Functional Neurology

THE TOOLBOX

Professional
Disclosures

NO
CONFLICTS
TO DISCLOSE.

What is neurology?

- Neurology is a branch of medicine dealing with disorders of the nervous system. Neurology deals with the diagnosis and treatment of all categories of conditions and disease involving the central and peripheral nervous systems, including their coverings, blood vessels, and all effector tissue, such as muscle.

What is functional medicine?

- Functional Medicine is a systems biology–based approach that focuses on identifying and addressing the root cause of disease. Each symptom or differential diagnosis may be one of many contributing to an individual's illness.

https://www.ifm.org/functional-medicine/what-is-functional-medicine/

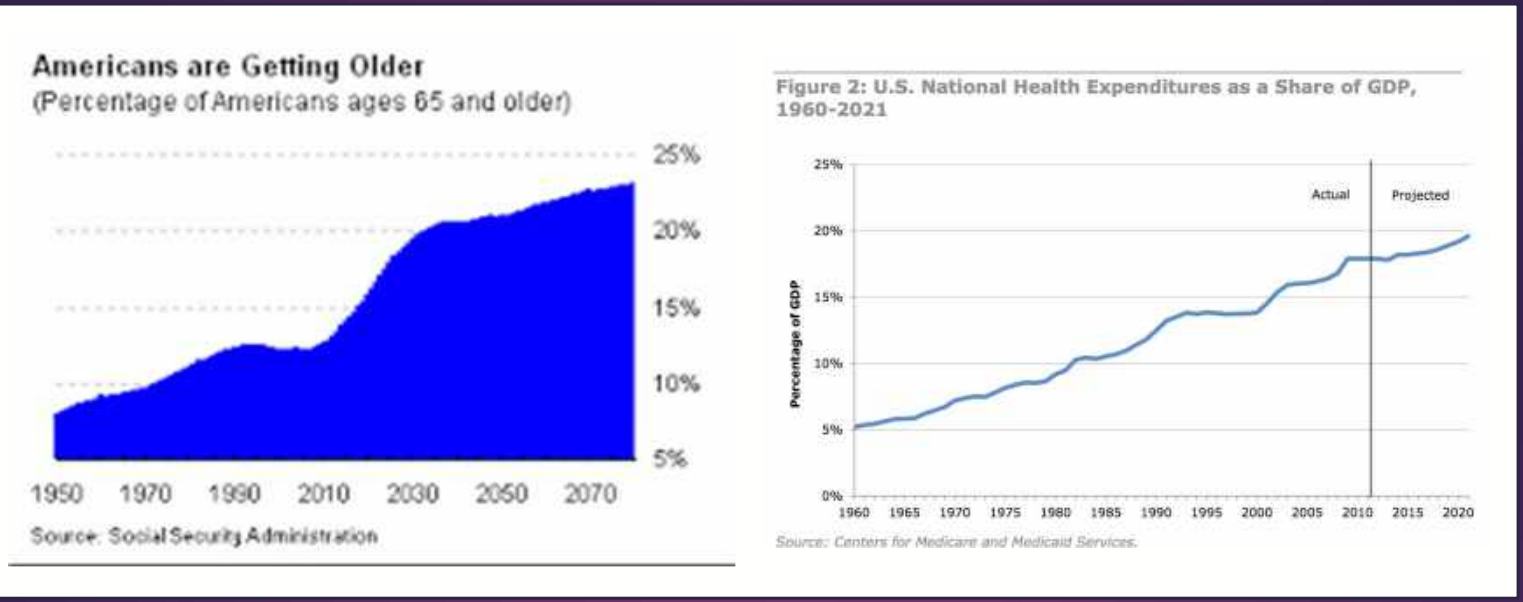
Why bother?

Disorders of the brain and spinal cord are common worldwide problems but have remained very difficult to treat. As a group they have diverse etiologies and …share an overall intractability as current therapies are largely limited to treatment of symptoms.

“Diagnose and Adios.”

Chronic Brain Diseases on the Rise in the U.S.

- Alzheimer's disease: 5.8 million
- ALS: 16,000
- Parkinson's disease: 930,000
- Multiple sclerosis: 1,000,000
- Migraine: 38,000,000



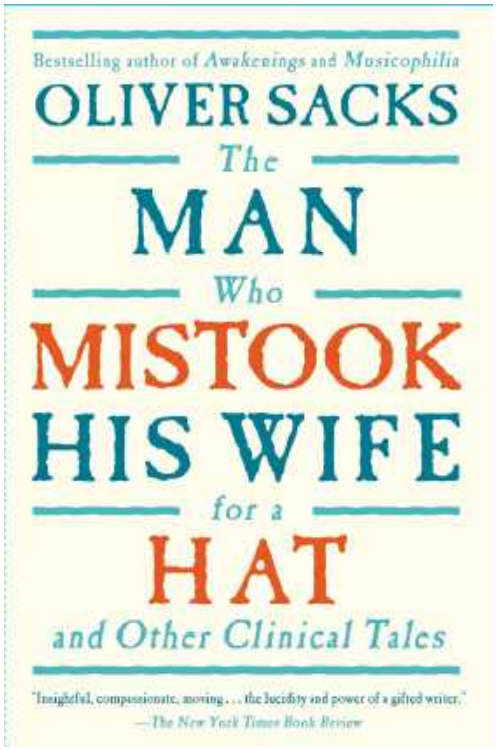
An evolving crisis…

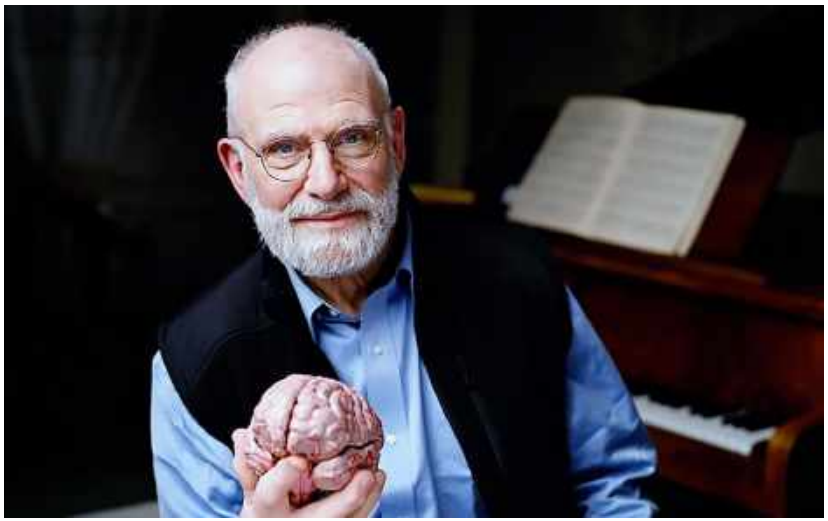
HAVE YOU CONSIDERED HOW YOU OR YOUR PATIENTS MIGHT BE AFFECTED?


$285,000

The healthcare system in our country is convoluted and broken.

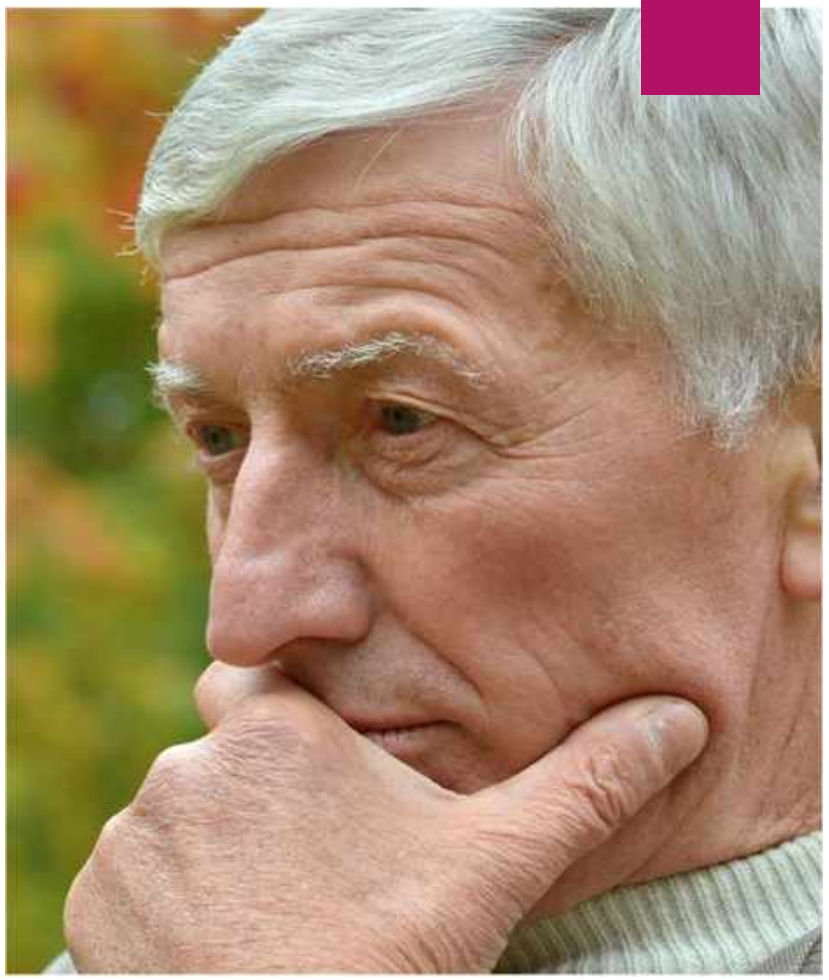

Google


Bestselling author of Awakenings and Musicophilia
OLIVER SACKS
The
MAN
Who
MISTOOK
HIS WIFE
for a
HAT
and Other Clinical Tales
"Insightful, compassionate, moving . . . the lucidity and power of a gifted writer."
—The New York Times Book Review



What our patients are looking for …

- In our office for a reason
- Sick and tired of being sick and tired…or in pain
- Frustrated
- Looking for answers that no one has figured out
- Looking for a professional who can provide hope
- Looking for a professional who is compassionate
- Looking for someone who listens
- Looking for someone with a good reputation
- Looking for a true specialist (not Dr. Google)
- Looking for alternatives to what they have already tried



The Institute for Functional Medicine

How to combine neurology and functional medicine?

Can't skip the foundations of neurology – The Neurological History

- Location
- Duration
- Severity
- Quality
- Context
- Modifying factor(s)
- Associated signs and symptoms
- Timing

- It is said that over 80% of diagnoses are made on history alone, a further 5-10% on examination and the remainder on investigation.

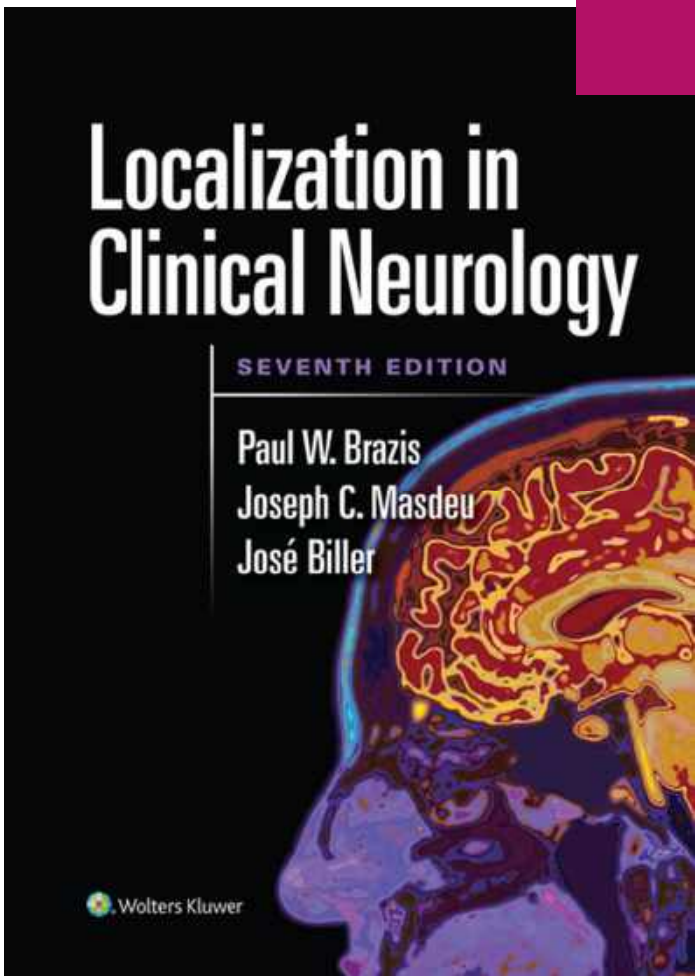
https://patient.info/doctor/history-and-physical-examination#ref-1

Neurological Examination

- Motor Examination
  - Bulk, Tone, Power
- Coordination
- Sensation
  - Pain/Temperature
  - Vibration/Proprioception
- Deep Tendon Reflexes and Primitive Reflexes
- Gait and Station

Localization: Where is the Lesion?

- Brain
  - Cortical or subcortical
- Brainstem
- Spinal cord
- Nerve roots (cervical, thoracic, lumbosacral)
- Plexus (brachial, lumbosacral)
- Peripheral nerve
- Neuromuscular junction
- Muscle



What is the diagnosis?

The information from the medical history combined with the neurological examination is what makes LOCALIZATION possible.

→

From this information, including localization of the lesion, the differential diagnosis is generated.

Categories of Neurological Disease

- Congenital
- Traumatic
- Infectious
- Vascular
  - Inflammatory
  - Ischemic/hemorrhagic
- Demyelinating
- Degenerative
- Neoplastic
- Toxic-Metabolic (including nutritional)
- Autoimmune
- Disorders of Function/Paroxysmal Disorders: Epilepsy, Migraine, Paroxysmal Movement Disorder (including dystonias), Narcolepsy and other sleep disorders, neuropsychiatric disorders (such as Tourette's syndrome).

What is your differential diagnosis and what tests are you going to use to sort this out?

(NOT A FISHING EXPEDITION.)

In some cases there are also diagnostic criteria

- 2017 Revised McDonald Criteria (Multiple sclerosis)
- International Classification of Headache Disorders – 3rd Revision
  - Migraine and migraine variants
  - Tension-type headache
  - Cluster Headache
- The El Escorial World Federation of Neurology (ALS)

MDS clinical diagnostic criteria (2015) – clinically established Parkinson's disease

Specificity at least 90%

- Parkinsonism – bradykinesia plus either rigidity or rest tremor[1]
- **Clinically established PD:[1]**
  - **Absence of absolute exclusion criteria; at least 2 supportive criteria; no 'red flags'**

Absolute exclusion criteria[1]

- Cerebellar signs
- Supranuclear gaze palsy
- Established diagnosis of BVFTD
- Parkinsonism restricted to the lower limbs only for >3 years
- Treatment with an antidopaminergic, or with dopamine-depletion agents
- Absence of response to levodopa
- Sensory–cortical loss
- No evidence for dopaminergic deficiency on functional imaging
- Other parkinsonism-inducing condition

Red flags[1]

- Rapid deterioration of gait
- Absence of motor symptom progression over 5 years
- Early bulbar dysfunction
- Respiratory dysfunction
- Early severe autonomic failure
- Early recurrent falls due to misbalance
- Disproportionate anterocollis
- Absence of common non-motor features of disease during >5 years
- Pyramidal tract signs
- Bilateral symmetric presentation

Supportive criteria[1]

- A clear and dramatic positive response to dopaminergic therapy
- Levodopa-induced dyskinesia
- Documentation of resting tremor of a limb
- A positive diagnostic test of either olfactory loss or cardiac sympathetic denervation on scintigraphy

BVFTD=behavioural variant frontotemporal dementia; MDS=movement disorder society

1. Postuma et al. Mov Disord 2015;30(12):1591–1601

Clinical Diagnostic Criteria for PROBABLE Alzheimer's Disease (1984)

- Dementia
- Deficits in two or more areas of cognition
- Progressive worsening of memory and other cognitive functions
- No disturbance of consciousness
- Onset between ages 40 and 90, most often after age 65; and
- Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive decline in memory and cognition

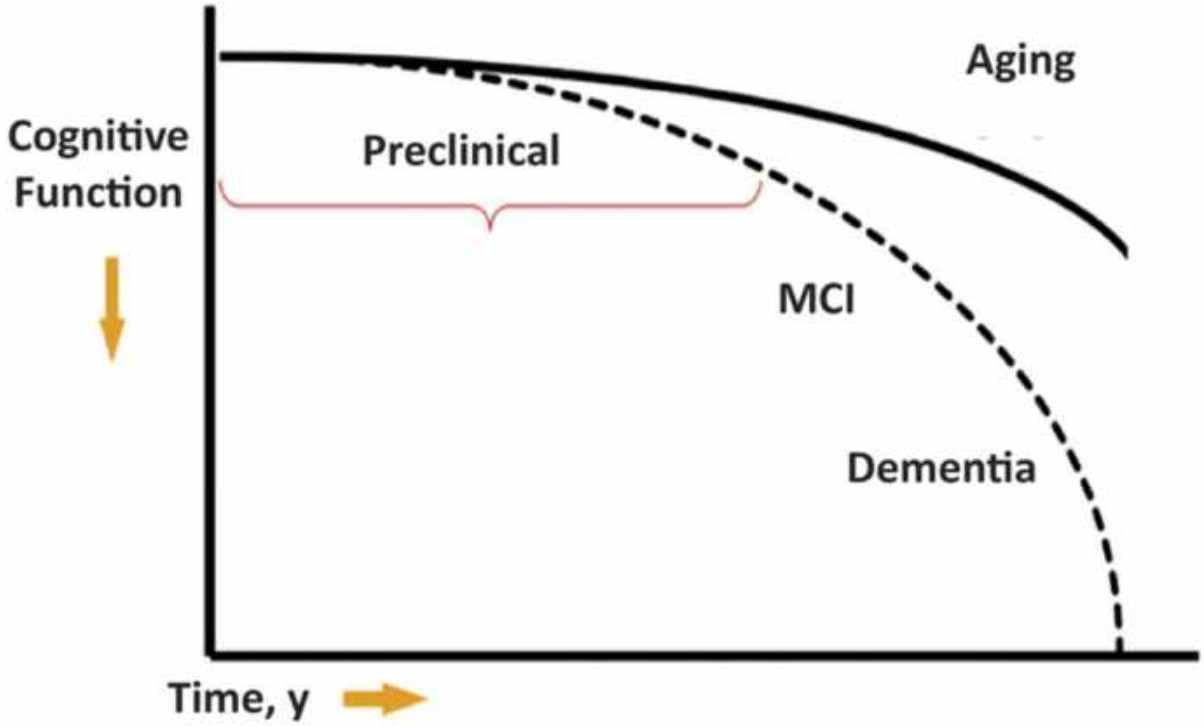
McKhann G, et al. Neurology 1984;34(7):939-944.

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

"The term "Alzheimer's disease" refers to an aggregate of neuropathologic changes and thus is defined *in vivo* by biomarkers and by postmortem examination, not by clinical symptoms."

