schierle GS. *Curr Opin Struct Biol.* 2019 Oct; 58:115-123.

292. Prion diseases. Ironside JW, Ritchie DL, Head MW. *Handb Clin Neurol.* 2017;145:393-403.

293. Prion Disease. Baldwin KJ, Correll CM. *Semin Neurol.* 2019 Aug;39(4):428-439.

294. Infectious and Sporadic Prion Diseases. Richard Knight. *Prog Mol Biol Transl Sci.* 2017;150,293-318.

295. Cellular and molecular mechanisms of prion disease. Sigurdson CJ, Bartz JC, Glatzel M. *Annu Rev Pathol.* 2019 Jan;14:497-516.

296. Prion protein misfolding. Kupfer L, Hinrichs W, Groschup MH. *Curr Mol Med.* 2009 Sep;9(7):826-35.

297. Protein misfolding and prion diseases. Cohen FE. *Mol Biol.* 1999 Oct;293(2):313-20.

298. The environmental dependency of protein folding best explains prion and amyloid diseases. Kelly JW. *Proc Natl Acad Sci USA.* 1998 Feb;95(3):930-32.

299. Amyloid fibril formation and protein misassembly: A structural quest for insights into amyloid and prion diseases. Kelly JW. *Structure.* 1997 May;5(5):595-600.

300. Transmissible spongiform encephalopathies, Amyloidosis and yeast prions: Common threads? Caughey B. *Nature Med.* 2000 Jul;6(7):751-54.

301. Deciphering the prion-like behavior of pathogenic protein aggregates in neurodegenerative diseases. Yoshida S, Hasegawa T. *Neurochem Int.* 2022 May;155:105307.

302. Biological activity and pathological implications of misfolded proteins. Bellotti V, Mangione P, Stoppini M. *Cell Mol Life Sci.* 1999 Jun;55(6-7):977-91.

303. Prion diseases: A unique transmissible agent or a model for neurodegenerative diseases? Ritchie DL, Barria MA. *Biomolecules.* 2021 Feb;11(2):207.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

304. Prion-like features of misfolded Aβ and tau aggregates. Morales R, Callegari K, Soto C. *Virus Res.* 2015 Sep;207:106-12.

305. Medicine: Prion-like behavior of amyloid-beta. Kim J, Holtzman DM. *Science.* 2010 Nov;330(6006):918-19.

306. The prion-like propagation hypothesis in Alzheimer's and Parkinson's disease.Duyckaerts C, Clavaguera F, Potier MC. *Curr Opin Neurol.* 2019 Apr;32(2):266-71.

307. Purified and synthetic Alzheimer's amyloid beta (Aβ) prions. Stohr J, Watts JC, Mensinger ZL, et al. *Proc Natl Acad Sci USA.* 2012;109:11025–11030.

308. Transmission and spreading of tauopathy in transgenic mouse brain. Clavaguera F, Bolmont T, Crowther RA, et al. *Nat Cell Biol.* 2009;11:909–913.

309. Heterotopic seeding of tau fibrillization by pre-aggregated Abeta provides potent seeds for prion-like seeding and propagation of tau-pathology in vivo. Vasconcelos B, Stancu IC, Buist A et al. *Acta Neuropathol.* 2016 Apr;131(4):549-69.

310. Aβ-induced acceleration of Alzheimer-related τ-pathology spreading and its association with prion protein. Gomes LA, Hipp SA, Rijal Upadhaya A, et al. *Acta Neuropathol.* 2019 Dec;138(6): 913-41.

311. Amyloid-beta (Aβ) plaques promote seeding and spreading of alpha-synuclein and tau in a mouse model of Lewy body disorders with Aβ pathology. Bassil F, Brown HJ, Pattabhiraman S, et al. *Neuron.* 2020 Jan;105(2):260-75.

312. Amyloidogenesis of SARS-CoV-2 Spike Protein. Nyström S, Hammarström P. *J Am Chem Soc.* 2022;144(20):8945-50.

313. Presence of a SARS-COV-2 protein enhances Amyloid Formation of Serum Amyloid A. Jana AK, Greenwood AB, Hansmann UHE. *J Phys Chem B.* 2021 Aug;125(32):9155-67.

314. Interactions between SARS-CoV-2 N-protein and α-synuclein accelerates amyloid formation. Semerdzhiev SA, Fakhree MAA, Segers-Nolten I, et al. *ACS Chem Neurosci.* 2022;13(1):143-50.

315. SARS-CoV-2 Proteins Interact with Alpha Synuclein and Induce Lewy Body-like Pathology In Vitro. Wu Z, Zhang X, Huang Z Ma K. *Int J Mol Sci.* 2022 Mar;23(6):3394.

316. Protein Misfolding in Prion and Prion-like diseases: Reconsidering a required role for protein loss of function. Leighton P, Allison WT. *J Alzheimer's Dis.* 2016.

317. Aging and Parkinson's Disease: Why is advancing age the biggest risk factor? Reeve A, Simcox E, Turnbull D. *Ageing Res Rev.* 2014.