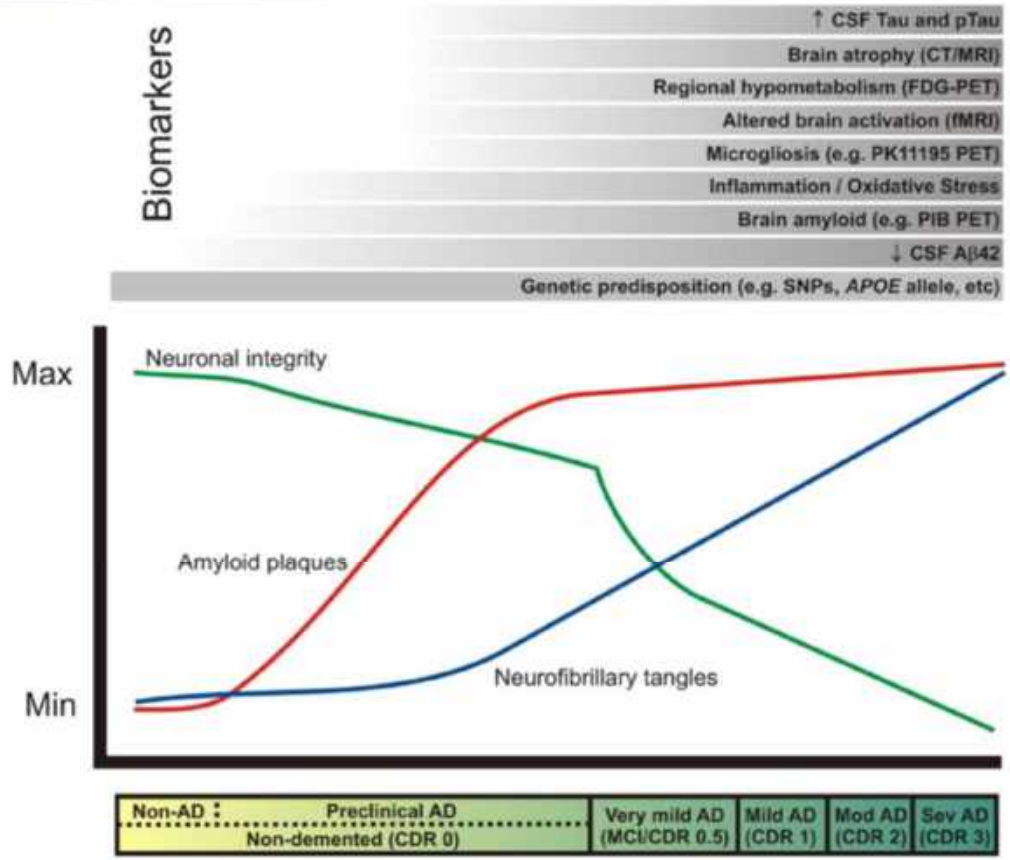
Jack, Clifford R., et al. Alzheimer's & Dementia 2018;14(4):535-562.

The Continuum of AD



Sperling RA, et al. *Alzheimers Dement*. 2011;7:280-292. With permission from Elsevier.

Hypothetical Time Course of AD Biomarker Changes in Relation to Pathological and Clinical Stages

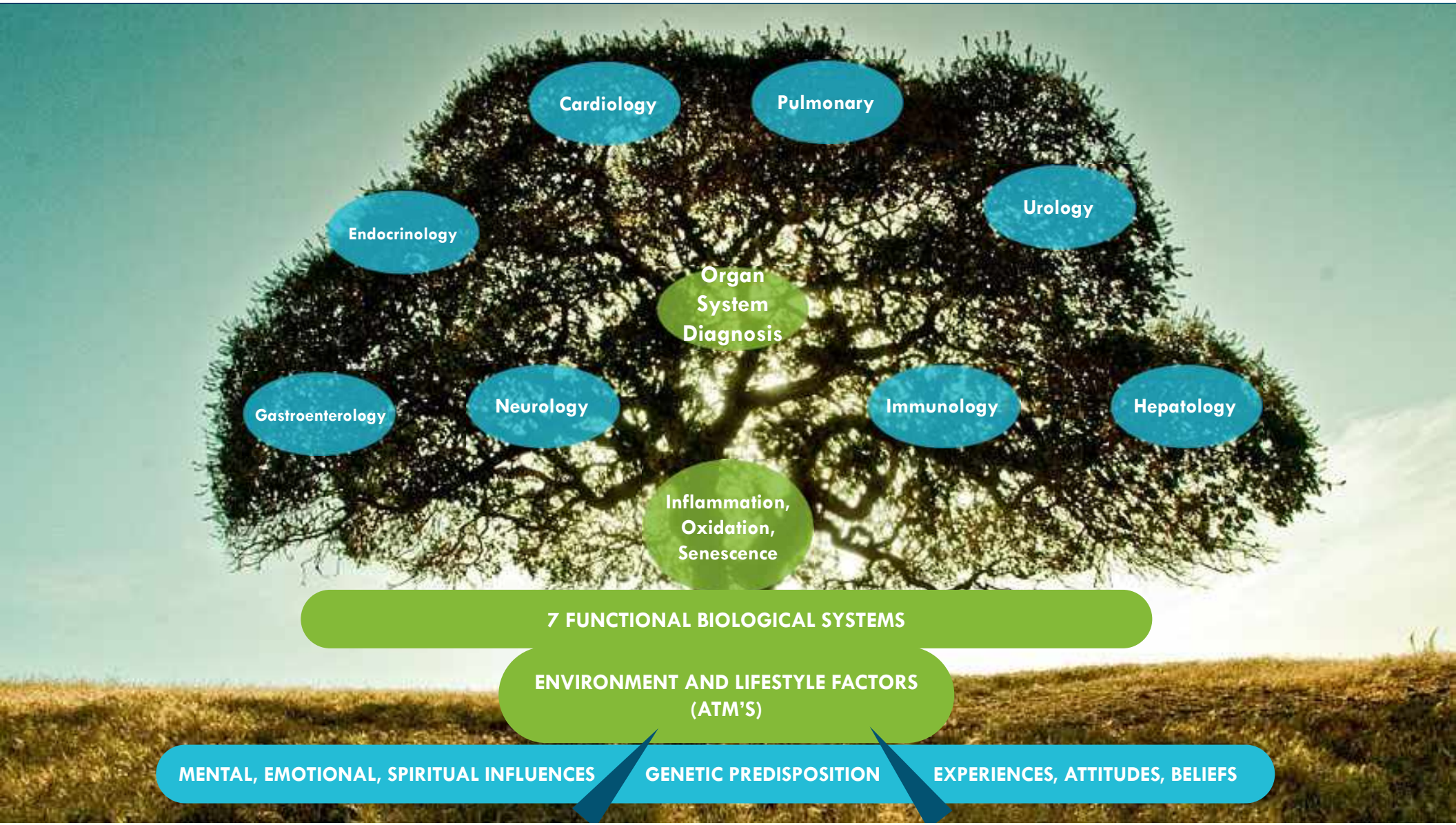


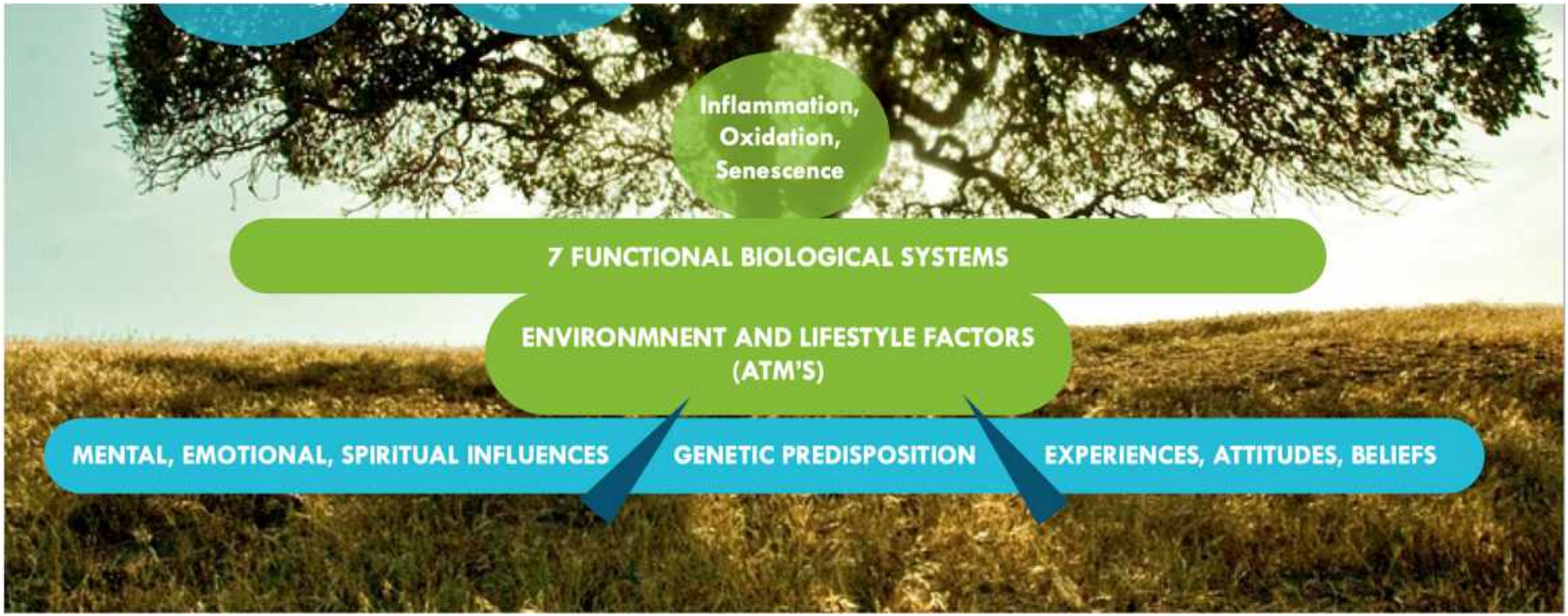
Reprinted by permission from Macmillan Publishers Ltd: Perrin RJ, et al. *Nature*. 2009;461:916-922.

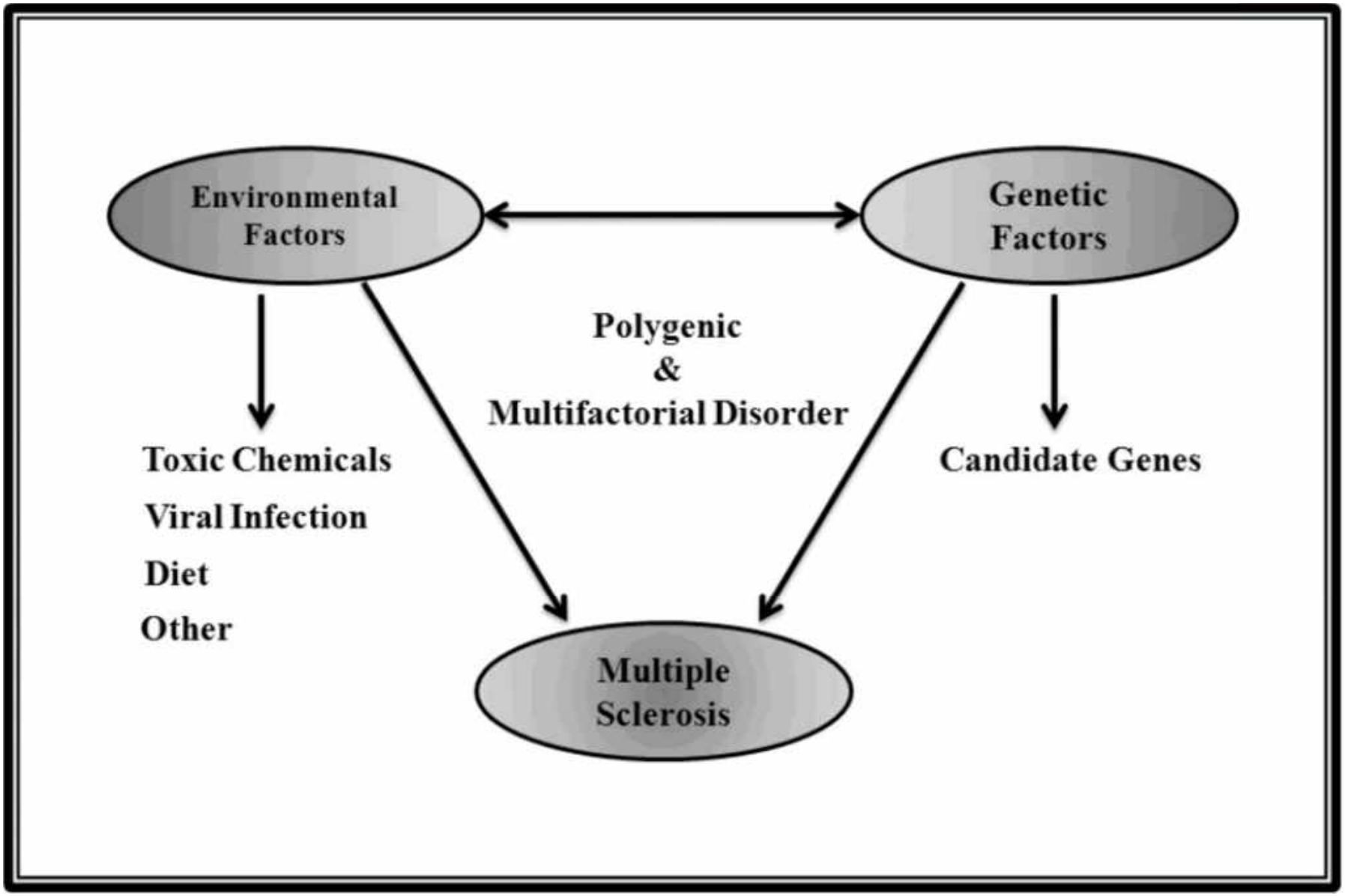
Neurology + Functional Medicine

This combination of neurology with functional medicine demands that you understand the disease, understand the diagnosis (including natural history of the disease and standards of care in managing the disorder), along with the ability to consider the unique factors that cause the disease in the individual patient.

The application of functional medicine is how we guide that patient through a program that ultimately accomplishes a change in the disease trajectory and a transformation of the individual affected by the disease (functional medicine).


Cardiology
Pulmonary
Urology
Endocrinology
Organ System Diagnosis
Gastroenterology
Neurology
Immunology
Hepatology
Inflammation, Oxidation, Senescence
7 FUNCTIONAL BIOLOGICAL SYSTEMS
ENVIRONMENT AND LIFESTYLE FACTORS (ATM'S)
MENTAL, EMOTIONAL, SPIRITUAL INFLUENCES
GENETIC PREDISPOSITION
EXPERIENCES, ATTITUDES, BELIEFS


Inflammation,
Oxidation,
Senescence
7 FUNCTIONAL BIOLOGICAL SYSTEMS
ENVIRONMNENT AND LIFESTYLE FACTORS
(ATM'S)
MENTAL, EMOTIONAL, SPIRITUAL INFLUENCES
GENETIC PREDISPOSITION
EXPERIENCES, ATTITUDES, BELIEFS


Environmental Factors
Genetic Factors
Polygenic & Multifactorial Disorder
Toxic Chemicals
Viral Infection
Diet
Other
Candidate Genes
Multiple Sclerosis

The lifetime risk for Parkinson's disease in the general population is 2%, [whereas] the risk of Parkinson's disease for the children of a patient is 4%, or twice the baseline risk for the general population.

HTTPS://WWW.NORTHSHORE.ORG/HEALTHY-YOU/PARKINSONS-DISEASE-GENETIC-RISK-FACTORS/

Chronic Inflammation

- Cardiovascular diseases
- Bone, Muscular & Skeletal diseases
- Neurological disorders
- Diabetic complications
- Metabolic Disorder complications
- Cancer

Inflammation

- Immune cells
- Antibodies
- Cytokines

7 FACTORS THAT CAUSE CHRONIC INFLAMMATION

- Poor sleep habits
- Eating inflammatory foods
- Sedentary lifestyle
- Chronic stress
- Social isolation
- Environmental toxins
- Chronic infections

Free Radicals

Unstable molecules with one or more unpaired electrons.

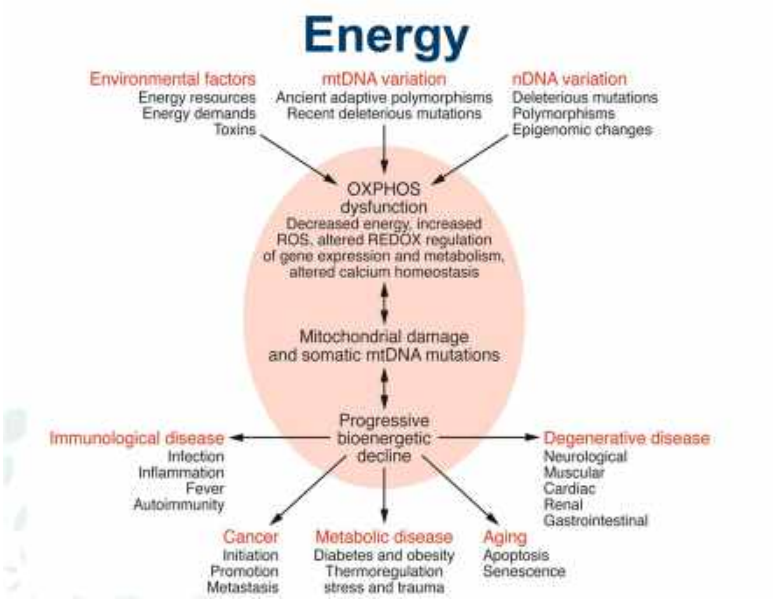
“Oxidation”

Cell signaling

Cell defense

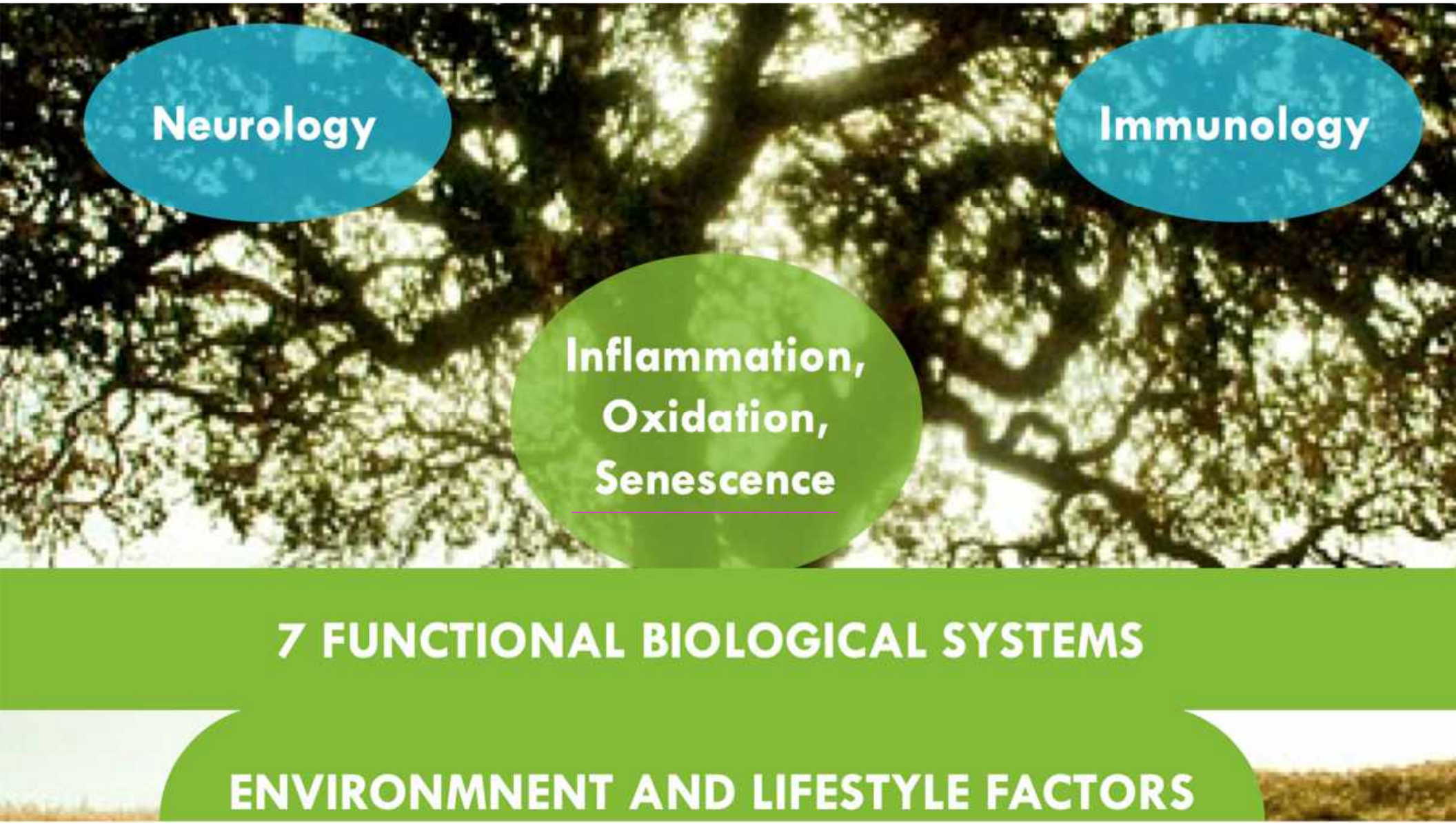
Tissue repair

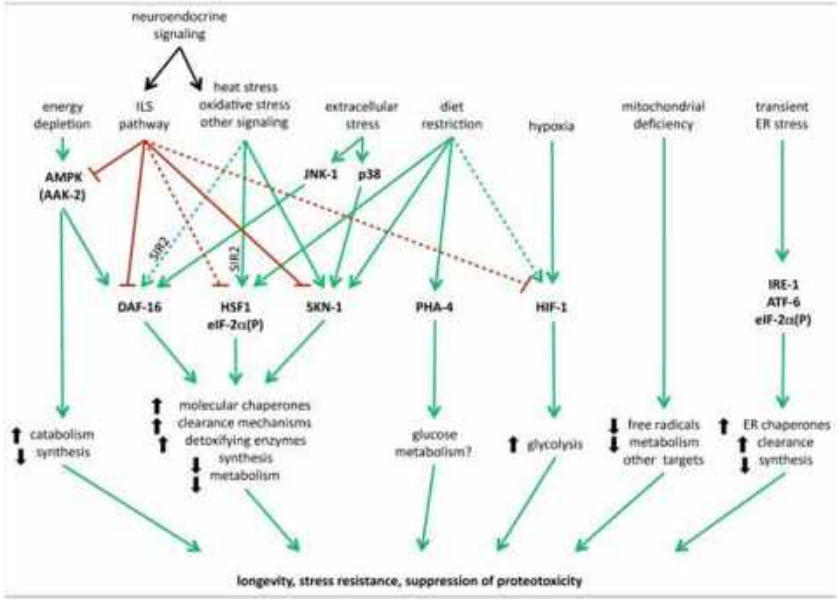
Regeneration



A Mitochondrial Bioenergetic Etiology of Disease

Wallace DC. J Clin Invest 2013; 123(4):1405-12.