318. Pathways of cellular proteostasis in aging and disease. Klaips CL, Jayaraj GG, Hartl FU. *J Cell Biol.* 2018 Jan;217(1):51-63.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

319. *Recherches sur la conductivité galvanique des électrolytes,* Svante Arrhenius doctoral dissertation. P. A. Norstedt & Söner, Royal publishing house, Stockholm. 1884.

320. *Species and Specificity: An Interpretation of the History of Immunology.* Pauline Mazumdar publ. Cambridge Univ Press. 1995:pp. 179-253.

321. *Life at the Cell and Below-Cell Level: The Hidden History of a Fundamental Revolution in Biology.* Gilbert Ling. Pacific Press, New York (2001).

322. *A Physical Theory of the Living State: The Association-Induction Hypothesis.* Ling GN. Waltham MA: Blaisdell;1962.

323. *Cells, Gels and the Engines of Life: A New Unifying Approach to Cell Function.* Gerald H. Pollack. publ. Ebner & Sons, Seattle WA. 2001.

324. Coronary microvascular dysfunction. Vancheri F, Longo G, Vancheri S, et al. *J Clin Med.* 2020 Sep;9(9):2880.

325. Cerebral small vessel disease alters neurovascular unit regulation of microcirculation integrity involved in vascular cognitive impairment. Yang Q, Wei X, Deng B, et al. *Neurobiol Dis.* 2022 Aug;170:105750.

326. Impaired perfusion and capillary dysfunction in prodromal Alzheimer's disease. Nielsen RB, Parbo P, Ismail R, et al. *Alzheimer's Dement (Amst).* 2020 May;12(1):e12032.

327. Diffuse microvascular dysfunction and loss of white matter integrity predict poor outcomes in patients with acute ischemic stroke. Rost NS, Cougo P, Lorenzano S, et al. *J Cereb Blood Flow Metab.* 2018 Jan;38(1):75-86.

328. Arterial stiffness and brain integrity: A review of MRI findings. Badji A, Sabra D, Bherer L, et al. *Ageing Res Rev.* 2019 Aug;53:100907.

329. Vascular aging and diseases of the small vessels. Rizzoni D, Rizzoni M, Nardin M, et al. *High Blood Press Cardiovasc Prev.* 2019 Jun;26(3):183-89.

330. Cerebral small vessel disease, cognitive impairment and vascular dementia. Sierra C. *Panminerva Med.* 2012 Sep;54(3):179-88.

331. Cerebral microvascular dysfunction and neurodegeneration in dementia. Han F. *Stroke Vasc Neurol.* 2019 Jun;4(2):105-07.

332. Microvascular dysfunction and cognitive impairment. De Silva TM, Faraci FM. *Cell Mol Neurobiol.* 2016 Mar;36(2):241-58.

333. Ion channel diseases. Hübner CA, Jentsch TJ. *Hum Mol Gen.* 2002 Oct;11(20):2435-45.

334. Ion channel diseases of the central nervous system. Li M, Lester HA. *CNS Drug Rev.* 2001 Summer;7(2):214-40.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

335. Ion channels in neurological disorders. Kumar P, Kumar D, Jha SK, et al. *Adv Protein Chem Struct Biol.* 2016;103:97-136.

336. *Molecular Biology of the Cell.* Alberts B, Johnson A, Lewis J, et al. publ. Garland Science, New York. 2007.

337. Structure of potassium channels. Kuang Q, Purhonen P, Hebert H. *Cell Mol Life Sci.* 2015 Oct;72(19):3677-93.

338. K(+) channels: Function-structural overview. González C, Baez-Nieto D, Valencia I, et al. *Compr Physiol.* 2012 Jul;2(3):2087-149.

339. Calcium channelopathies and Alzheimer's disease: Insight into therapeutic success and failures. Chakraborty S, Stutzmann GE. *Eur J Pharmacol.* 2014 Sep;739:83-95.

340. Calcium channelopathies. Felix R. *Neuromolecular Med.* 2006;8(3):307-18.

341. Calcium signaling and neurodegenerative diseases. Bezprozvanny I. *Trends Mol Med.* 15(3):89-100.

342. Calcium channelopathies: Voltage-gated calcium channels. Adams PJ, Snutch TP. *Subcell Biochem.* 2007;45:215-51.

343. Calcium channelopathies in the central nervous system. Jen J. *Curr Opin Neurobiol.* 1999 Jun; 9(3):274-80.

344. Elevating the levels of calcium ions exacerbate Alzheimer's disease via inducing the production and aggregation of β-amyloid protein and phosphorylated tau. Guan PP, Cao LL, Wang P. *Int J Mol Sci.* 2021 May;22(11):5900.

345. Acceleration of amyloid beta-peptide aggregation by physiological concentrations of calcium. Isaacs AM, Senn DB, Yuan M, et al. *J Biol Chem.* 2006 Sep;281(38):27916-923.

346. Calcium signaling and amyloid toxicity in Alzheimer's disease. Demuro A, Parker I, Stutzmann GE. *J Biol Chem.* 2010 Apr;285(17):12463-68.

347. Role of calcium modulation in the pathophysiology and treatment of Alzheimer's disease. Baracaldo-Santamaría D, Avendaño-Lopez SS, Ariza-Salamanca DF, et al. *Int J Mol Sci.* 2023 May;24(10):9067.

348. Intracellular injection of brain extracts from Alzheimer's disease patients triggers unregulated Ca^{2+} release from intracellular stores that hinders cellular bioenergetics. Pensalfini A, Umar AR, Glabe C, et al. *Cells.* 2022 Nov;11(22):3630.

349. Calcium ions aggravate Alzheimer's disease through the aberrant activation of neuronal networks, leading to synaptic and cognitive deficits. Guan PP, Cao LL, Yang Y, et al. *Front Mol Neurosci.* 2021 Dec;14:757515.

350. Neurological channelopathies. Graves TD, Hanna MG. *Postgrad Med J.* 2005 Jan;81(951):20-32.

351. Neurological channelopathies. Kullman DM. *Annu Rev Neurosci.* 2010;33:151-72.

352. Molecular biology of channelopathies: Impact on diagnosis and treatment. Avanzini G, Franceschetti S, Avoni P, et al. *Exp Rev Neurother.* 2004 May;4(3):519-39.

353. Axonal ion channel dysfunction in amyotrophic lateral sclerosis. Bostock H, Sharief MK, Reid G, et al. *Brain.* 1995 Feb;118(1):217-25.

354. Axonal dysfunction precedes motor neuronal death in amyotrophic lateral sclerosis. Iwai Y, Shibuya K, Misawa S, et al. *PLoS One.* 2016 Jul;11(7):0158596.

355. Axonal excitability in amyotrophic lateral sclerosis: Axonal excitability in ALS. Park SB, Kiernan MC, Vucic S. *Neurotherapeutics.* 2017 Jan;14(1):78-90.

356. Amyotrophic lateral sclerosis—electrophysiologic aspects of its pathophysiology and new therapeutic options. Kuwabara S. *Brain Nerve.* 2010 Aug;62(8):885-91.

357. Altered axonal excitability properties in amyotrophic lateral sclerosis: Impaired potassium channel function related to disease stage. Kanai K, Kuwabara S, Misawa S, et al. *Brain.* 2006 Apr;129(Pt 4):953-62.

358. Concurrent sodium channelopathies and amyotrophic lateral sclerosis supports shared pathogenesis. Franklin JP, Cooper-Knock J, Baheerathan A, et al. *Amyotroph Lateral Scler Frontotemporal Degener.* 2020 Nov;21(7-8):627-30.

359. Potassium channels and their emerging role in Parkinson's disease. Zhang L, Zheng Y, Xie J, et al. *Brain Res Bull.* 2020 Jul;160:1-7.

360. Potassium channels: A potential therapeutic target for Parkinson's disease. Zhang L, Zheng Y, Xie J, et al. *Neurosci Bull.* 2018 Apr;34(2):341-48.

361. α-synuclein-induced Kv4 channelopathy in mouse vagal motoneurons drives nonmotor parkinsonian symptoms. Chiu WH, Kovacheva L, Musgrove RE, et al. *Sci Adv.* 2021 Mar;7(11):eabd3994.

362. The potential role of voltage-dependent anion channel in the treatment of Parkinson's disease. He Y, Wang W, Yang T, et al. *Oxid Med Cell Longev.* 2022 Oct;2022:4665530.

363. Potassium channels in Parkinson's disease: Potential roles in its pathogenesis and innovative molecular targets for treatment. Chen X, Feng Y, Quinn RJ, et al. *Pharmacol Rev.* 2023 Mar:PHARMREV-AR-2022-000743.

364. Converging roles of ion channels, calcium, metabolic stress, and activity pattern of substantia nigra dopaminergic neurons in health and Parkinson's disease. Duda J, Pötschke C, Liss B. *Neurochem.* 2016 Oct;139(Suppl 1):156-78.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

365. Huntington's disease skeletal muscle is hyperexcitable owing to chloride and potassium channel dysfunction. Waters CW, Varuzhanyan G, Talmadge RJ, et al. *Proc Natl Acad Sci USA.* 2013 May;110(22):9160-65.

366. Pathophysiology of Huntington's disease: Time-dependent alterations in synaptic and receptor function. Raymond LA, André VM, Cepeda C, et al. *Neuroscience.* 2011 Dec;198:252-73.

367. Potassium channel dysfunction in neurons and astrocytes in Huntington's disease. Zhang X, Wan JQ, Tong XP. *CNS Neurosci Ther.* 2018 Apr;24(4):311-18.

368. Ion channel dysfunction in astrocytes in neurodegenerative diseases. Wang S, Wang B, Shang D, et al. *Front Physiol.* 2022 Feb;13:814285.

369. Progressive Cl^- channel defects reveal disrupted skeletal muscle maturation in R6/2 Huntington's mice. Miranda DR, Wong M, Romer S, et al. *J Gen Physiol.* 2017 Jan;149(1):55-74.