Neurology
Immunology
Inflammation,
Oxidation,
Senescence
7 FUNCTIONAL BIOLOGICAL SYSTEMS
ENVIRONMNENT AND LIFESTYLE FACTORS



Factors detrimental to protein folding

Stressors	- pathophysiological states (fever, inflammation, infection, hypoxia, reperfusion, *etc.*) - hormonal imbalance (thyroid and growth hormone, IGF-I, *etc.*), emotional/psychological stress - nutrient intake and imbalance - amino acid analogues (including from food sources - azetidine, canavanine) - physical stress (temperature, irradiation, UV light, mechanical stress) - environmental stressors (heavy/transition metals, alcohols, arsenates, pesticides, mutagens, irritants, *etc.*) - aberrant physiological conditions (oxidation, osmolarity, pH) - trauma, injury - antibiotics and anti-inflammatory drugs (puromycin, tetracycline, NSAID, indomethacin) - alcohols, nicotine - anesthetics
"Activities of daily living"	- respiration, glycolysis - neurotransmission - bursts of protein synthesis (differentiation) - signaling
Mutations, Polymorphisms, Mistranslation	- protein conformation - subunit stoichiometry - protein stability
Damaged/ mutated chaperones	- protein misfolding

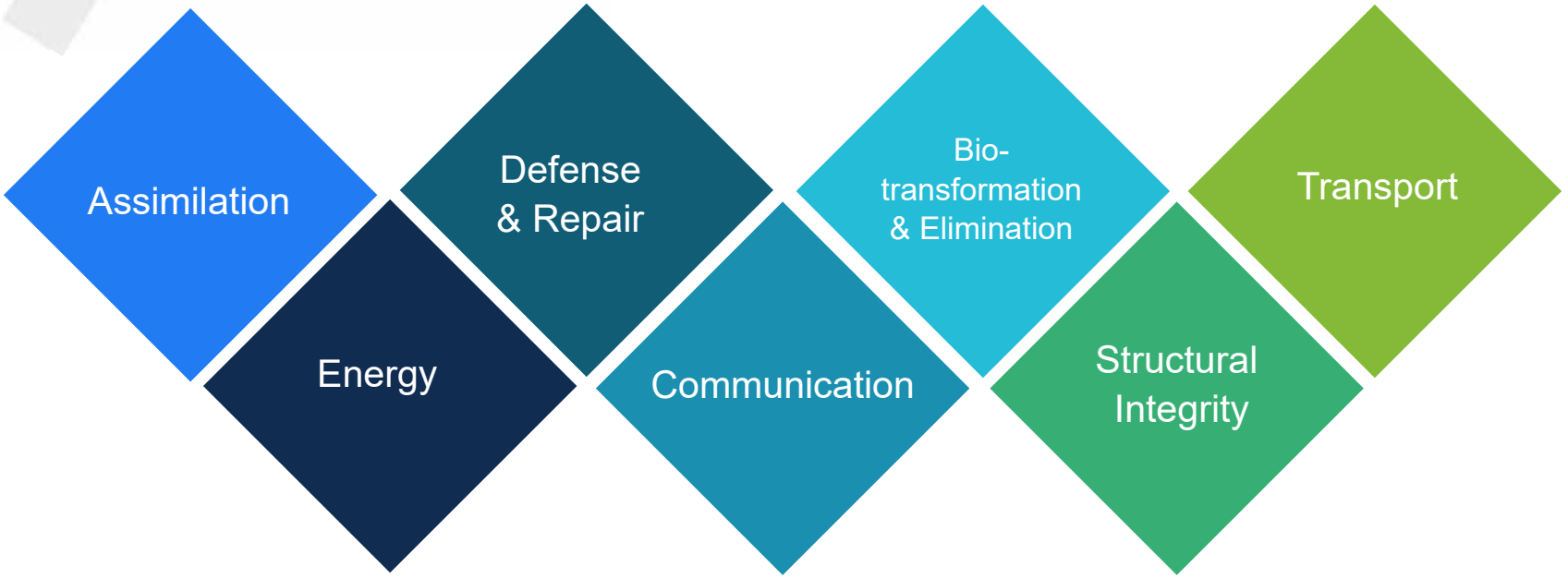
protein misfolding → protein conformation diseases of aging

chaperonopathies

Protein homeostasis in models of aging and age-related conformational disease

Kikis EA, Gidalevitz T, et al. *Adv Exp Med Biol*. 2010;694:138-159. doi:10.1007/978-1-4419-7002-2_11

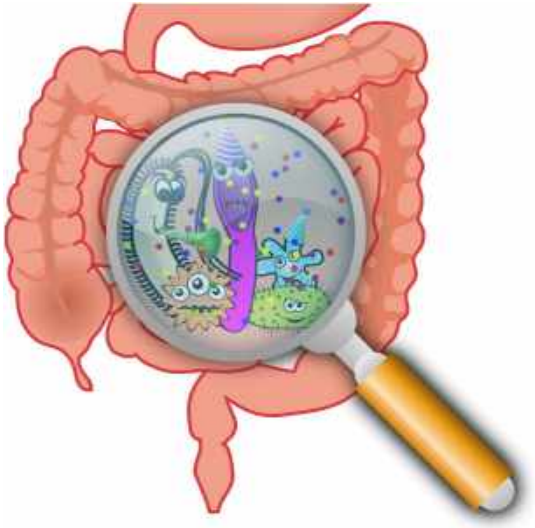
THE SEVEN FUNCTIONAL BIOLOGICAL SYSTEMS:



Assimilation

Assimilation

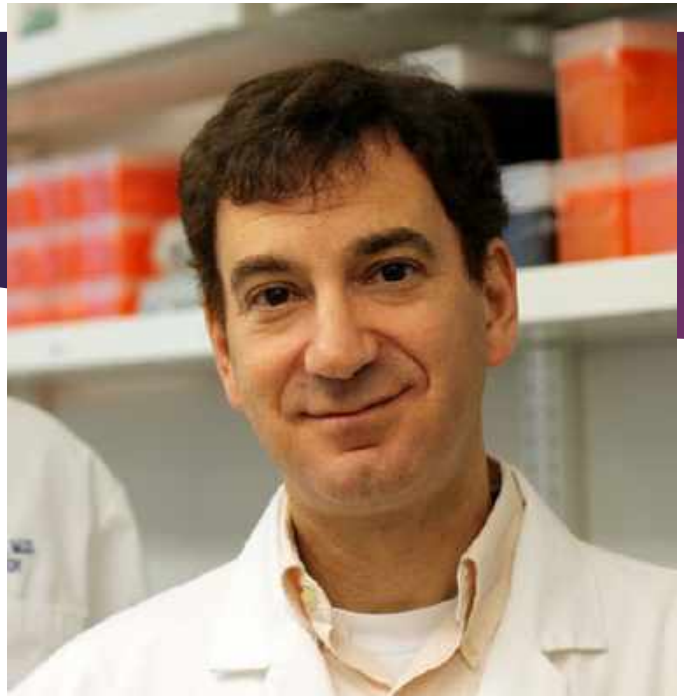
- Making food part of the cell
- Ingestion, digestion, absorption, and assimilation
- Requires adequate intake of nutrients, adequate breakdown of nutrients (masticatory, enzymatic and chemical such as HCl and bile), hormones, microbial balance and diversity ("microbiome"), gut barrier and immune function, transporter function.
- Inadequate nutrient intake, inadequate chewing, hypochlorhydria, intrinsic factor deficiency, pancreatic enzyme deficiency, SIBO/dysbiolsis.
- Alzheimer's: decreased Firmicutes, increased Bacteriodetes, and decreased Bifidobacterium compared to controls.*
- In Alzheimer's models there are a variety of negative effects of an altered microbiome as demonstrated in studies using germ-free mice, as well as a positive or beneficial effects following probiotic treatment.**

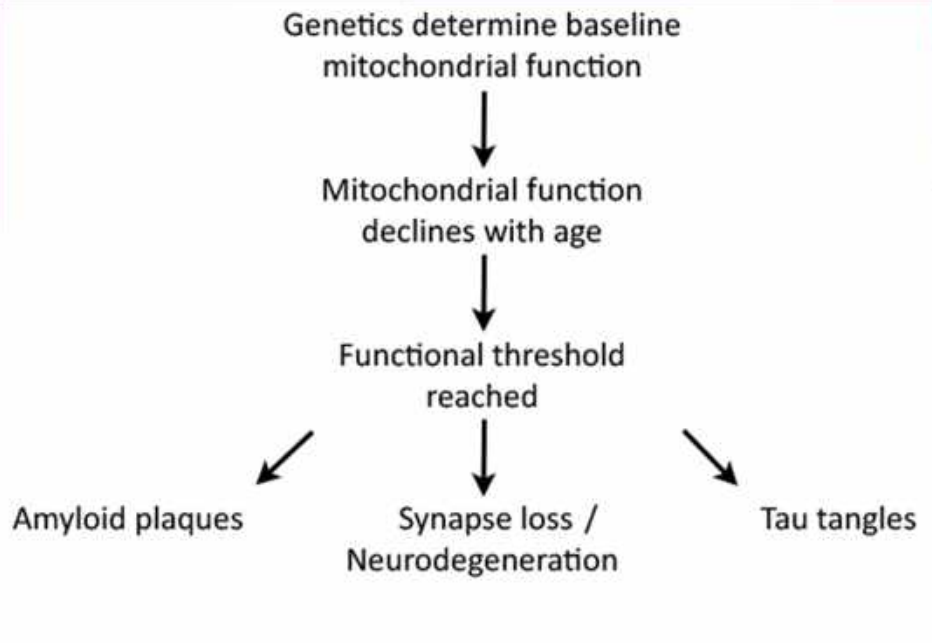


*Vogt NM, et al. Scientific Reports. October 2017;7:e13537.

**Jiang C, et al. Journal of Alzheimer's disease 2017;58(1):1-15.

Energy





The Mitochondrial "Cascade" Hypothesis

Russell Swerdlow, M.D., University of Kansas Alzheimer's Disease Center & Landon Center on Aging

Defense & Repair

Defense & Repair

- Represented by the coordinated efforts of white blood cells (humoral and cellular immunity), cytokines, bioactive molecules (omega 3 & 6 fatty acids),etc.
- Key role in protection and repair of damaged tissue
- Major presence in the gut
- Able to distinguish self from non-self
- Aberrations in Defense & Repair are associated with chronic infections and autoimmunity
  - Lipopolysaccharides (LPS) enter the blood through a compromised gut barrier and act as a major driver of inflammation.
  - Have been found to cause build up of amyloid beta-42 in Alzheimer's susceptible brains.*
- Alzheimer's-infection associations: HSV-1, Chlamydia pneumonia, Helicobacter pylori, and Borrelia burgdorferi.

*Lee JW, et al. Journal of Neuroinflammation 2008;5;37.

Anti-herpetic Medications and Reduced Risk of Dementia in Patients with Herpes Simplex Virus Infections—a Nationwide, Population-Based Cohort Study in Taiwan

Nian-Sheng Tzeng [1,2] · Chi-Hsiang Chung [3,4,5] · Fu-Huang Lin [4] · Chien-Ping Chiang [6] · Chin-Bin Yeh [1,7] · San-Yuan Huang [1,7] · Ru-Band Lu [1,8,9,10,11,12] · Hsin-An Chang [1,2] · Yu-Chen Kao [1,13] · Hui-Wen Yeh [1] · Wei-Shan Chiang [1,14] · Yu-Ching Chou [4] · Chang-Huei Tsao [5] · Yung-Fu Wu [5] · Wu-Chien Chien [4,5]

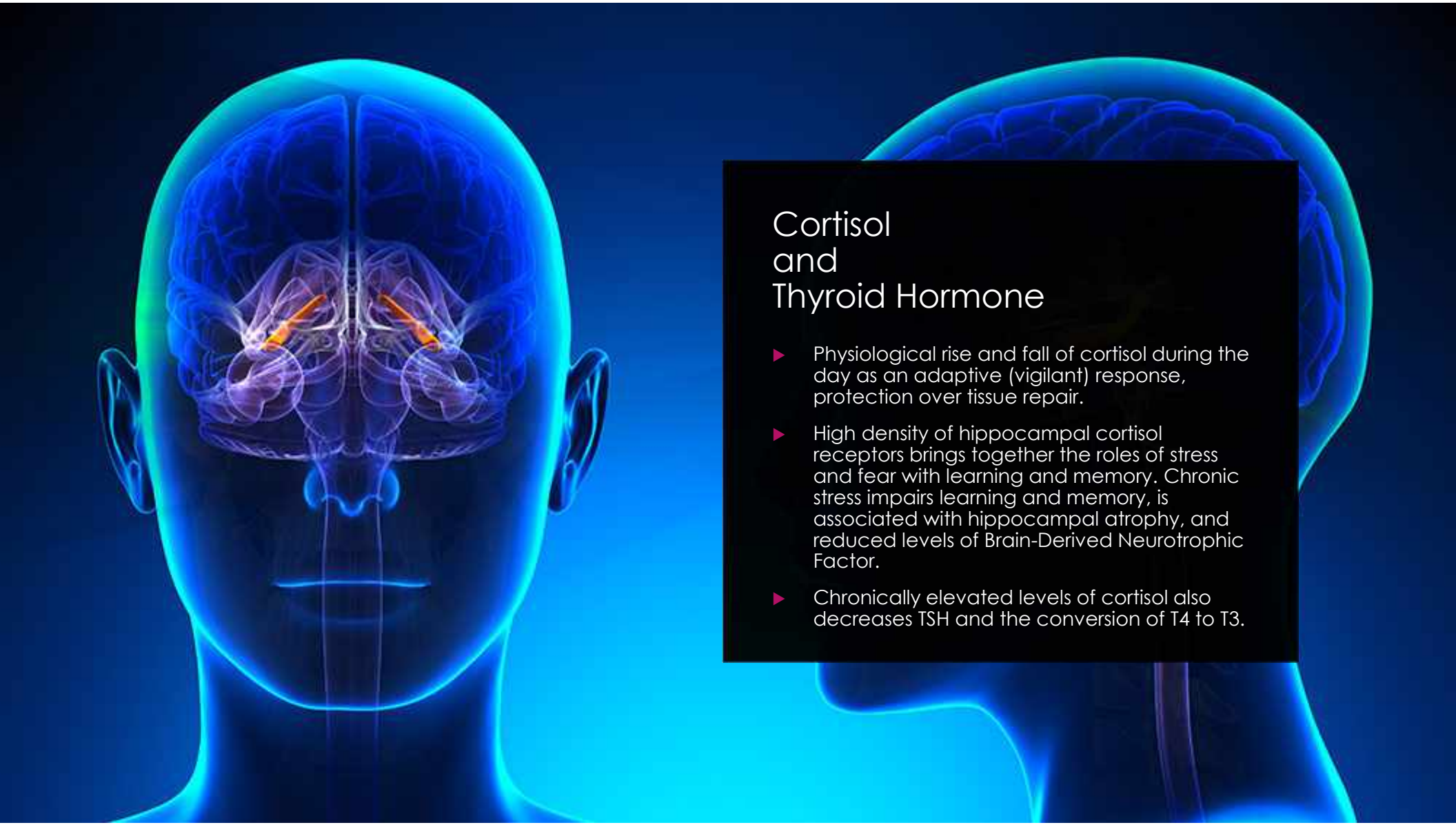
Neurotherapeutics 2018 https://doi.org/10.1007/s13311-018-0611-x

Abstract

This retrospective cohort study is to investigate the association between herpes simplex virus (HSV) infections and dementia, and the effects of anti-herpetic medications on the risk involved, using Taiwan's National Health Insurance Research Database (NHIRD). We enrolled a ed sex- and age-matc ariable Cox proportio his analysis revealed an adjusted hazard ratio of 2.564 (95% CI: 2.351-2.795, $P < 0.001$) for the development of dementia in the HSV-infected cohort relative to the non-HSV cohort. Thus, patients with HSV infections may have a 2.56-fold increased risk of developing dementia. A risk reduction of dementia development in patients affected by HSV infections was found upon treatment with anti-herpetic medications (adjusted HR = 0.092 [95% CI 0.079-0.108], $P < 0.001$). The usage of anti-herpetic medications in the treatment of HSV infections was associated with a decreased risk of dementia. These findings could be a signal to clinicians caring for patients with HSV infections. Further research is, therefore, necessary to explore the underlying mechanism(s) of these associations.

An adjusted hazard ratio of 2.564 for the development of dementia (Alzheimer's, Vascular, and All types) in the HSV-infected cohort.

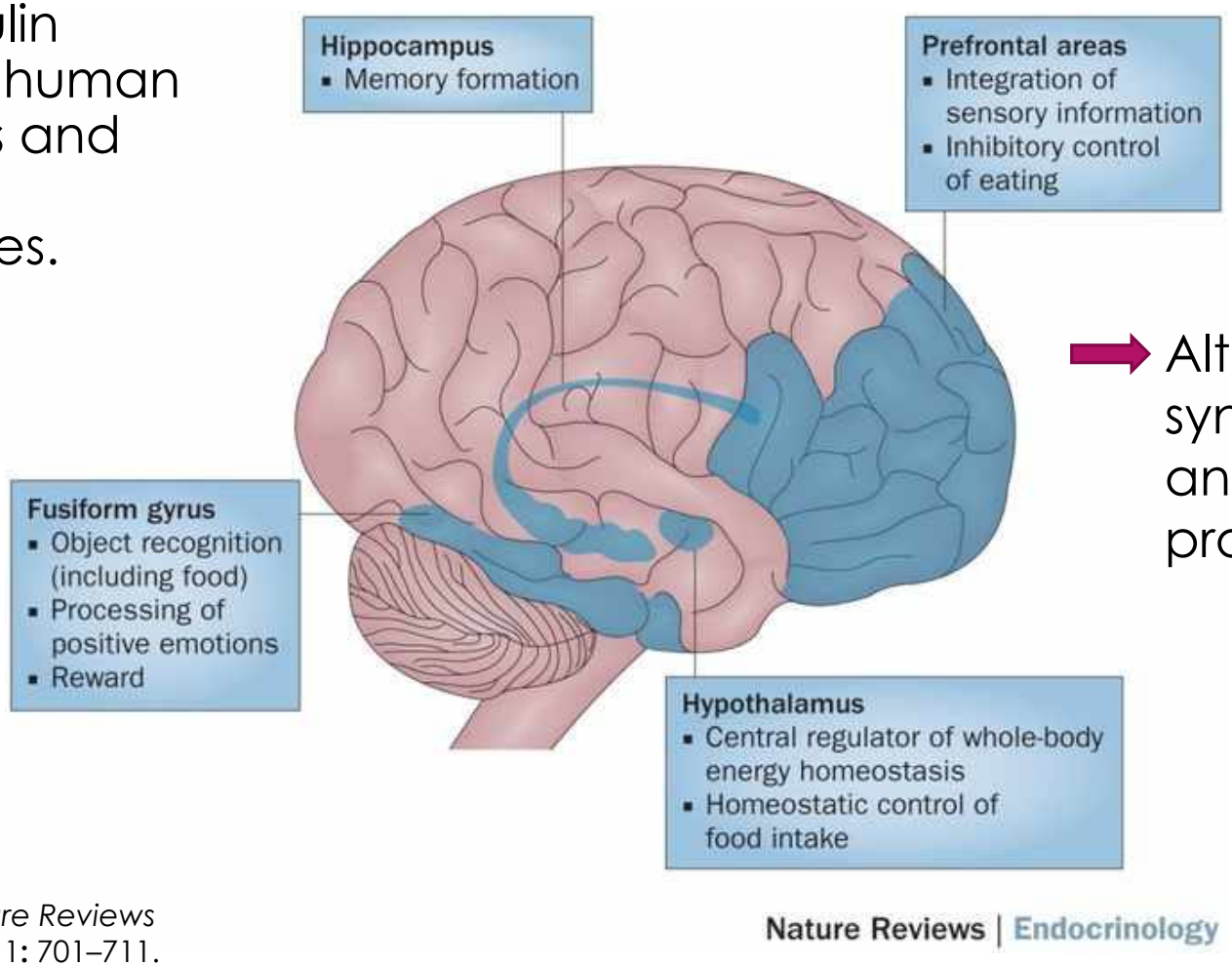
Communication



Cortisol and Thyroid Hormone

- Physiological rise and fall of cortisol during the day as an adaptive (vigilant) response, protection over tissue repair.
- High density of hippocampal cortisol receptors brings together the roles of stress and fear with learning and memory. Chronic stress impairs learning and memory, is associated with hippocampal atrophy, and reduced levels of Brain-Derived Neurotrophic Factor.
- Chronically elevated levels of cortisol also decreases TSH and the conversion of T4 to T3.