370. Mechanisms of altered skeletal muscle action potentials in the R6/2 mouse model of Huntington's disease. Miranda DR, Reed E, Jama A, et al. *Am J Physiol Cell Physiol.* 2020 Jul;319(1):C218-C232.

371. Striatal synaptic dysfunction and altered calcium regulation in Huntington's disease. Raymond LA. *Biochem Biophys Res Comm.* 2017 Feb;483(4):1051-62.

372. Microglial voltage-gated sodium channels modulate cellular response in Alzheimer's disease- a new perspective on an old problem. Cătălin B, Mitran S, Ciorbagiu M, et al. *Rom J Morphol Embryol.* 2015;56(1):21-25.

373. Analyzing and modeling the dysfunction of inhibitory neurons in Alzheimer's disease. Perez C, Ziburkus J, Ullah G. *PLoS One.* 2016 Dec;11(12):e0168800.

374. Voltage-gated sodium channel dysfunctions in neurological disorders. Barbieri R, Nizzari M, Zanardi I, et al. *Life (Basel).* 2023 May;13(5):1191.

375. Reduced cooperativity of voltage-gated sodium channels in the hippocampal interneurons of an aged mouse model of Alzheimer's disease. Perez C, Ullah G. *Eur Biophys J.* 2018 Jul;47(5):539-47.

376. Na^+ and K^+ ion imbalances in Alzheimer's disease. Vitvitsky VM, Garg SK, Keep RF, et al. *Biochim Biophys Acta.* 2012 Nov;1822(11):1671-81.

377. Calcium dyshomeostasis and lysosomal Ca^{2+} dysfunction in amyotrophic lateral sclerosis. Tedeschi V, Petrozziello T, Secondo A. *Cells.* 2019 Oct;8(10):1216.

378. Dysfunction of neuronal calcium signaling in neuroinflammation and neurodegeneration. Fairless R, Williams SK, Diem R. *Cell Tissue.* 2014 Aug;357(2):455-62.

379. Role of calcium modulation in the pathophysiology and treatment of Alzheimer's disease. Fairless R, Williams SK, Diem R, et al. *Int J Mol Sci.* 2023 May;24(10):9067.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

380. Role of calcium dysregulation in Alzheimer's disease and its therapeutic implications. Joshi M, Joshi S, Khambete M, Degani M. *Chem Biol Drug Des.* 2023 Feb;101(2):453-68.

381. On the role of store-operated calcium entry in acute and chronic neurodegenerative diseases. Secondo A, Bagetta G, Amantea D. *Front Mol Neurosci.* 2018 Mar;11:87.

382. Neuronal calcium signaling, mitochondrial dysfunction, and Alzheimer's disease. Supnet C, Bezprozvanny I. *J Alzheimers Dis.* 2010; 20(Suppl 2):S487-98.

383. Calcium, mitochondrial dysfunction and slowing the progression of Parkinson's disease. Surmeier DJ, Halliday GM, Simuni T. *Exp Neurol.* 2017 Dec;298(Pt B):202-209.

384. Calcium and Parkinson's disease. Surmeier DJ, Schumacker PT, Guzman JD, et al. *Biochem Biophys Res Commun.* 2017 Feb;483(4):1013-19.

385. Calcium signaling and neurodegenerative diseases. Bezprozvanny I. *Trends Mol Med.* 2009 Mar;15(3):89-100.

386. Impaired mitochondrial energy metabolism in Alzheimer's disease: Impact on pathogenesis via disturbed epigenetic regulation of chromatin landscape. Salminen A, Haapasalo A, Kauppinen A, et al. *Prog Neurobiol.* 2015 Aug;131:1-20.

387. Disturbed mitochondrial dynamics and neurodegenerative disorders. Burté F, Carelli V, Chinnery PF, Yu-Wai-Man P. *Nat Rev Neurol.* 2015 Jan;11(1):11-24.

388. Protein Folding and Misfolding, Endoplasmic Reticulum Stress in Neurodegenerative Diseases: In Trace of Novel Drug Targets. Penke B, Bogár F, Fülöp L. *Curr Protein Pept Sci.* 2016;17(2):169-82.

389. Dysfunction of Endoplasmic Reticulum (ER) and Mitochondria (MT) in Alzheimer's Disease: The Role of the ER-MT Cross-Talk. Volgyi K, Juhász G, Kovacs Z, Penke B. *Curr Alzheimer Res.* 2015;12(7):655-72.

390. Cellular stress responses in protein misfolding diseases. Duennwald ML. *Future Sci OA.* 2015 Sep 1;1(2):FSO42.

391. Compromised autophagy and neurodegenerative diseases. Menzies FM, Fleming A, Rubinsztein DC. Nat Rev Neurosci. 2015 Jun;16(6):345-57.

392. In vivo aspects of protein folding and quality control. Balchin D, Hayer-Hartl M, Hartl FU. *Science.* 2016 Jul 1;353(6294):4354.