Impaired insulin action in the human brain: causes and metabolic consequences.



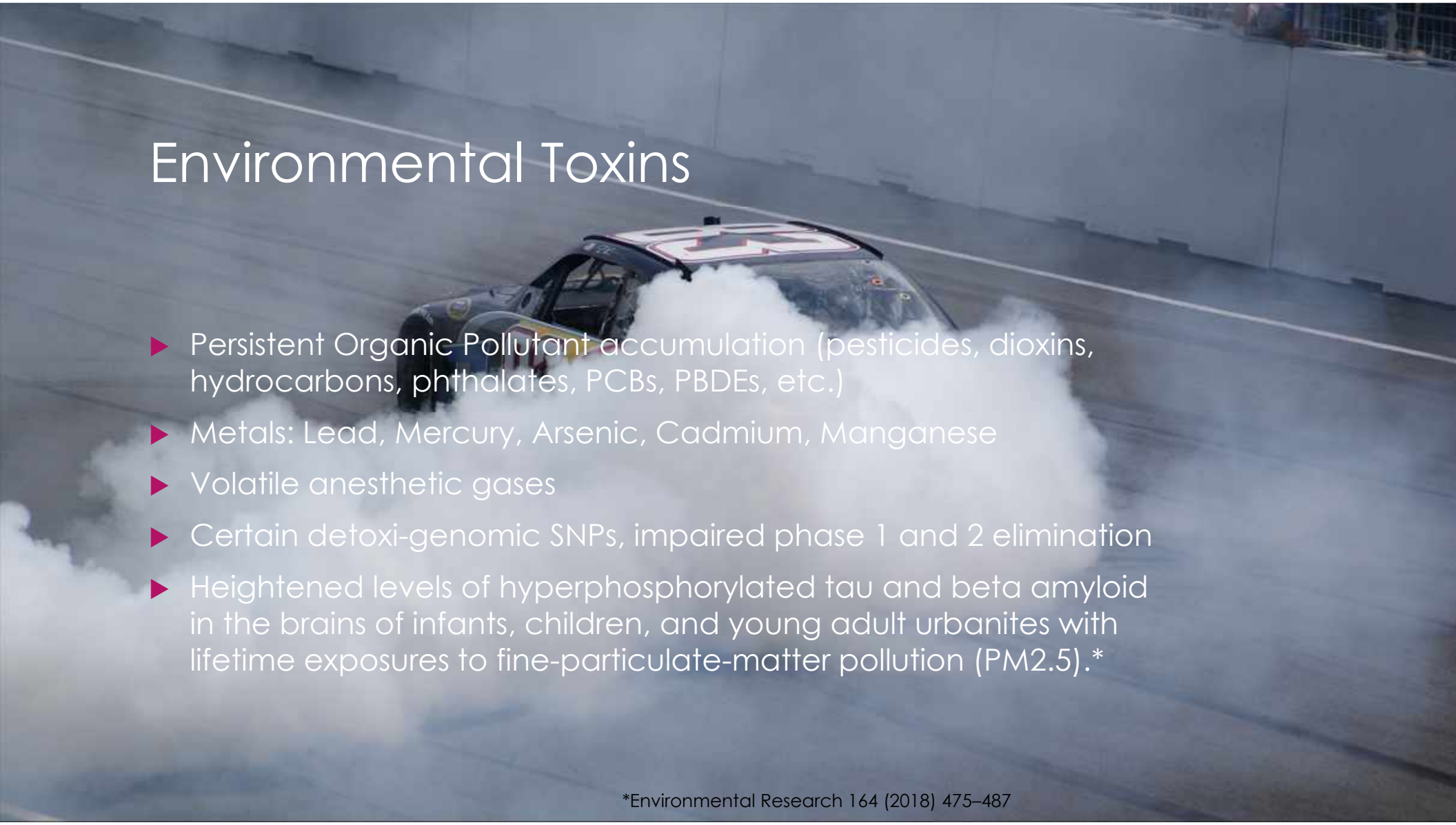
➡ Alterations in synaptic activity and cognitive processing.

*Martin, H., et al. Nature Reviews Endocrinology 2015;*11: 701–711.

Biotransformation & Elimination

The Glymphatic System

- Waste clearance system from the brain
- "Glymphatic" comes from the glial cells (support cells for neurons), including microglia, astrocytes, oligodendrocytes, and ependyma.
- Promotes elimination of soluble proteins and metabolites from the CNS and helps distribute non-waste compounds such as glucose, lipids, amino acids, and neurotransmitters.
- Primarily active during sleep.
- Impairment of the glymphatic system implicated in Alzheimer's disease (Nat Rev Neurol 2015;11(8):457-470.)
- Mouse model: Acute and chronic sleep deprivation stimulated astrocytic phagocytosis of presynaptic elements of large synapses and microglial activation. "Microglial priming may predispose the brain to further damage." (Bellesi M, et al. The Journal of Neuroscience 2017; 37(21):5263–5273)

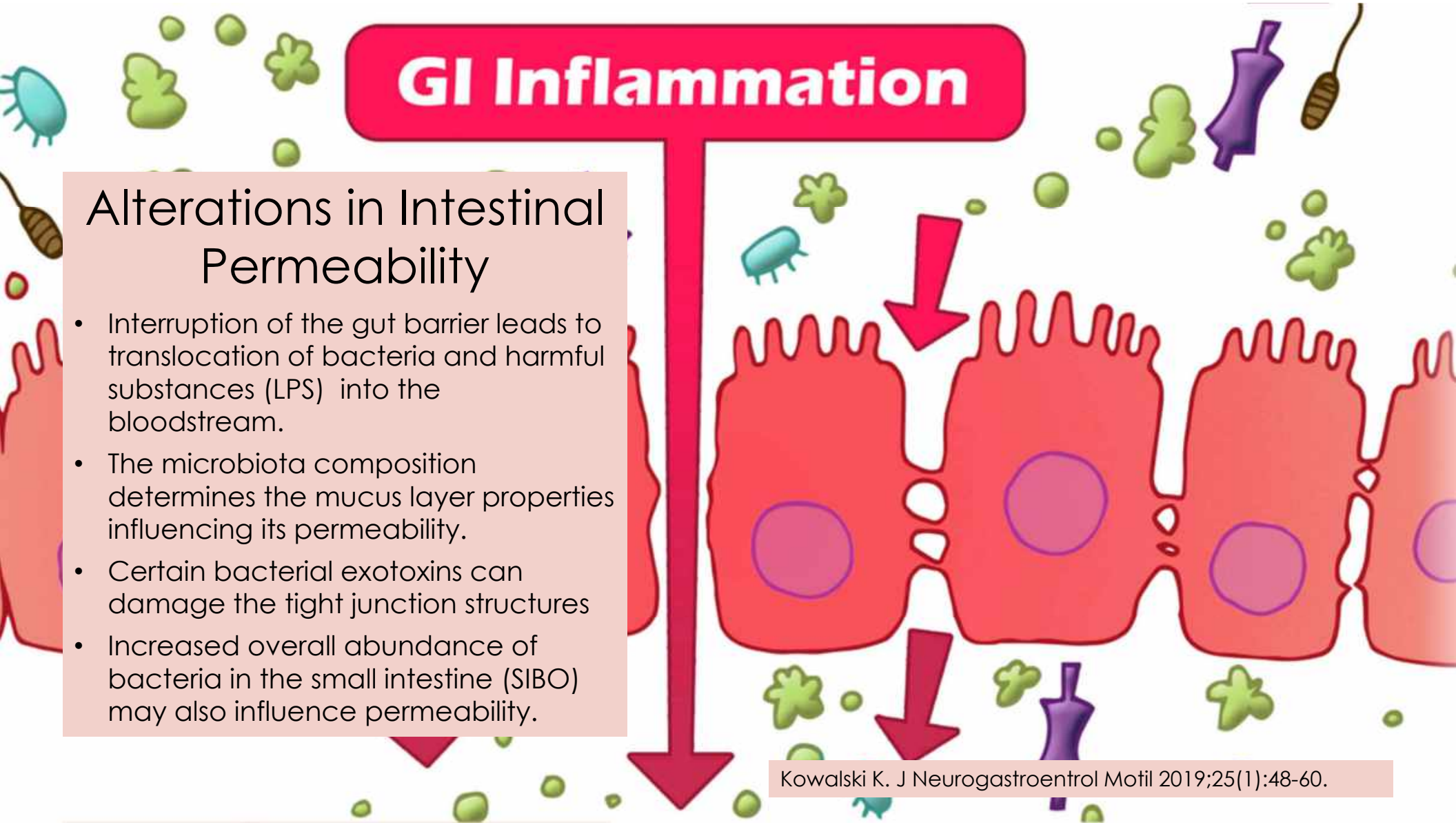


Environmental Toxins

- Persistent Organic Pollutant accumulation (pesticides, dioxins, hydrocarbons, phthalates, PCBs, PBDEs, etc.)
- Metals: Lead, Mercury, Arsenic, Cadmium, Manganese
- Volatile anesthetic gases
- Certain detoxi-genomic SNPs, impaired phase 1 and 2 elimination
- Heightened levels of hyperphosphorylated tau and beta amyloid in the brains of infants, children, and young adult urbanites with lifetime exposures to fine-particulate-matter pollution (PM2.5).*

*Environmental Research 164 (2018) 475–487

Structural Integrity



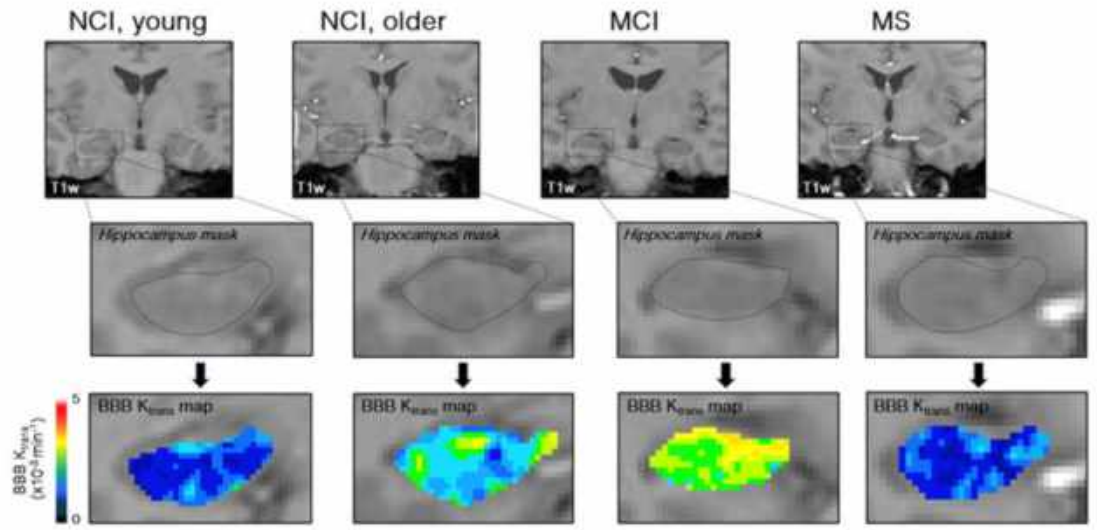
Alterations in Intestinal Permeability

- Interruption of the gut barrier leads to translocation of bacteria and harmful substances (LPS) into the bloodstream.
- The microbiota composition determines the mucus layer properties influencing its permeability.
- Certain bacterial exotoxins can damage the tight junction structures
- Increased overall abundance of bacteria in the small intestine (SIBO) may also influence permeability.

Kowalski K. J Neurogastroentrol Motil 2019;25(1):48-60.

Alterations in Blood-Brain Barrier Permeability

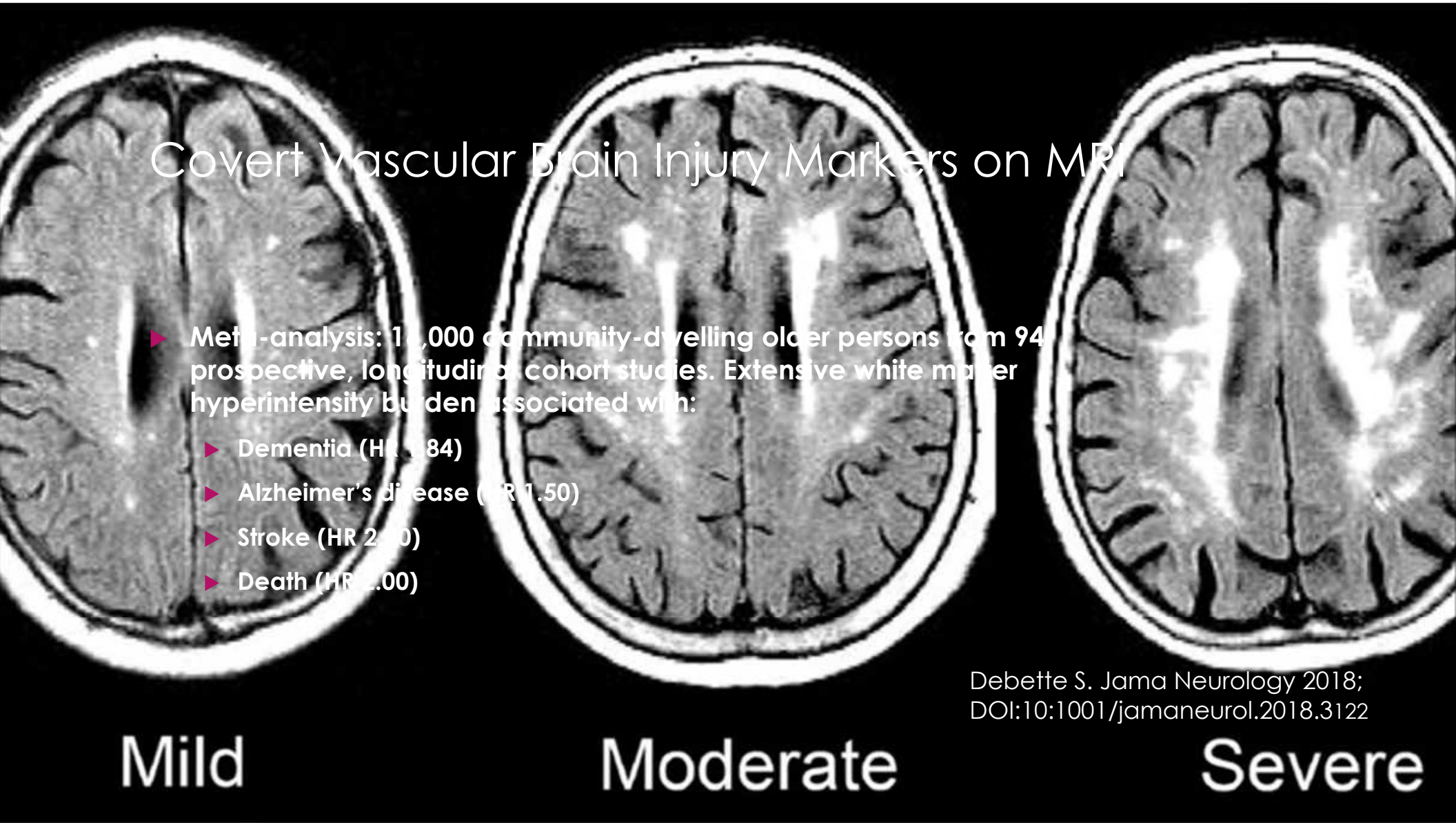
- Blood-brain barrier breakdown during normal aging occurs initially in the hippocampus but is more pronounced in MCI compared to age-matched neurologically intact controls.
- Leads to tissue accumulation of potentially neurotoxic blood-derived products that normally do not enter the brain but can damage neurons when vessels become leaky.
- Vascular leakage over time associated with excessive microglial stimulation and increased neuroinflammatory signaling, leading to increased amyloid beta 42 production, tau phosphorylation, hippocampal and cortical atrophy.



Montagne A. *Neuron*. 2015;85(2): 296–302.

Transport

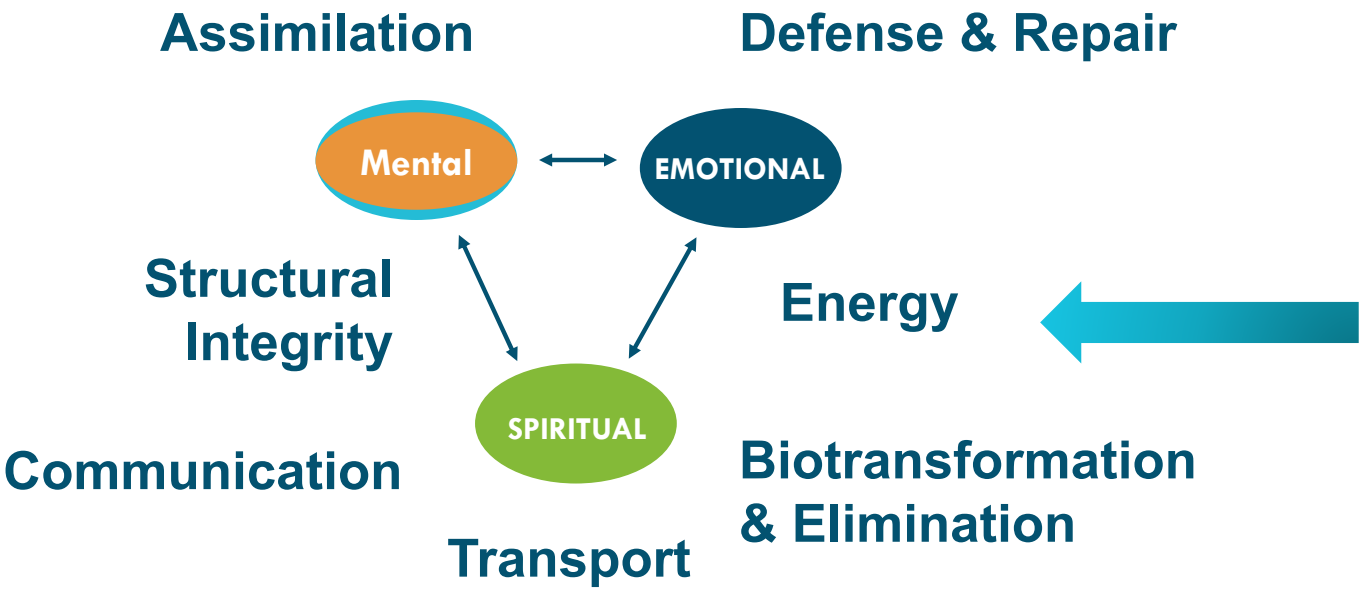
Covert Vascular Brain Injury Markers on MRI



- Meta-analysis: 1[illegible],000 community-dwelling older persons from 94 prospective, longitudinal cohort studies. Extensive white matter hyperintensity burden associated with:
  - Dementia (HR [illegible].84)
  - Alzheimer's disease (HR 1.50)
  - Stroke (HR 2.[illegible]0)
  - Death (HR [illegible].00)

Debette S. Jama Neurology 2018;
DOI:10:1001/jamaneurol.2018.3122

Lifestyle is Medicine



1. Sleep
2. Movement
3. Nutrition
4. Stress
5. Relationships

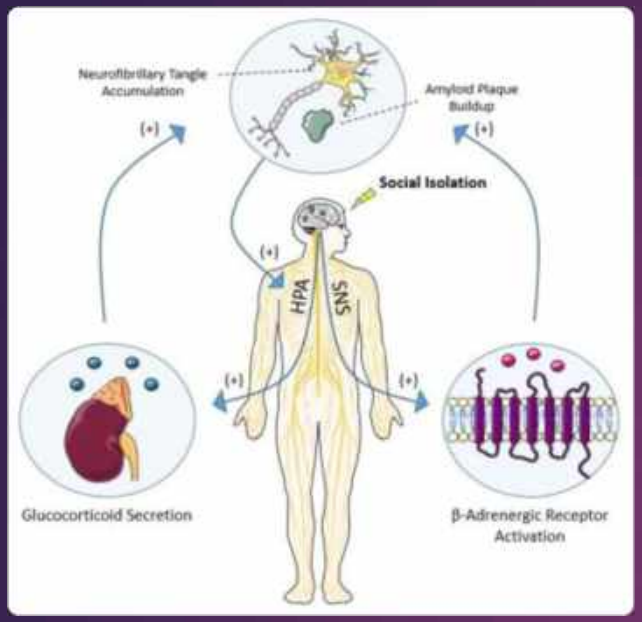
THE VALUE OF SLEEP

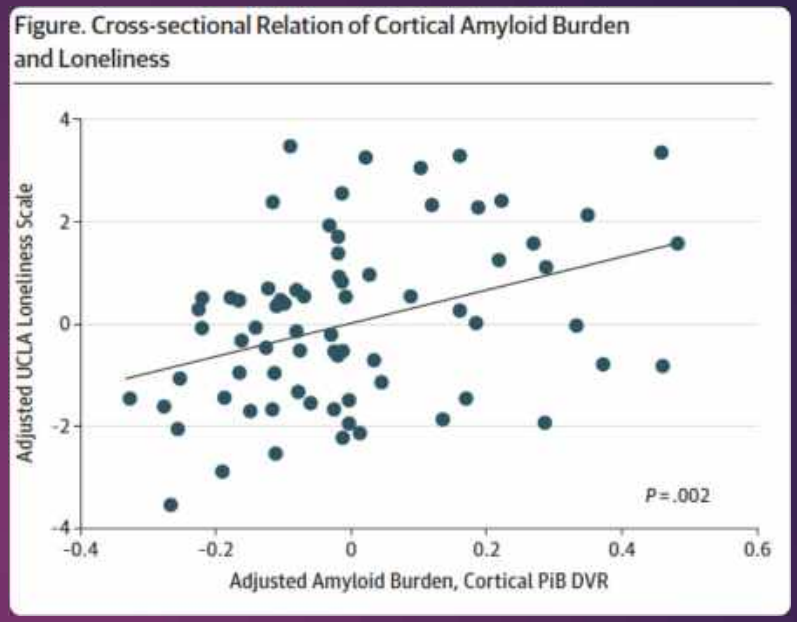
THE BENEFITS OF MOVEMENT

THE POWER OF FOOD

STRESS RESILIENCE

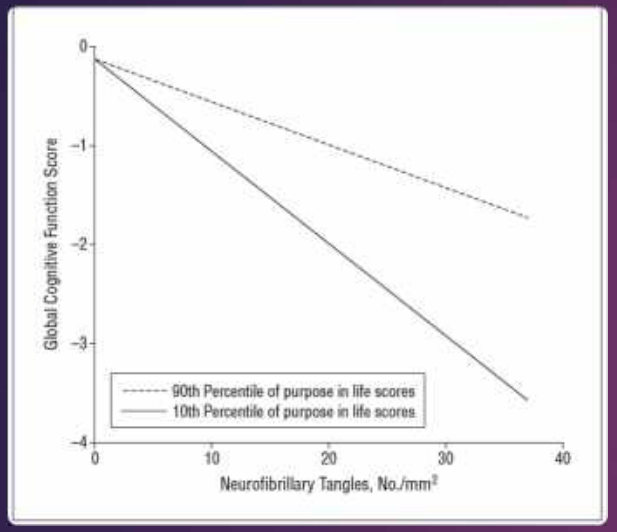
STRONG RELATIONSHIPS

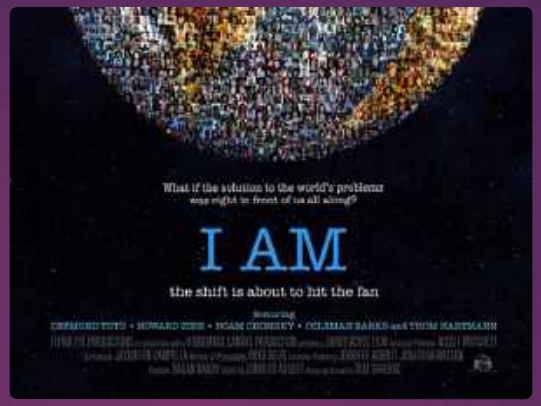


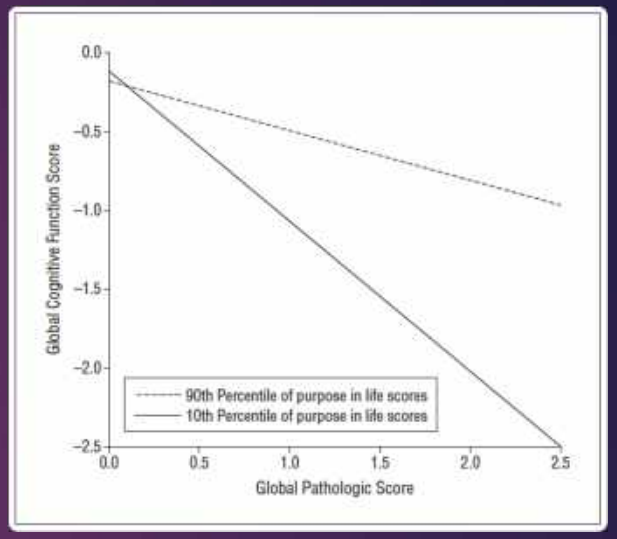


Association of Higher Cortical Amyloid Burden with Loneliness in Cognitively Normal Adults

Donovan NJ, et al. JAMA Psychiatry 2016;73(12):1230-37.
Friedler MS, et al. Acta Neuropathol 2015;129(4):493-509.





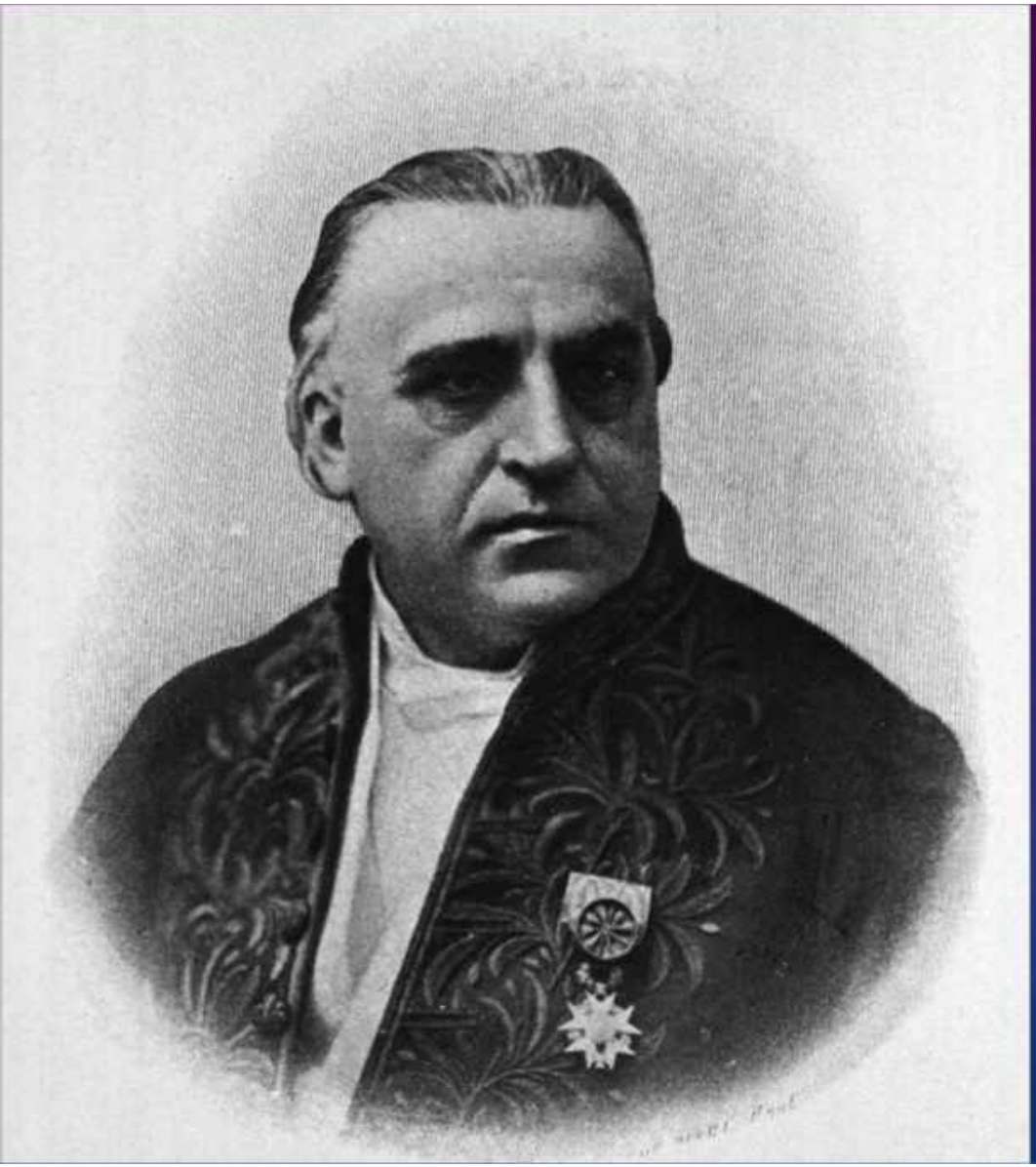


Effect of Purpose in Life on the Relation Between Alzheimer Disease Pathologic Changes on Cognitive Function in Advanced Age: 246 Older Persons from the Rush Memory and Aging Project

Boyle PA, et al. Arch Gen Psychiatry 2012; 69(5):499-506.

Roy Walford, ALS, and The Dream of Longevity

LESSONS LEARNED FROM THE FIELD AND THE LAB

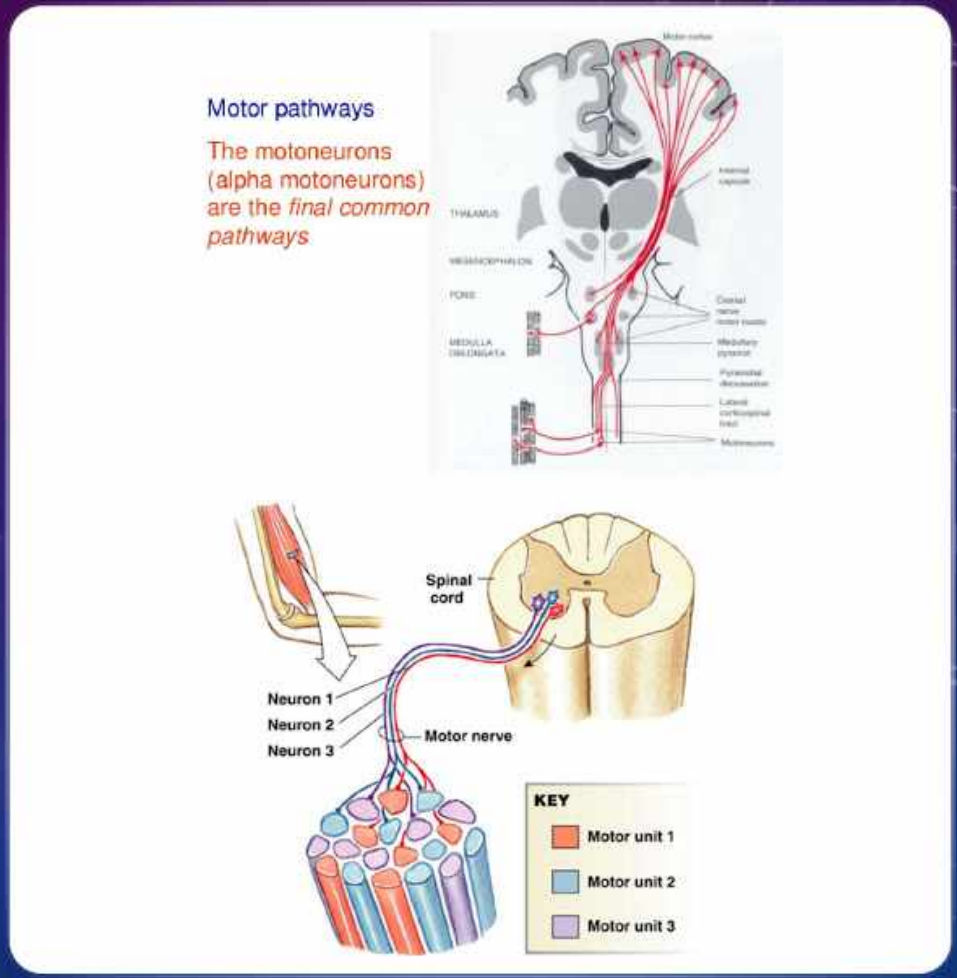


JEAN-MARTIN CHARCOT: THE FATHER OF NEUROLOGY

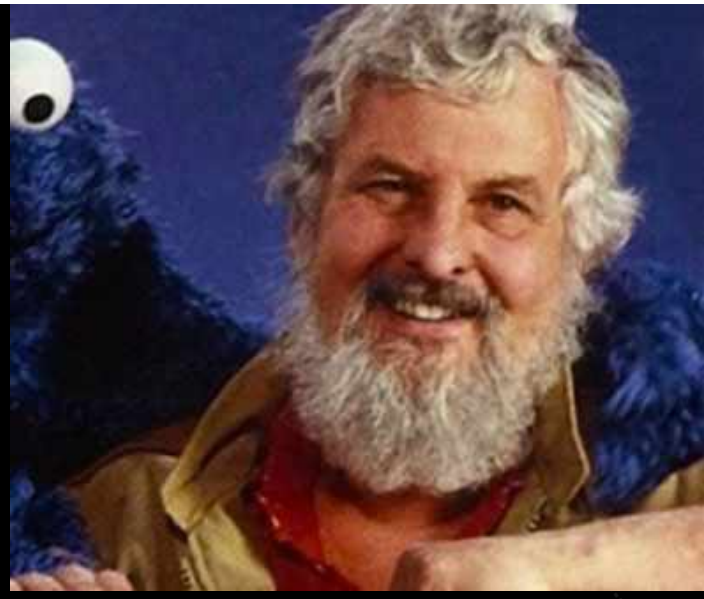
- B. 1825 (Paris, France), D. 1893 (Nièvre, France)
- Described and diagnosed the first cases of ALS as a specific neurological disease
- Found that lesions within the lateral column of the spinal cord resulted in chronic progressive paralysis and contractures (no atrophy of muscles), while lesions of the anterior horn of the spinal cord resulted in paralysis without contractures (with atrophy of muscles)
- Findings supported his hypothesis at the time that the motor component of the spinal cord consisted of a two-part system and that the location of the lesion results in a varying clinical presentation.
- 1874 - “Amyotrophic Lateral Sclerosis” (synonymous with “Charcot’s disease”)

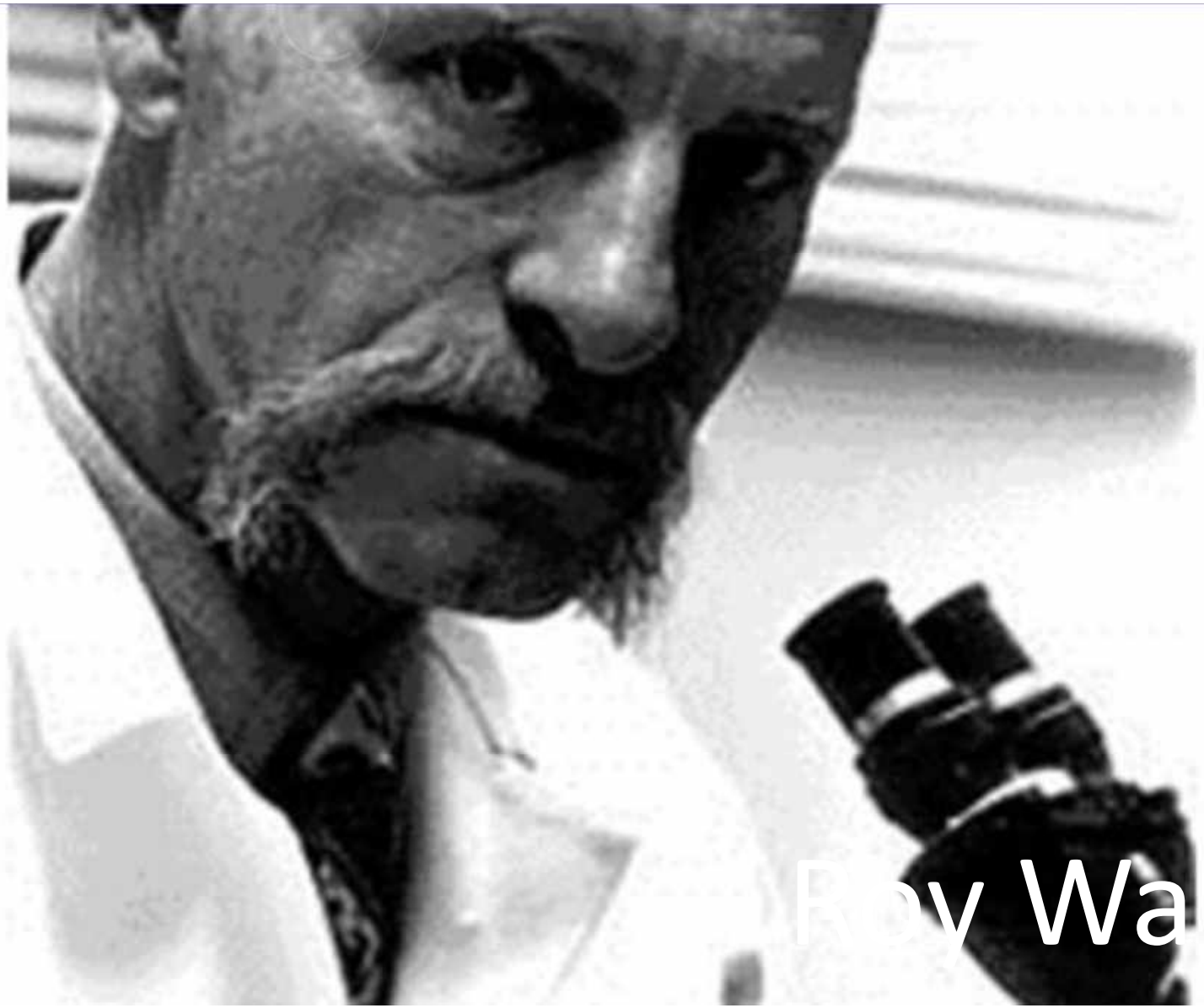
WHAT IS ALS?

- **Amyotrophic Lateral Sclerosis**
- **A-myo-trophic** comes from the Greek, “A” means no, “Myo” refers to muscle, and “Trophic” means nourishment.
- **Lateral** identifies the area of the spinal cord where portions of the nerve cells that signal and control muscles, called Motor Neurons, are located.
- Sclerosis refers to scarring or hardening in the region of the lateral spinal cord.