393. Proteostasis impairment in protein-misfolding and -aggregation diseases. Hipp MS, Park SH, Hartl FU. *Trends Cell Biol.* 2014 Sep;24(9):506-14.

394. Quality control in the endoplasmic reticulum protein factory. Sitia R, Braakman I. *Nature.* 2003 Dec 18;426(6968):891-4.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

395. Protein degradation and protection against misfolded or damaged proteins. Goldberg AL. *Nature.* 2003 Dec 18;426(6968):895-9.

396. The endoplasmic reticulum membrane ion channels and changes in membrane capacitance. Maruyama Y. *Jpn J Physiol.* 1997;47 (Suppl 1):S18.

397. Role of TRPV channels in endoplasmic reticulum calcium homeostasis. Haustrate A, Prevarskaya N, Lehen'kyi V. *Cells.* 2020 Jan;9(2):317.

398. Endoplasmic reticulum-mediated signaling in cellular microdomains. Biwer LA, Isakson BE. *Acta Physiol (Oxf).* 2017 Jan;219(1):162-75.

399. New and notable ion-channels in the sarcoplasmic/endoplasmic reticulum: Do they support the process of intracellular Ca^{2+} release? Takeshima H, Venturi E, Sitsapesan R. *J Physiol.* 2015 Aug;593(15):3241-51.

400. Ca^{2+} homeostasis and endoplasmic reticulum (ER) stress: An integrated view of calcium signaling. Krebs J, Agellon LB, Michalak M. *Biochem Biophys Res Commun.* 2015 Apr;460(1):114-21.

401. In vivo aspects of protein folding and quality control. Balchin D, Hayer-Hartl M, Hartl FU. *Science.* 2016 Jul 1;353(6294):aac4354.

402. The unfolded protein response: mechanisms and therapy of neurodegeneration. Smith HL, Mallucci GR. *Brain.* 2016 Aug;139(Pt 8):2113-21.

403. Protein misfolding in the endoplasmic reticulum as a conduit to human disease. Wang M, Kaufman RJ. *Nature.* 2016 Jan 21;529(7586):326-35.

404. Protein degradation and protection against misfolded or damaged proteins. Goldberg AL. *Nature.* 2003 Dec 18;426(6968):895-9.

405. Cellular stress responses in protein misfolding diseases. Duennwald ML. *Future Sci OA.* 2015 Sep 1;1(2):FSO42.

406. Endoplasmic reticulum stress and lipids in health and diseases. Celik C, Lee SYT, Yap WS, et al. *Prog Lipid Res.* 2023 Jan;89:101198.

407. Protein folding and misfolding, endoplasmic reticulum stress in neurodegenerative diseases: In trace of novel drug targets. Penke B, Bogár F, Fülöp L. *Curr Protein Pept Sci.* 2016;17(2):169-82.

408. Endoplasmic reticulum and the unfolded protein response: Dynamics and metabolic integration. Bravo R, Parra V, Gatica D, et al. *Int Rev Cell Mol Biol.* 2013;301:215-90.

409. Endoplasmic reticulum stress and unfolded protein response in neurodegenerative diseases. Ghemrawi R, Khair M. *Int J Mol Sci.* 2020 Aug;21(17):6127.

410. Autophagy: Many paths to the same end. Cuervo AM. *Mol Cell Biochem.* 2004 Aug; 263(1):55-57.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

411. Regulation of neuronal autophagy and the implications in neurodegenerative diseases. Cai Q, Ganesan D. *Neurobiol Dis.* 2022 Jan;162:105582.

412. Exploring the role of autophagy dysfunction in the neurodegenerative disorders. Rana T, Behl T, Sehgal A, et al. *Mol Neurobiol.* 2021 Oct;58(10):4886-4905.

413. The role of autophagy in neurodegenerative disease. Nixon RA. *Nature Med.* 2013 Aug;19(8): 983-97.

414. Lysosomal physiology. Xu H, Ren D. *Annu Rev Physiol.* 2015;77:57-80.

415. Regulation of lysosomal ion homeostasis by channels and transporters. Xiong J, Zhu MX. *Sci China Life Sci.* 2016 Aug;59(8):777-91.

416. Lysosomal ion channels as decoders of cellular signals. Li P, Gu M, Xu H *Trends Biochem Sci* 2019 Feb; 44(2):110-24

417. The role of lysosomal ion channels in lysosome dysfunction. Kendall RL, Hollan A. *Inhal Toxicol.* 2021 Feb;33(2):41-54.

418. The lysosome: From waste bag to potential therapeutic target. Appelqvist H, Wäster P, Kågedal K. *J Mol Cell Biol.* 2013 Aug;5(4):214-26.

419. Lysosomal potassium channels: Potential roles in lysosomal function and neurodegenerative diseases. Feng X, Zhao Z, Li Q, Tan Z. *Neurol Disord Drug Targets.* 2018;17(4):261-66.