Ray Wa

ST. PETERSBURG TIMES, SUNDAY, NOVEMBER 23, 1947

Boys Quit Reno While Ahead $8,000

RENO, Nev. — (UP) — The Rover boys of the roulette wheel, two ex-Chicago university students who plunged their $300 savings on a "system," decided yesterday not to buck Lady Luck further and get out while they still had $8,000 in winnings.

Albert Hibbs, a mathematics master from Chillicothe, O., and Roy Walford of San Diego, announced they were heeding the advice of Columnist Billy Rose and would leave Reno "while they still have carfare home."

For amateurs, they didn't do bad in two weeks in this gamblingest city. They parlayed their $300 to $8,300 at two casinos before their "progressive pay-lay" betting system bowed to the inevitable laws of chance and started losing.

They won $6,000 in 40 hours at the Palace club playing the number 21 after logging the wheel to find out what number it favored the most. Then they went to Harold's club and jotted down numbers there until they thought they "had it." Sixty hours play over three days brought them a net of $2,300.

Since they each worked the wheels half the time, they each took out a net of $4,000. They thus were paid $80 an hour for their "work" at the wheel.

Veteran gamblers grunted and ... proclaimed it "pure luck" in... insisting "there's no such thing as a roulette system."

The pair of ex-students, both serious looking, had announced they wanted to make enough to buy a small yacht to explore the Caribbean and Central American areas studying tropical diseases.

Walford said they would go to San Diego to spend Thanksgiving with his family.

After that — maybe Las Vegas or Reno again. They pondered the offer of Harold Smith, Harold's club manager, who offered to let them "take a million bucks off me" if they could with their system.

Walford sported a shaved head and Salvador Dali moustache, and had a deep love for the arts and counterculture.

He rode a motorcycle and once broke his leg while attempting a wheelie on Santa Monica Boulevard.

After graduating medical school, in 1947, Walford and his friend Al Hibbs discovered a pattern of reappearing numbers on roulette wheels. With a $200 loan from Walford's aunt, they won $8300 in Reno, then $30K more in Las Vegas, bought a yacht, and sailed the Caribbean for the next 18 months.

Walford was into theater and wrote a farcical adaptation of Christopher Marlowe's "Dr. Faustus."

He once arranged the entertainment for a pathology convention in Los Angeles, including The Manhattan Transfer, a fashion show, a punk band, and cabaret singers. The show ended with Walford on stage in an automaton pose for 10–15 minutes. The pathologists didn't know what hit them.

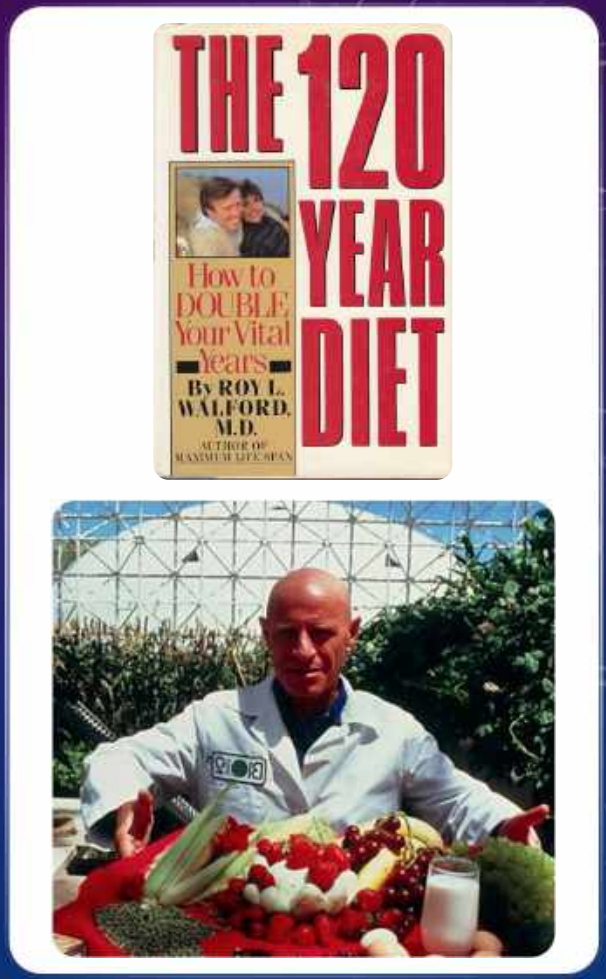
He also supplemented his income by performing a balancing act in which he was held aloft by a weight-lifter.

He traveled with the Living Theater, writing reviews for the Los Angeles Free Press. He wrote about the underground drug scene in Amsterdam before it became well known.

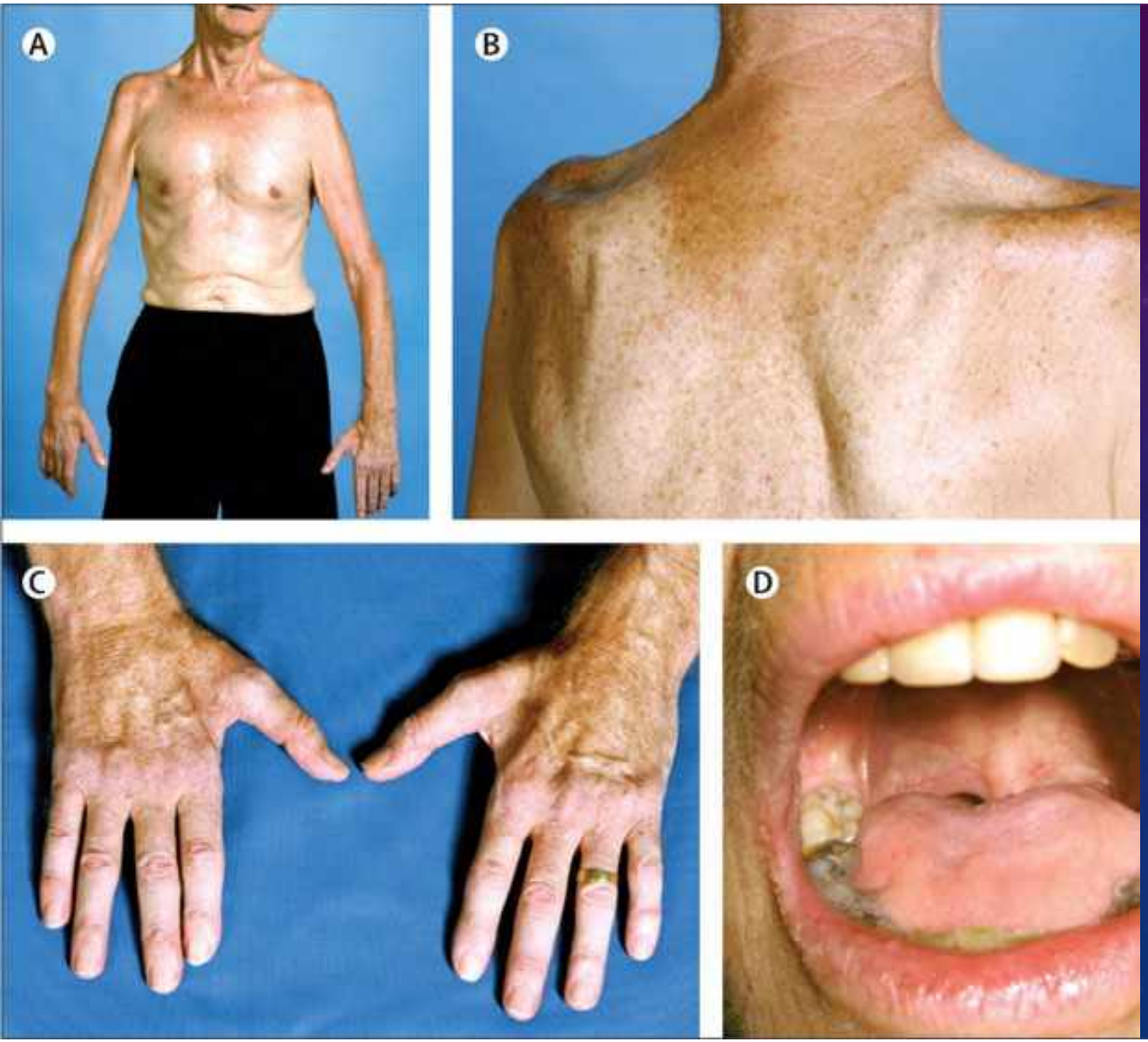
He walked across India in a loincloth measuring the rectal temperatures of holy men, and once traversed the African continent on foot.

ROY WALFORD

- Published more than 340 scientific papers, authored 7 books, served on numerous committees, and won many prestigious awards.
- Most famous book: *The 120 Year Diet*, based on the principle that a nutrient-dense diet consisting of about a third calories less than typically recommended by the USDA had the potential to extend life expectancy by several decades.
- His approach became known as the CRON diet (Calorie Restriction with Optimal Nutrition).




Roy Walford,
Born June 29, 1924
Died April 27, 2004
of ALS



GENERAL CLINICAL PRESENTATION

- Insidious loss of function or gradual, slowly progressive weakness in 1 or more regions of the body without changes in the ability to feel.
- Bladder and bowel function, and eye movement, are preserved
- 70 to 80% of patients begin with limb involvement while 20 to 25% of patients present with slurred speech and difficulty swallowing (bulbar symptoms). The frequency of upper limb versus lower limb involvement is about equal.
- Although ALS is 20% more common in men than women, women have a greater frequency of bulbar onset than men.

A TYPICAL ONSET PRESENTATION

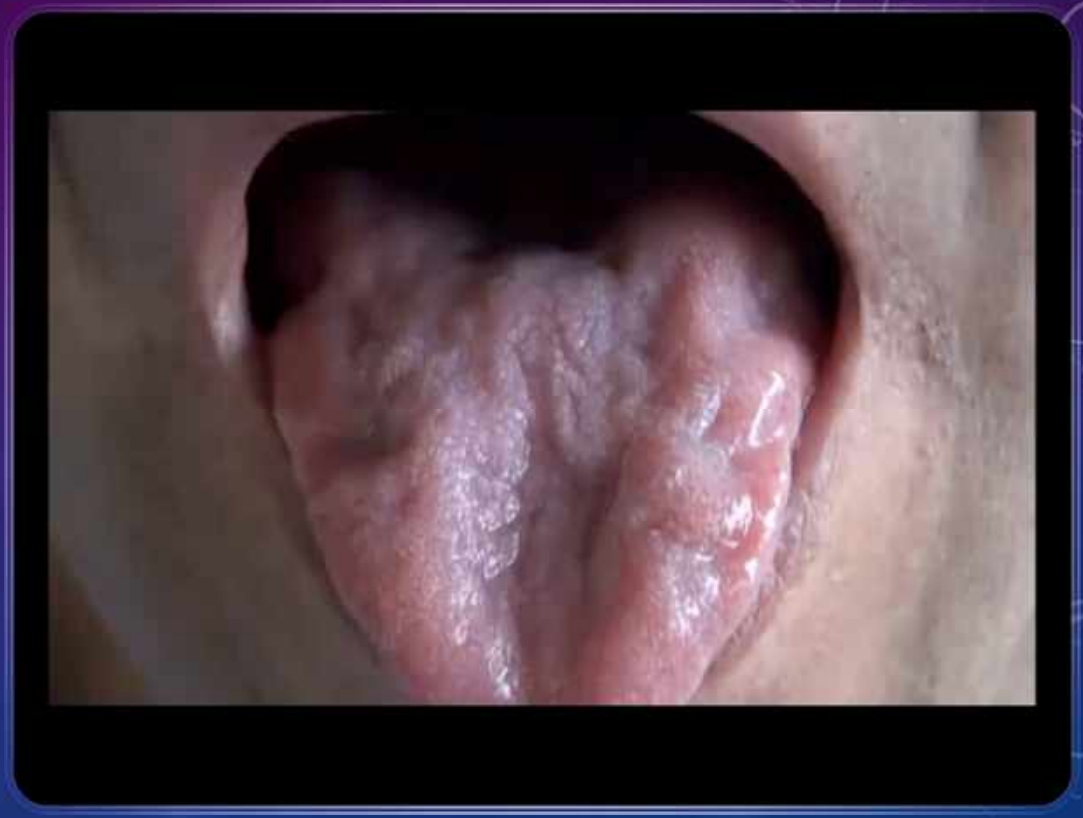
Lower limb onset: tripping, stumbling, or awkwardness when running. Foot drop or slapping gait.

Upper limb onset: reduced finger dexterity, cramping, stiffness, and weakness of intrinsic hand muscles, a history of difficulty buttoning clothes, picking up small objects, or turning a key, wrist drop.

Bulbar onset: slurring or slowness of speech, hyper-nasal, strained or a strangled voice quality, swallowing difficulty, drooling, aspiration, or choking.

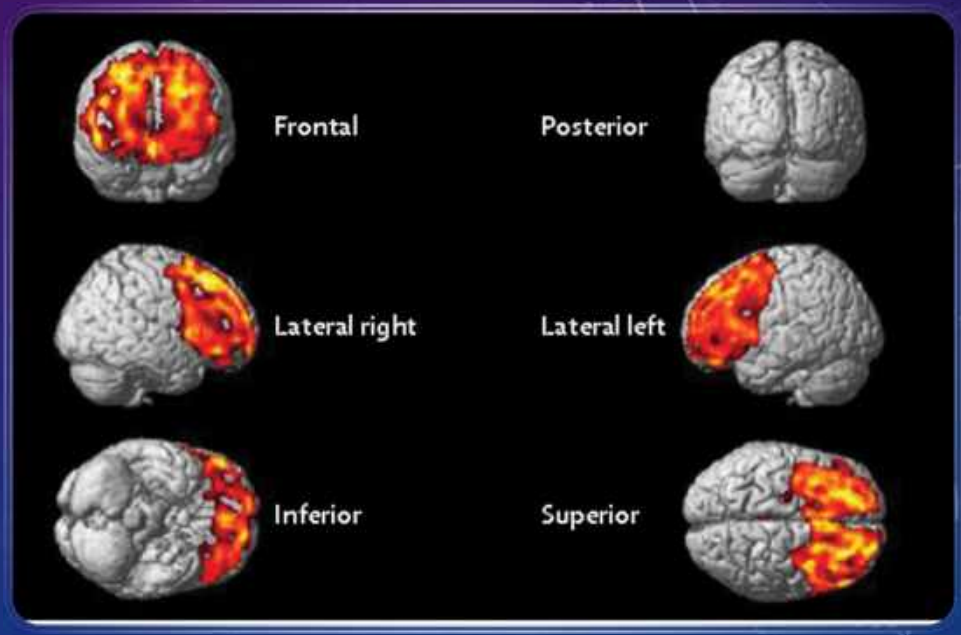
THE NEUROLOGICAL EXAMINATION

- Weakness, difficulty with speech and swallowing, unsteadiness, truncal weakness causing difficulty maintaining an erect posture, spastic tone, brisk or depressed deep tendon reflexes (maybe a mixture of both), muscle atrophy and fasciculations.
- It's very important to look for tongue fasciculations.



NEURO-BEHAVIORAL ASPECTS OF ALS

- About 29% of typical ALS patients will experience emotional difficulties characterized by involuntary crying or laughing (Pseudo-Bulbar Affect).
- Up to 20% of ALS patients demonstrate dementia.
- 30% of ALS patients develop cognitive impairment without dementia.
- Up to half of ALS patients are cognitively normal.
- **Executive function impairment** (most common) can reflect disturbances in reasoning, judgment, sequencing, ordering, inferring, regulating emotions, planning, retrieval inefficiency, and a person's ability to be self-aware.



^{18}F-fluorodeoxyglucose PET analysis show three-dimensional rendering of the brain cortical surface in which patients with ALS with cognitive symptoms show hypometabolism compared with healthy controls. Uptake is substantially impaired in the frontal and anterior cingulate cortex. Chiò, A., et al. *The Lancet Neurology* 13 (2014): 1228-1240.

PATHOGENESIS OF AMYOTROPHIC LATERAL SCLEROSIS

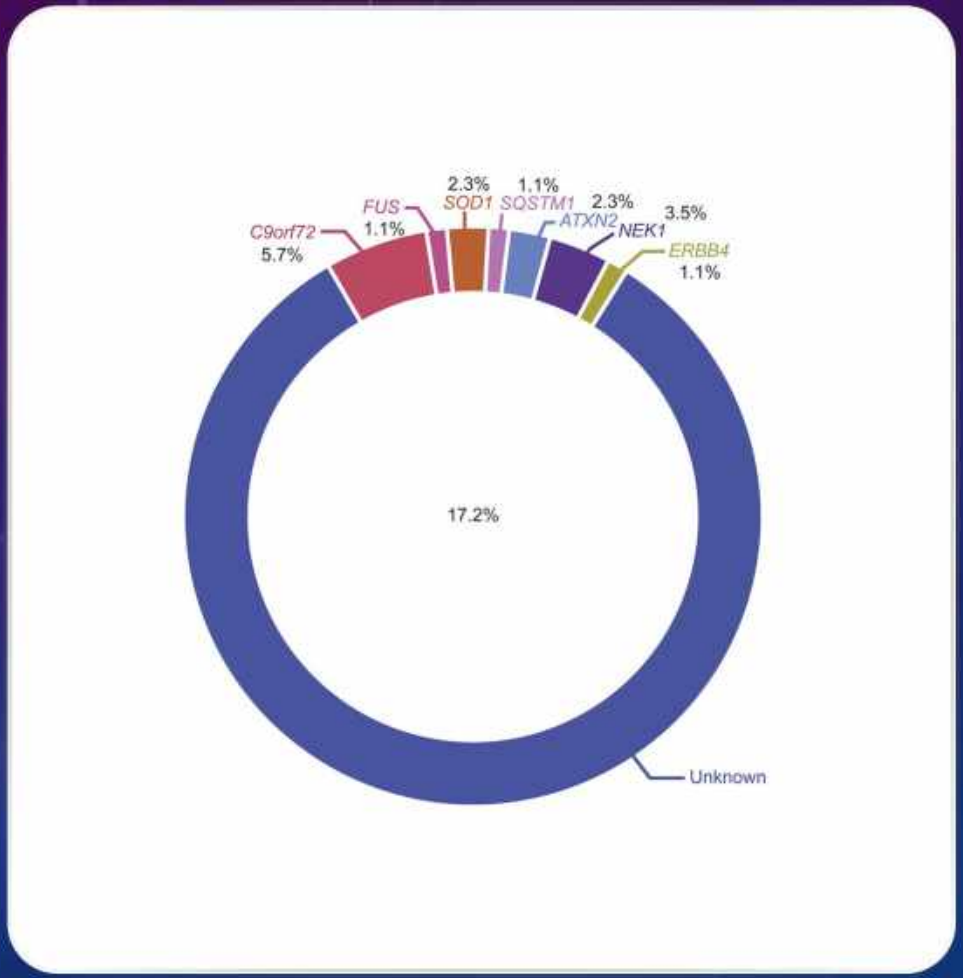
"It remains probable that ALS is the final end point of a number of different pathogenic pathways, converging on the clinical presentation. Different individuals may have contributions from different pathways…."

Morgan S and Orrell RW. British Medical Bulletin 2016;119(1):87-98.

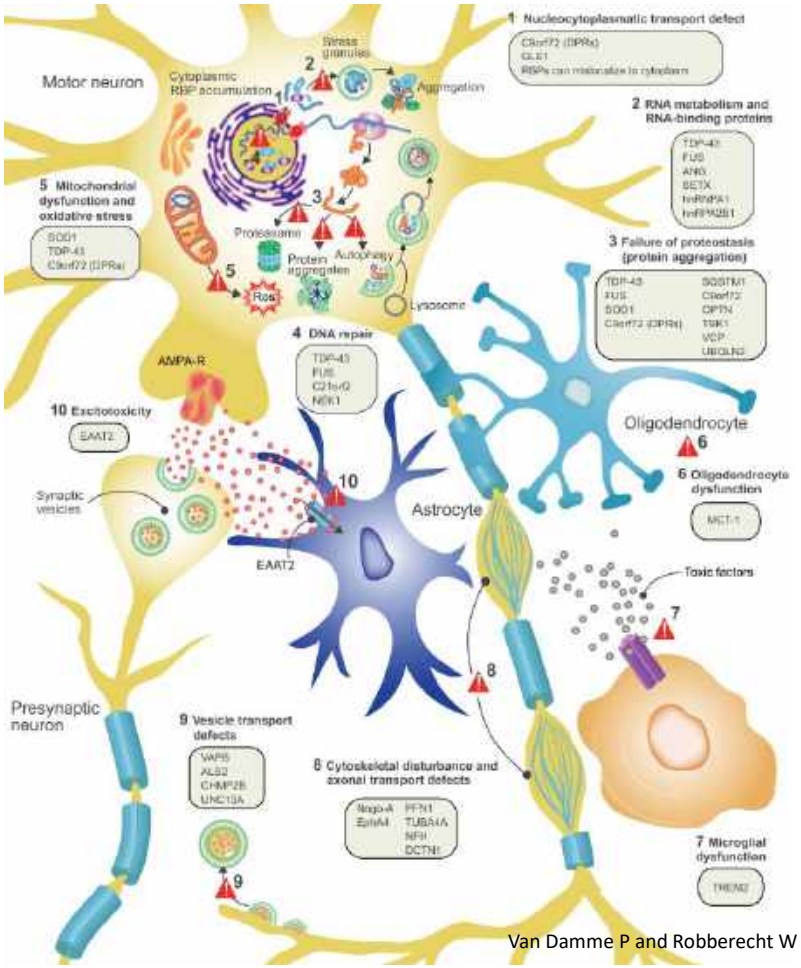
COMMON GENETIC CONTRIBUTIONS TO sALS

GENETIC VARIATIONS: C9ORF72, SOD1, TARDBP/TDP-43, AND FUS MOST COMMON (OVER 25 GENES IDENTIFIED).

Gibson SB, et al. *Neurology*. 2017;89(3):226–233.



1. Nucleocytoplasmic transport defect
2. RNA metabolism and RNA-binding proteins
3. Failure of proteostasis (protein aggregation)
4. DNA repair abnormalities
5. Mitochondrial dysfunction and oxidative stress
6. Oligodendrocyte dysfunction
7. Microglial dysfunction
8. Cytoskeletal disturbances and axonal transport defects
9. Vesicle transport defects
10. Excitotoxicity



Van Damme P and Robberecht W et al. Dis Model Mech. 2017; 10(5): 537–549.

Mechanisms Implicated in ALS

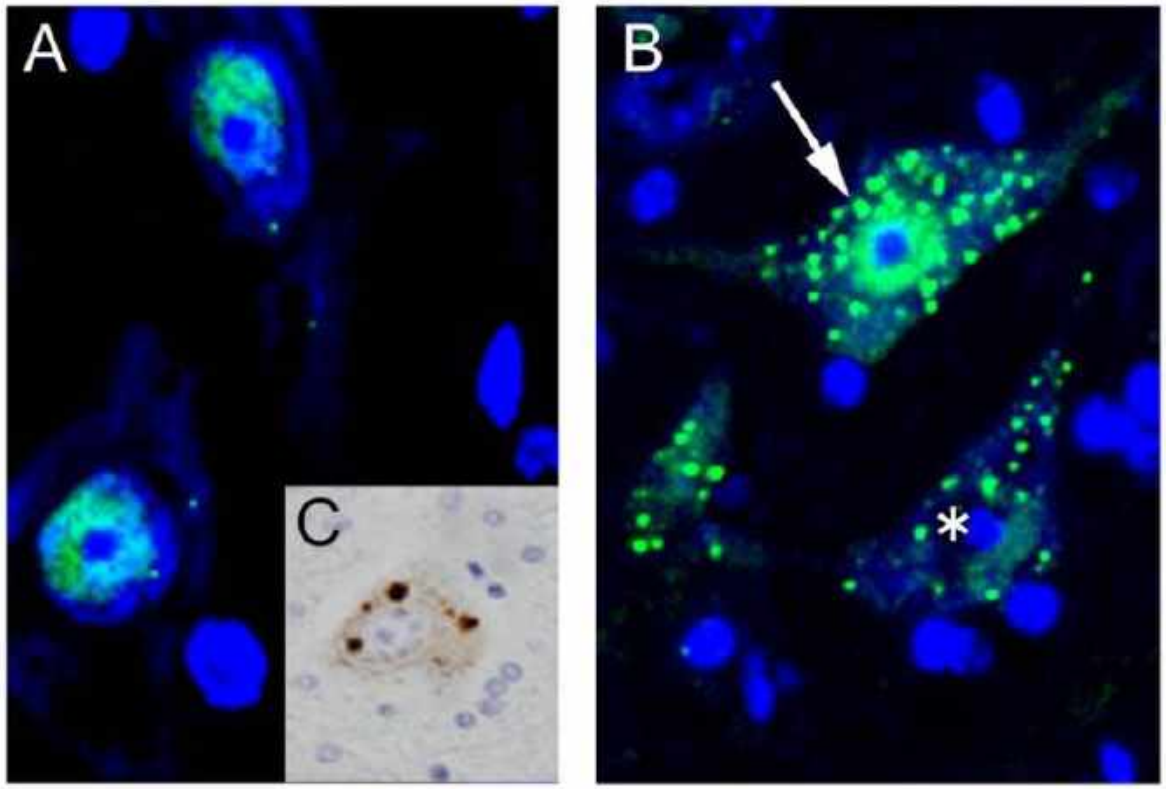
THREE KEY PIECES TO THE PUZZLE

TDP-43

Caspases

The concept of proteostasis

Pathological TDP-43 Cytoplasmic Inclusions



Found in 97% of cases of ALS

（A） TDP-43 (green) is localized in the nucleus of motor neurons of normal mice. (B) In the motor neurons of AR2 mice, there are numerous TDP-43-positive inclusions in the cytoplasm (arrow) with reduced or absent (asterisk) TDP-43 immunoreactivity in the nucleus. (C) TDP-43 mis-localization seen in AR2 motor neurons is quite similar to TDP-43 pathology in a spinal motor neuron of an ALS patient (DAB).

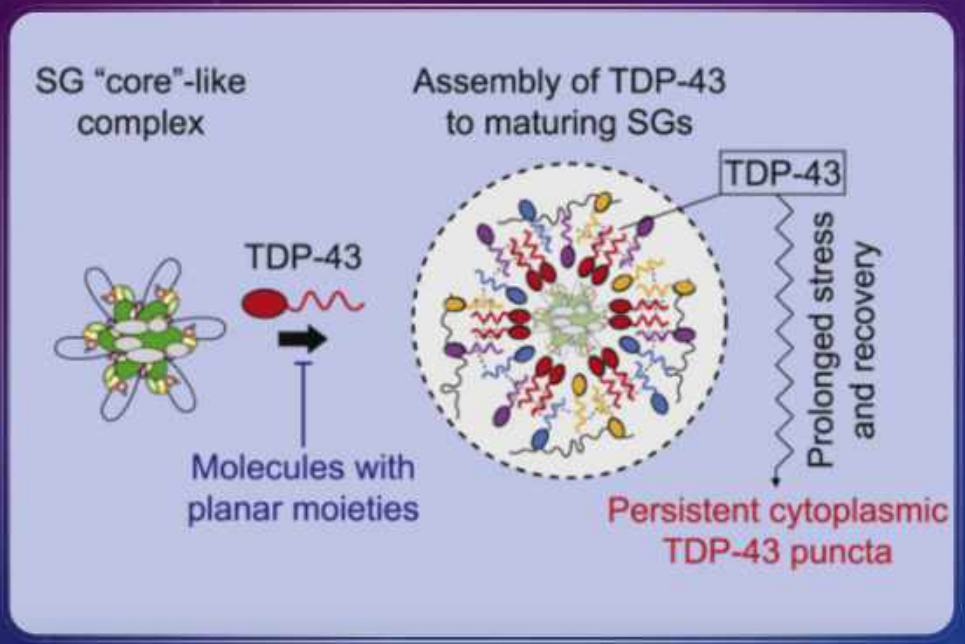
Green: TDP-43, blue: TO-PRO-3**.**

Yuki, M., Tanaka, H., Sasaki, K. *et al. Nat Commun* **3,** 1254 (2012). https://doi.org/10.1038/ncomms2264

TDP-43 (TRANSACTIVE RESPONSE DNA-BINDING PROTEIN): NORMAL FUNCTION

- Transcribed from the *TARDBP* gene.
- TDP-43 is a widely expressed nuclear protein that binds both DNA and RNA.
- Found within the cell nucleus in most tissues and is involved in many of the steps of protein production.
- Attaches to DNA and regulates transcription and repairs DNA breaks.

TDP-43 AND STRESS GRANULES



Fang MY, et al. Neuron 2019;103(5):802-819.

- Stress granules (SGs) are cytoplasmic membrane-less organelles that form in response to various external stimuli and are essential to cell survival following stress.
- SGs protect RNA from harmful conditions. The accumulation of RNAs into dense globules safeguards the information coded in their RNA sequence.
- TDP-43 is recruited to these SGs.
- SGs are formed following exposure to various environmental stresses (oxidative, osmotic, heat shock, viral infection).
- Form in a reversible manner.

CASPASES PLAY A KEY ROLE IN PROGRAMMED CELL DEATH (APOPTOSIS)

Caspases are a family of protein-cutting enzymes (cysteine-dependent, aspartate-specific proteases) – 11 in humans. Play a key role in apoptosis – the removal of unwanted or damaged cells.

When activated, caspases initiate "death" programs (apoptosis) by destroying key components of the cellular infrastructure and activating factors that mediate damage to the cells

Upstream initiators (activated by the cell-death signal, e.g., TNF-alpha) and downstream executioners (directly mediate the events that lead to the demise of the cell).

Executioner caspases activate the machinery that degrades DNA – one example is caspase-3.

Frielander RM. N Engl J Med 2003; 348:1365-1375.

CASPASES ARE ALSO INVOLVED IN NON-APOPTOTIC CELL DEATH

- Necroptosis - inflammatory cell death; a backup cell death defense mechanism that is triggered when apoptosis is hindered, such as during pathogen infection;
- Pyroptosis – a primary cellular response following the sensing of potentially damaging insults, which include pathogen ligands, DAMPs, altered levels of host metabolites and environmental irritants.
- Autophagy – the removal of unnecessary or dysfunctional cellular components;
- Amitotic catastrophe – a cell death mechanism that occurs during mitosis in cells that have accumulated DNA damage

Shalini S, et al. *Cell Death Differ*. 2015;22(4):526–539.

Frank D and Vince JE. Cell Death Differ. 2019;26:99-114.

CASPASES ARE INVOLVED IN INFLAMMATION AND IMMUNITY

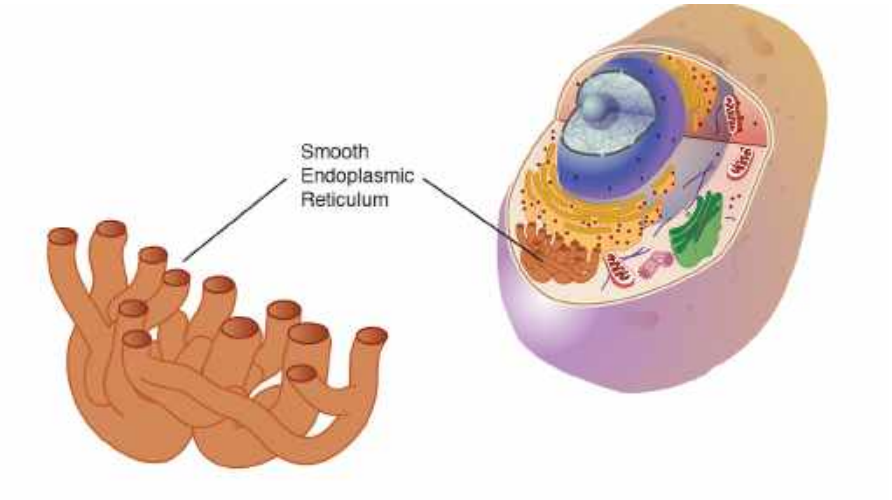
Function in the processing and maturation of interleukin (IL) cytokine family members, IL-1 beta and IL-18.

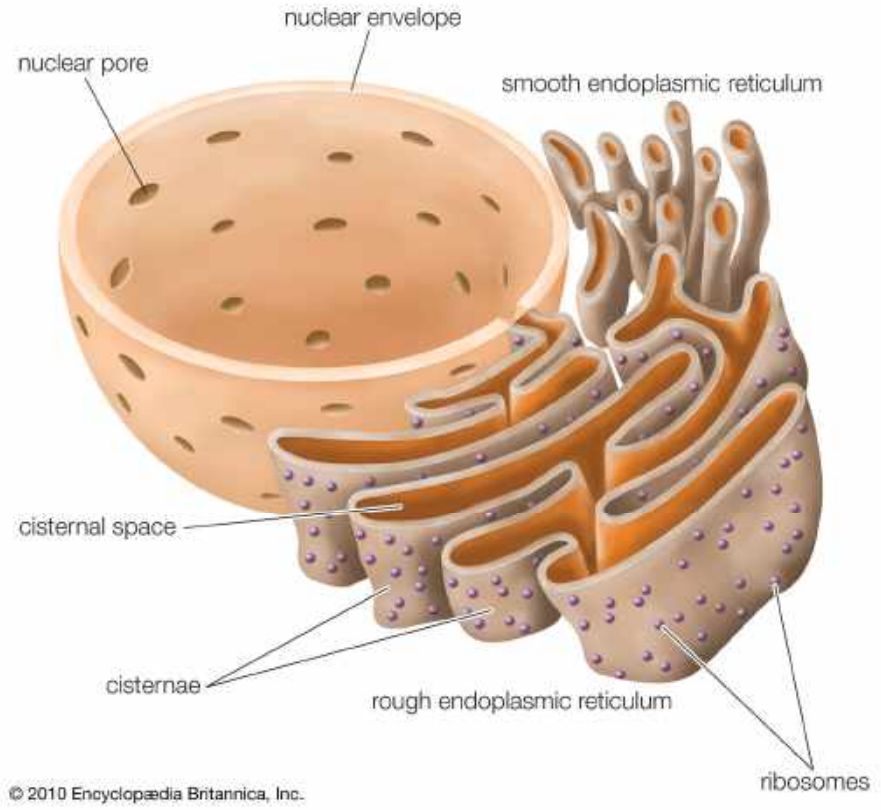
Important mediators of the innate immune response - thus termed “inflammatory caspases” (human caspases -1, -4, -5, and -12).

Internal or external cellular insults (viral or bacterial infection, toxin exposure, environmental irritants and metabolites) activate different pattern-recognition receptors which leads to formation of large, multiprotein “inflammasome” complexes. These inflammasomes, in turn, activate the inflammatory caspases.

Shalini S, et al. *Cell Death Differ*. 2015;22(4):526–539.

The Endoplasmic Reticulum





INFLAMMATION INDUCES TDP-43 MIS-LOCALIZATION AND AGGREGATION

In 2015, Ana Sofia Correla and colleagues at the Center for Research at Laval University in Quebec reported that lipopolysaccharide (LPS)-induced inflammation can promote TDP-43 mis-localization and aggregation.

In culture, microglia and astrocytes exhibited TDP-43 mis-localization after exposure to LPS.

Likewise, treatment of the motoneuron-like NSC-34 cells with TNF-alpha (TNF-α) increased the cytoplasmic levels of TDP-43.

In addition, the chronic intraperitoneal injection of LPS at a dose of 1mg/kg in TDP-43^{A315T} transgenic mice exacerbated the pathological TDP-43 accumulation in the cytoplasm of spinal motor neurons and it enhanced the levels of TDP-43 aggregation.

These results suggest that inflammation may contribute to development or exacerbation of TDP-43 proteinopathies in neurodegenerative disorders, such as ALS.

Correia AS, et al. PLoS ONE 2015; 10(10): e0140248.
doi:10.1371/journal.pone.0140248

DEREGULATION OF TDP-43 TRIGGERS NF-KB

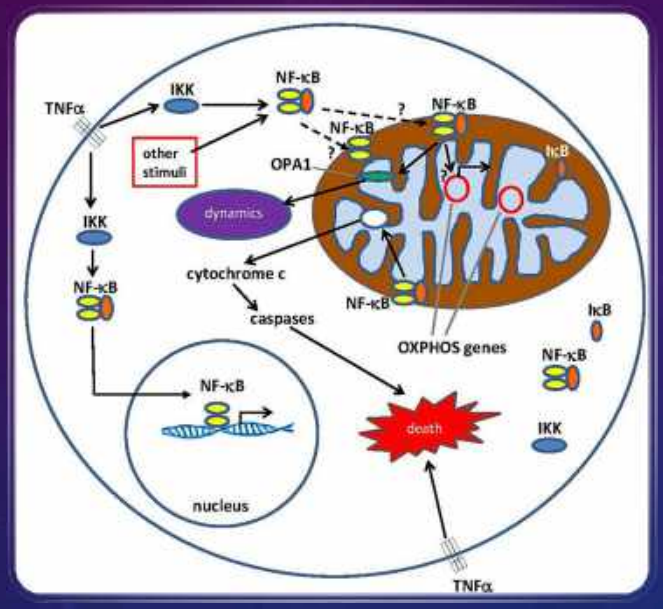
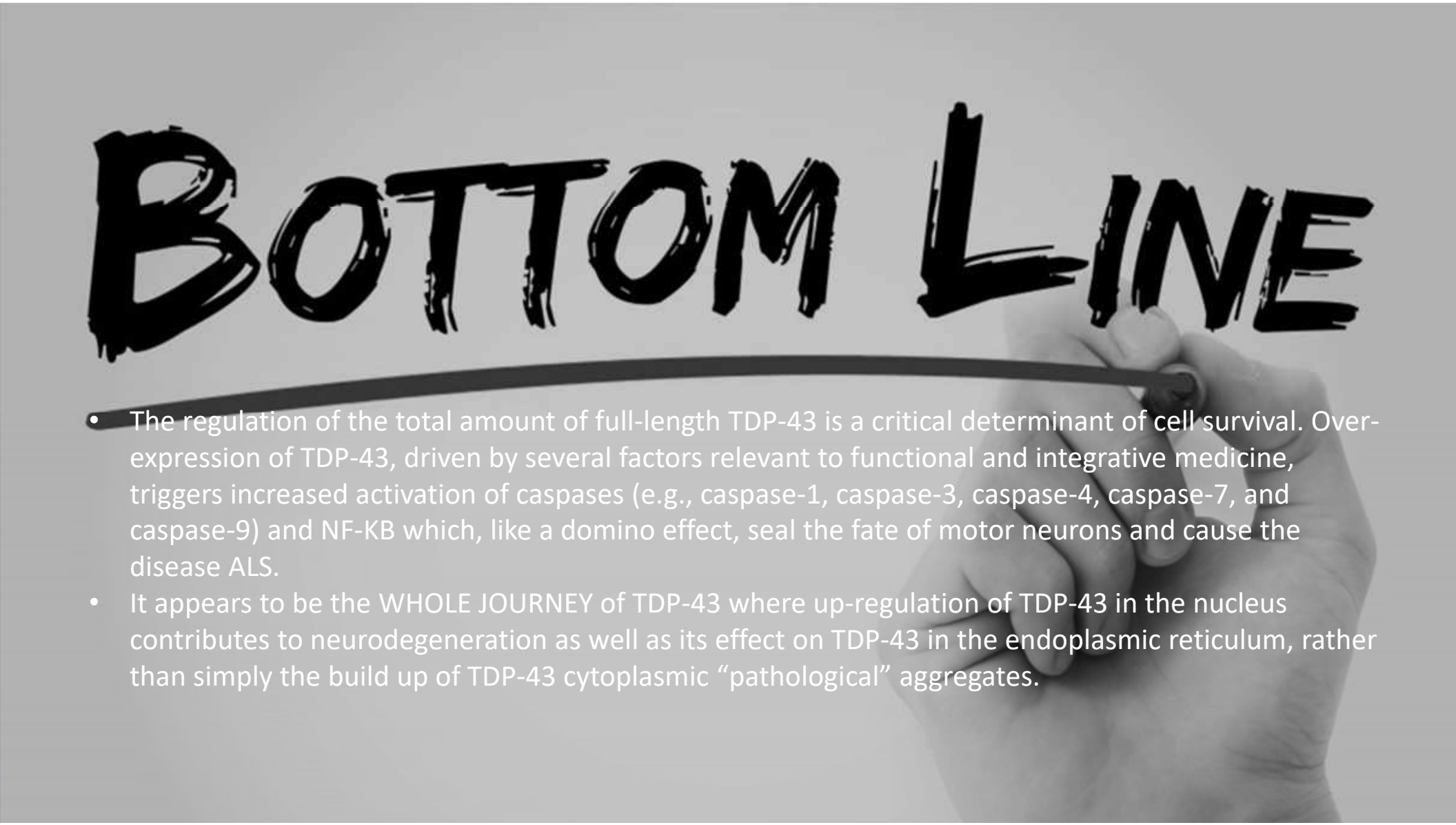


Image from Albensi, B. Front. Cell Dev. Biol., 07 August 2019 | https://doi.org/10.3389/fcell.2019.0015

- Deregulation of TDP-43 in amyotrophic lateral sclerosis (where the production of TDP-43 exceeds the rate of degradation) triggers nuclear factor kappa-B-mediated pathological pathways.
  - Higher amounts of TDP-43 triggers the production of more proinflammatory cytokines and neurotoxic mediators after stimulation with LPS or ROS.
  - TDP-43 over expression in neurons increases their vulnerability to toxic mediators

PROTEOSTASIS

Proteostasis is the idea that there are competing and integrated pathways within cells that control the formation, folding, trafficking and degradation of proteins present within and outside the cell.