420. Lysosomal potassium channels. Huang P, Xu M, Wu Y, et al. *Handb Exp Physiol.* 2023;278:127-52.

421. Altered mitochondria, energy metabolism, voltage-dependent anion channel, and lipid rafts converge to exhaust neurons in Alzheimer's disease. Ferrer I. *Bioenerg Biomembr.* 2009 Oct;41(5):425-31.

422. Is the mitochondrial outer membrane protein VDAC1 therapeutic target for Alzheimer's disease? Reddy PH. *Biochim Biophys Acta.* 2013 Jan;1832(1):67-75.

423. VDAC1, mitochondrial dysfunction, and Alzheimer's disease. Shoshan-Barmatz V, Nahon-Crystal E, Shteinfer-Kuzmine A, et al. *Pharmacol Res.* 2018 May;131:87-101.

424. Mitochondrial potassium channels. Szewczyk A, Jarmuszkiewicz W, Kunz WS. *IUBMB Life.* 2009 Feb;61(2):134-43.

425. Mitochondrial ion channels in aging and related diseases. Ashrafuzzaman M. *Curr Aging Sci.* 2022;240:97-109.

426. A guide to the pharmacology of mitochondrial potassium channels. Augustynek B, Kunz WS, Szewczyk A. *Handb Exp Pharmacol.* 2017;240:103-127.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

427. Role of mitochondrial ion channels in cell death. Ryu SY, Peixoto PM, Teijido O, et al. *Biofactors.* 2010 Jul; 36(4):255-63.

428. Mitochondrial ion channels: Gatekeepers of life and death. O'Rourke B, Cortassa S, Aon MA. *Physiology (Bethesda).* 2005 Oct; 20:303-15.

429. Synaptic, mitochondrial, and lysosomal dysfunction in Parkinson's disease. Nguyen M, Wong YC, Ysselstein D, et al. *Trends Neurosci.* 2019 Feb;42(2):140-49.

430. The overcrowded crossroads: Mitochondria, α-synuclein, and the endolysosomal system interaction in Parkinson's disease. Lin KJ, Lin KL, Chen SD, et al. *Int J Mol Sci.* 2019 Oct;20(21):5312.

431. Critical appraisal on mitochondrial dysfunction in Alzheimer's disease. Ahmad F, Sachdeva P. *Aging Med (Milton).* 2022 Jul; 5(4):272-80.

432. Autophagy impairment with lysosomal and mitochondrial dysfunction is an important characteristic of oxidative stress-induced senescence. Tai H, Wang Z, Gong H, et al. *Autophagy.* 2017 Jan;13(1):99-113.

433. Coordination of mitochondrial and lysosomal homeostasis mitigates inflammation and muscle atrophy during aging. Irazoki A, Martinez-Vicente M, Aparicio P, et al. *Aging Cell.* 2022 Apr;21(4):e13583.

434. Mitochondrial ROS-induced lysosomal dysfunction impairs autophagic flux and contributes to M1 macrophage polarization in a diabetic condition. Yuan Y, Chen Y, Peng T, et al. *Clin Sci (Lond).* 2019 Aug;133(15):1759-77.

435. Mitochondrial dysfunction in the development and progression of neurodegenerative diseases. Johnson J, Mercado-Ayon E, Mercado-Ayon Y, et al. *Arch Biochem Biophys.* 2021 May;702:108698.

436. Mitochondrial dysfunction in Huntington's disease. Carmo C, Naia L, Lopes C, et al. *Adv Exp Med Biol.* 2018;1049:59-83.

437. Mitochondrial and vascular lesions as a central target for the development of Alzheimer's disease and Alzheimer disease-like pathology in transgenic mice. Aliev G, Seyidova D, Lamb BT, et al. *Neurol Res.* 2003 Sep;25(6):665-74.

438. Mitochondrial dysfunction, protein misfolding and neuroinflammation in Parkinson's disease: Roads to biomarker discovery. Picca A, Guerra F, Calvani R, et al. *Biomolecules.* 2021 Oct;11(10):1508.

439. Mitochondrial unfolded protein response: an emerging pathway in human diseases. Zhu L, Zhou Q, He L, et al. *Free Rad Biol Med.* 2021 Feb;163:125-34.

440. Unfolded protein response-dependent communication and contact among endoplasmic reticulum, mitochondria, and plasma membrane. Saito A, Imaizumi K. *Int J Mol Sci.* 2018 Oct;19(10):3215.

441. Mitochondria, calcium-dependent neuronal death and neurodegenerative disease. Duchen MR. *Pflugers Arch.* 2012 Jul;464(1):111-21.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

442. TRP channels in disease. Nilius B. *Biochim Biophys Acta.* 2007 Aug;1772(8):805-12.

443. An overview on transient receptor potential channels superfamily. Tsagareli MG, Nozadze I. *Behav Pharmacol.* 2020 Aug;31(5):413-34.

444. TRP channels as emerging therapeutic targets for neurodegenerative diseases. Zhu L, Zhou Q, He L, et al. *Front Physiol.* 2020 Apr;11:238.

445. TRPM channels in human diseases. Tsagareli MG, Nozadze I, et al. *Cells.* 2020 Dec;9(12):2604.

446. Roles of TRPM2 in oxidative stress. Tsagareli MG, Nozadze I, et al. *Cell Calcium.* 2011 Sep;50(3):279-87.

447. TRPMs and neuronal cell death. Tsagareli MG, Nozadze I. *Pflugers Arch.* 2005 Oct;451(1):243-49.

448. New frontiers on ER stress modulation: Are TRP channels the leading actors? Vestuto V, Di Sarno V, Musella S, et al. *Int J Mol Sci.* 2022 Dec;24(1):185.

449. The TRPM2 channel nexus from oxidative damage to Alzheimer's pathologies: An emerging novel intervention target for age-related dementia. Vestuto V, Di Sarno V, Musella S, et al. *Ageing Res Rev.* 2018 Nov;47:67-69.

450. TRPM2 channel in oxidative stress-induced mitochondrial dysfunction and apoptotic cell death. Malko P, Ding R, Jiang LH. *Adv Protein Chem Struct Biol.* 2021;125:51-72.

451. The microglial NLRP3 inflammasome is activated by amyotrophic lateral sclerosis proteins. Deora V, Lee JD, Albornoz EA, et al. *Glia.* 2020 Feb;68(2):407-21.

452. NLRP3 inflammasome activation in a transgenic amyotrophic lateral sclerosis model. Deora V, Lee JD, Albornoz EA, et al. *Inflammation.* 2018 Feb;41(1):93-103.

453. Aggregated tau activates NLRP3-ASC inflammasome exacerbating exogenously seeded and non-exogenously seeded tau pathology in vivo. Stancu IC, Cremers N, Vanrusselt H, et al. *Acta Neuropathol.* 2019 Apr;137(4):599-617.

454. NLRP3 inflammasome activation drives tau pathology. Ising C, Venegas C, Zhang S, et al. *Nature.* 2019 Nov;575(7784):669-673.

455. Soluble α-synuclein-antibody complexes activate the NLRP3 inflammasome in hiPSC-derived microglia. Trudler D, Nazor KL, Eisele YS, et al. *Proc Natl Acad Sci USA.* 2021 Apr;118(15):e2025847118.

456. Inflammasome signaling in brain function and neurodegenerative disease. eka MT, McManus RM, Latz E. *Nat Rev Neurosci.* 2018 Oct;19(10):610-21.

457. Triggering of inflammasome by aggregated alpha-synuclein, an inflammatory response in synucleinopathies. Codolo G, Plotegher N, Pozzobon T, et al. *PLoS One.* 2013;8:e55375.

458. The role of the inflammasome in neurodegenerative diseases. Piancone F, La Rosa F. *Molecules.* 2021 Feb;26(4):953.

459. Neuronal NLRP# is a parkin substrate that drives neurodegeneration in Parkinson's disease. Panicker N, Kam TI, Wang H, et al. *Neuron.* 2022 Aug;110(15):2422-37.

460. *Biologically Closed Electric Circuits.* Björn Nordenström. Nordic Publications. 1983.

461. Aether, fields & energy dynamics in living bodies - Part I. Thorp KE, Thorp JA, Walker PR. *G Med Sci.* 2021;2(5):014-025.

462. Aether, fields & energy dynamics in living bodies - Part II. Thorp KE, Thorp JA, Walker PR. *G Med Sci.* 2021;2(6):001-020.

463. Aether, fields & energy dynamics in living bodies - Part III. Thorp KE, Thorp JA, Walker PR. *G Med Sci.* 2021;2(6):021-047.

464. Consequence of macromolecular crowding on aggregation propensity and structural stability of haemoglobin under glycating conditions. Hasan S, Naeem A. *Int J Biol Macromiol.* 2020 Nov;162:1044-53.

465. The kinetics of islet amyloid polypeptide phase-separated system and hydrogel formation are critically influenced by macromolecular crowding. Chun SY, Son MK, Park CR. *Biochem J.* 2021 Aug;478(15):3025-46.

466. Protein unfolding in a crowded milieu: What crowding can do to a protein undergoing unflolding? Stepanenko OV, Povarova OI, Sulatskaya AI, et al. *J Biomol Struct Dyn.* 2016 Oct;34(10):2155-70.

467. What macromolecular crowding can do to a protein. Stepanenko OV, Povarova OI, Sulatskaya AI. *Int J Mol Sci.* 2014 Dec;15(12):23090-140.

468. Peculiarities of super-folder GFP folding in a crowded milieu. Stepanenko OV, Stepanenko OV, Kuznetsova IM, et al. *Int J Mol Sci. 2016* Oct;17(11):1805.

469. Intrinsically disordered proteins in a crowded milieu: When chaos prevails within the cellular gumbo. Fonin AV, Darling AL, Kuznetsova IM, et al. *Cell Mol Life Sci.* 2018 Nov;75(21):3907-29.

470. What macromolecular crowding can do to a protein. Kuznetsova IM, Turoverov KK, Uversky VN. *Int J Mol Sci.* 2014 Dec;15(12):23090-140.

471. Protein folding and assembly in confined environments: Implications for protein aggregation in hydrogels and tissues. Simpson LW, Good TA, Leach JB. *Biotechnol Adv.* 2020 Sep:42:107573.

472. Stability of protein-specific hydration shell on crowding. Huang KY, Kingsley CN, Sheil R, et al. *J Am Chem Soc.* 2016 Apr;138(16):5392-402.

473. From Levinthal's paradox to the effects of cell environmental perturbation on protein folding. Zeng J, Huang Z. *Curr Med Chem.* 2019;26(42):7537-54.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

474. Folding, stability and shape of proteins in crowded environments: Experimental and computational approaches. Samiotakis A, Wittung-Stafshede P, Cheung MS. *Int J Mol Sci.* 2009 Feb;10(2):572-88.

475. Effects of macromolecular crowding agents on protein folding in vitro and in silico. Christiansen A, Wang Q, Cheung MS, et al. *Biophys Rev.* 2013 Jun;5(2):137-145.

476. Macromolecular crowding: Macromolecules friend or foe? Mittal S, Chowhan RK, Singh LR. *Biochim Biophys Acta.* 2015 Sept;1850(9):1822-31.

477. Effect of macromolecular crowding on protein folding dynamics at the secondary structure level. Mukherjee S, Waegele MM, Chowdhury P, et al. *J Mol Biol.* 2009 Oct;393(1):227-36.

478. Effects of macromolecular crowding on the folding and aggregation of glycosylated MUC5AC. Jing W, Qin Y, Tong J. *Biochem Biophys Res Comm.* 2020 Sep;529(4):984-90.

479. The effect of macromolecular crowding on chaperone-mediated protein folding. Martin J, Hartl FU. *Proc Natl Acad Sci USA.* 1997 Feb;94(4):1107-12.

480. Intrinsically disordered proteins in crowded milieu: When chaos prevails within the cellular gumbo. Fonin AV, Darling AL, Kuznetsova IM, et al. *Cell Mol Life Sci.* 2018 Nov;75(21):3907-29.

481. On protein folding in crowded conditions. Gomez D, Huber K, Klumpp S. *J Phys Chem Lett.* 2019 Dec;10(24):7650-56.

482. The effects of macromolecular crowding on the mechanical stability of protein molecules. Yuan JM, Chyan CL, Zhou HX, et al. *Protein Sci.* 2008 Dec;17(12):2156-66.

483. Protein aggregation in crowded environments. Ellis RJ, Minton AP. *Biol Chem.* 2006 May;387(5):485-97.

484. Arterial stiffness and cognitive function. Joly L. *Geriatr Psychol Neuropsychiatr Vieil.* 2017 Mar;15(1):83-88.

485. Review of the potential role of arterial stiffness in the pathogenesis of Alzheimer's disease. Hughes TM, Craft S, Lopez OL. *Neurodegen Dis Manag.* 2015;5(2):121-35.

486. Arterial stiffness and cardiovascular autonomic dysfunction in patients with Parkinson's disease. Kim JS, Lee SH, Oh YS, et al. *Neurodegen Dis.* 2017;17(2-3):89-96.

487. Carotid arterial stiffness and cerebral blood flow in amnestic mild cognitive impairment. Tomoto T, Sugawara J, Tarumi T, et al. *Curr Alzheimer Res.* 2020;17(12):1115-25.

488. Arterial stiffness and impaired renal function in patients with Alzheimer's disease. Oh YS, Kim JS, Park JW, et al. *Neurol Sci.* 2017 Jul;37(3):451-57.

489. Association of arterial stiffness with cognition in patients with Lewy body disorder. Ryu DW, Kim JS, Lee JE, et al. *Neurol Sci.* 2017 Jul;38(7):1307-13.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901

490. Arterial stiffness and medial temporal lobe atrophy in elders with memory disorders. Lilamand M, Vidal JS, Plichart M, et al. *J Hypertens.* 2016 Jul;34(7):1331-37.

491. Central hemodynamics and arterial stiffness in idiopathic and multiple system atrophy. Franzen K, Fliegen S, Koester J, et al. *J Neurol.* 2017 Feb;264(2):327-32.

492. Relationship between arterial stiffness and cognitive function in elderly subjects with complaints of memory loss. Hanon O, Haulon S, Lenoir H, et al. *Stroke.* 2005 Oct;36(10):1120-25.

493. Arterial stiffness and brain integrity: A review of MRI findings. Badji A, Sabra D, Bherer L, et al. *Ageing Res Rev.* 2019 Aug;53:100907.

494. *The Logic of Scientific Discovery.* Karl Popper. publ. Routledge; 2002.

Thorp KE, Thorp JA, Northrup C, Thorp EM, Peters SE, Walker PR. Energy Dynamics in Dementia & the Neurodegenerative Diseases: A New Causal Paradigm. G Med Sci. 2023;4(1):348-405. https://www.doi.org/10.46766/thegms.neuro.22062901