- The regulation of the total amount of full-length TDP-43 is a critical determinant of cell survival. Over-expression of TDP-43, driven by several factors relevant to functional and integrative medicine, triggers increased activation of caspases (e.g., caspase-1, caspase-3, caspase-4, caspase-7, and caspase-9) and NF-KB which, like a domino effect, seal the fate of motor neurons and cause the disease ALS.
- It appears to be the WHOLE JOURNEY of TDP-43 where up-regulation of TDP-43 in the nucleus contributes to neurodegeneration as well as its effect on TDP-43 in the endoplasmic reticulum, rather than simply the build up of TDP-43 cytoplasmic “pathological” aggregates.

From Poljsak B. Bosn J Basic Med Sci 2012; 12 (2): 122-126.

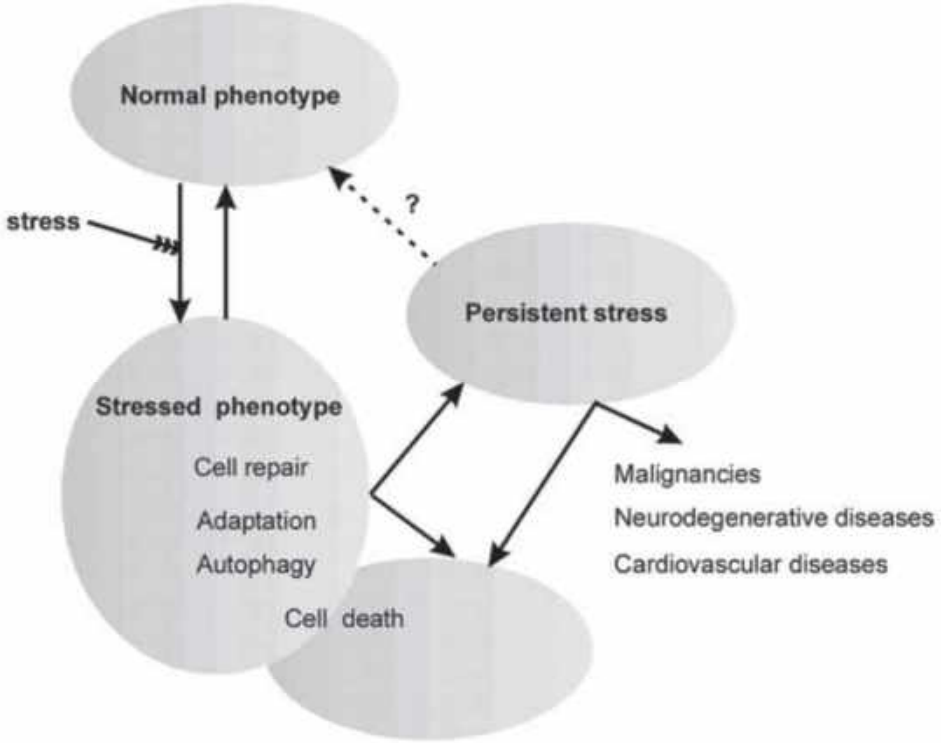


FIGURE 1. Cellular responses to stress and their consequences

TRANSIENT STRESS VERSUS CHRONIC STRESS

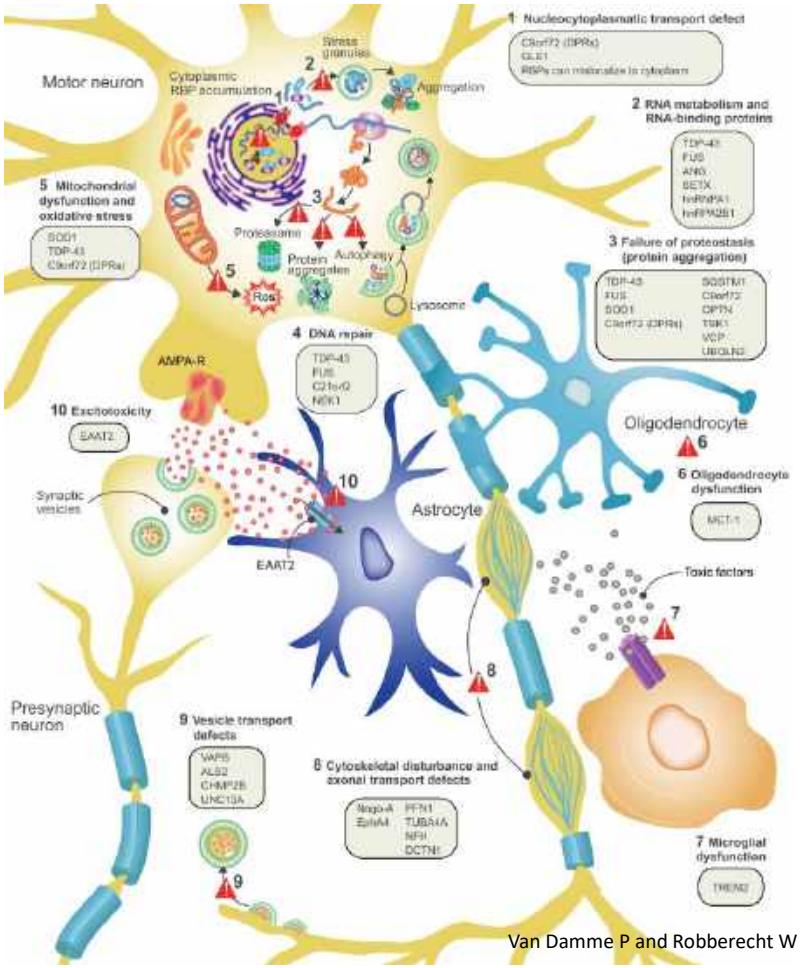
Transient Stress

- Increased TDP-43 →
- Stress granules →
- Caspase activation →
- "Healthy" proteostasis →
- Stress resolves (no disease).

Chronic Stress in the ALS Susceptible Cell

- Increased TDP-43 →
- Stress granules (initially) →
- Caspase activation →
- Loss of proteostasis →
- Further caspase activation, NF-KB activation, and a domino-like effect triggering multiple mechanisms associated with ALS →
- Formation of TDP-43 inclusions (possibly a protective response?) →
- **Amyotrophic Lateral Sclerosis**.

1. Nucleocytoplasmic transport defect
2. RNA metabolism and RNA-binding proteins
3. Failure of proteostasis (protein aggregation)
4. DNA repair abnormalities
5. Mitochondrial dysfunction and oxidative stress
6. Oligodendrocyte dysfunction
7. Microglial dysfunction
8. Cytoskeletal disturbances and axonal transport defects
9. Vesicle transport defects
10. Excitotoxicity



Van Damme P and Robberecht W et al. Dis Model Mech. 2017; 10(5): 537–549.

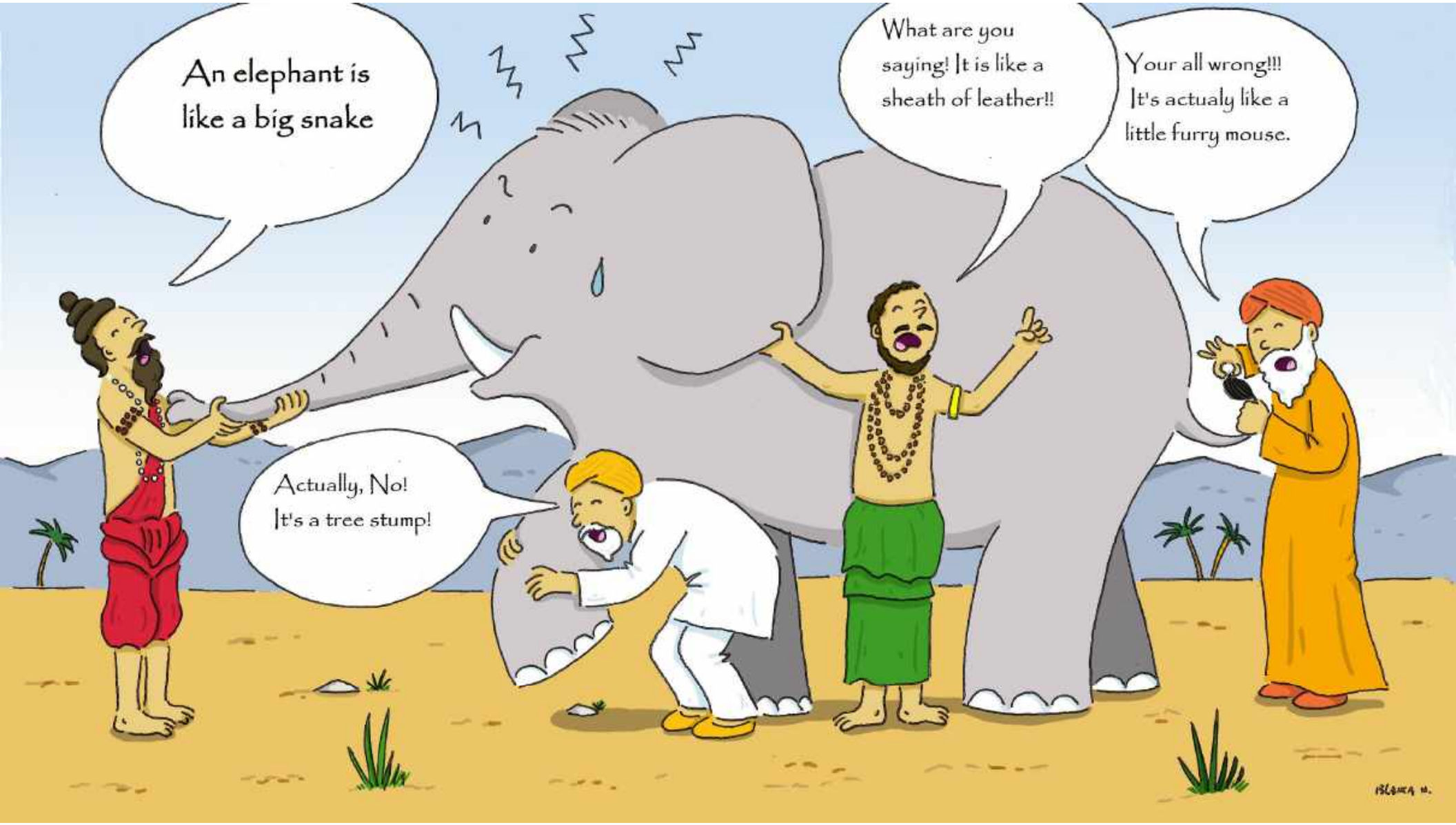
Mechanisms Implicated in ALS

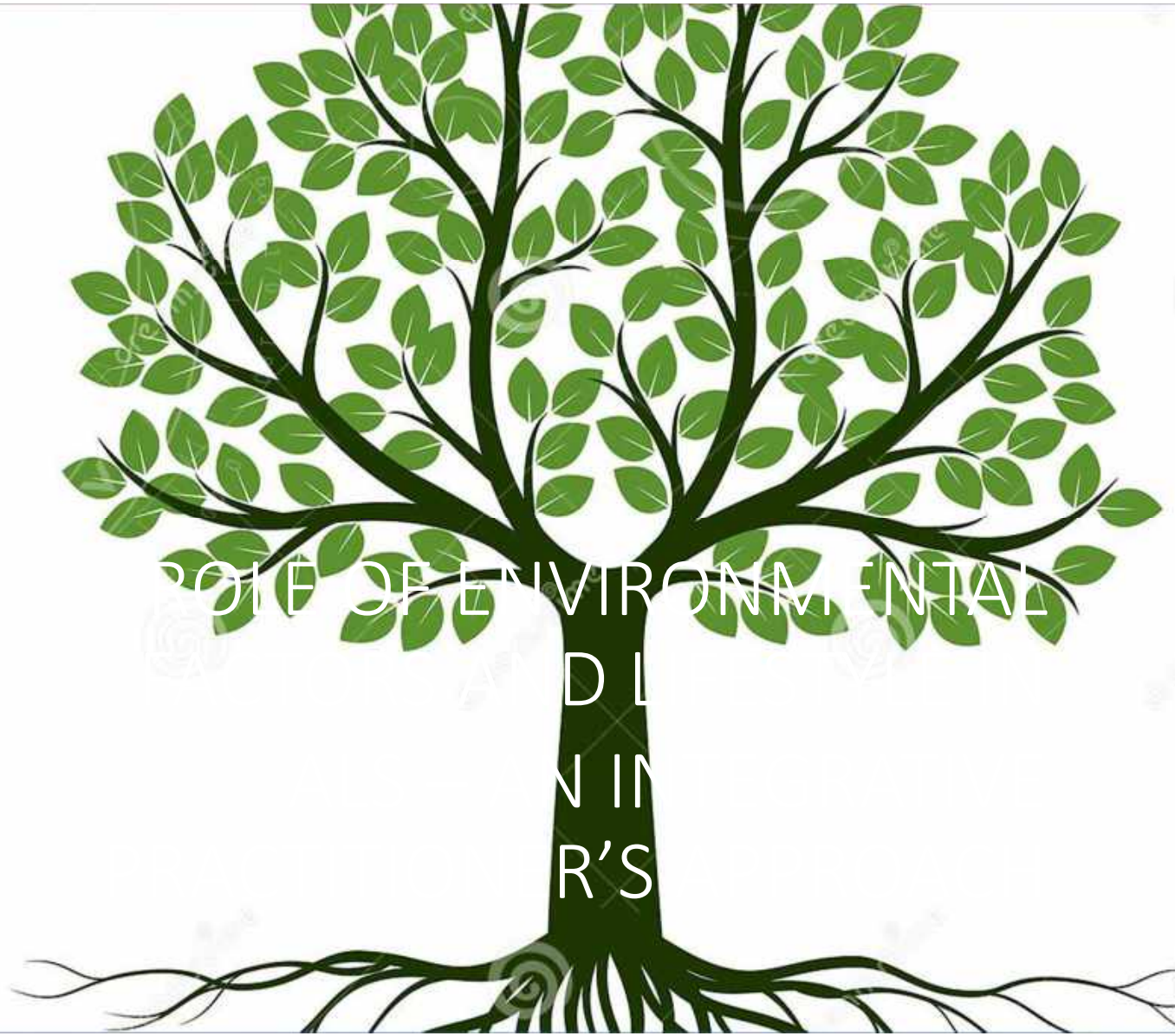
TDP-43 IS LINKED TO ALL KNOWN MECHANISMS OF ALS

1. TDP-43 pathology disrupts nuclear pore complexes and nucleocytoplasmic transport in ALS/FTD
2. TDP-43: a DNA and RNA binding protein with roles in neurodegenerative diseases
3. Partial Failure of Proteostasis Systems Counteracting TDP-43 Aggregates in Neurodegenerative Diseases
4. Motor neuron disease-associated loss of nuclear TDP-43 is linked to DNA double-strand break repair defects
5. TDP-43 induces mitochondrial damage [including increased ROS] and activates the mitochondrial unfolded protein response
6. Cell-autonomous requirement of TDP-43, an ALS/FTD signature protein, for oligodendrocyte survival and myelination
7. Microglial activation correlates with disease progression and upper motor neuron clinical symptoms in amyotrophic lateral sclerosis. ("TDP-43 pathology was more extensive in the motor cortex of cases with rapid progression of disease.")
8. TDP-43 causes neurotoxicity and cytoskeletal dysfunction in primary cortical neurons
9. Disrupted neuronal trafficking (vesicle transport defects) in amyotrophic lateral sclerosis [linked to TDP-43]
10. Impairment of Mitochondrial Calcium Buffering Links Mutations in C9ORF72 and TARDBP in iPS-Derived Motor Neurons from Patients with ALS/FTD (leading to excitotoxicity)

REFERENCES FOR PREVIOUS SLIDE

1. Chou CC, et al. Nat Neurosci. 2018;21(2):228-239. doi: 10.1038/s41593-017-0047-3.
2. Warraich ST, et al. In J Biochem Cell Biol. 2010;42(10):1606-9.
3. Cascella R, et al. Int J Mol Sci. 2019;20(15). pii: E3685.
4. Mitra J, et al. Proc Natl Acad Sci USA 2019;116(10):4696-4705.
5. Wang P, et al. PLoS Genet. 2019;15(5):e1007947.
6. Wang J, et al. PNAS 2018 115 (46) E10941-E10950.
7. Brettschneider J, et al. PLoS One 2012;7(6):e39216.
8. Baskaran P, et al. PLOS ONE 2018;13(5): e0196528.
9. Burk K, et al. Acta Neuropathol 2019; 137(6): 859–877.
10. Dafinca R. Stem Cell Reports 2020; pii: S2213-6711(20)30113-2.


An elephant is like a big snake
Actually, No! It's a tree stump!
What are you saying! It is like a sheath of leather!!
Your all wrong!!! It's actualy like a little furry mouse.



ROLE OF ENVIRONMENTAL
D L
N IN
R'S

A BROAD DEFINITION OF CELLULAR STRESS

A variety of environmental factors, including infections, biotoxins, chemical agents, electromagnetic radiation, hypoxia, hypercapnia, and aspects of lifestyle all contribute to inflammation and oxidative stress.

AN INTEGRATIVE APPROACH: 5 PILLARS

- Identify
- Investigate
- Integrate
- Restore
- Regenerate

IDENTIFY

- **Differential Diagnosis**
  - **ALS**
  - Syringobulbia/syringomyelia
  - Brainstem tumors
  - Stroke
  - Demyelinating disorder (like MS)
  - Cervical stenosis
  - Transverse myelitis
  - Lower motor neuron lesions as might be seen with radiculopathy, plexopathy, or neuropathies.

DIAGNOSTIC TESTING

- Nerve conduction study with electromyography (NCV/EMG)
- Blood or urine studies for various causes of neuropathy including serum/urine protein electrophoresis, sed rate, thyroid and parathyroid hormone disorders, heavy metals, B12, Lyme, antiganglioside GM1 antibodies.
- Spinal fluid examination
- X-rays, MRI (Brain, spinal cord), myelography
- Muscle/nerve biopsy

Table 2 | Criteria for diagnosis of ALS

Criteria	Definite ALS	Probable ALS	Possible ALS	Suspected ALS
El Escorial criteria, 1994[51]	Upper and lower motor neuron signs in three regions	Upper and lower motor neuron signs in at least two regions, with upper motor neuron signs rostral to lower motor neuron signs	Upper and lower motor neuron signs in one region, upper motor neuron signs alone in two or more regions, or lower motor neuron signs rostral to upper motor neuron signs	Lower motor neuron signs only, in two or more regions
Revised Airlie House criteria, 1998[52] (incorporating the Awaji–Shima criteria, 2008[53])*	Clinical or electrophysiological evidence, demonstrated by the presence of upper and lower motor neuron signs in the bulbar region and at least two spinal regions, or the presence of upper and lower motor neuron signs in three spinal regions	Clinical or electrophysiological evidence, demonstrated by upper and lower motor neuron signs in at least two spinal regions, with some upper motor neuron signs necessarily rostral to the lower motor neuron signs	Clinical or electrophysiological signs of upper and lower motor neuron dysfunction in only one region, or upper motor neuron signs alone in two or more regions, or lower motor neuron signs rostral to upper motor neuron signs	NA

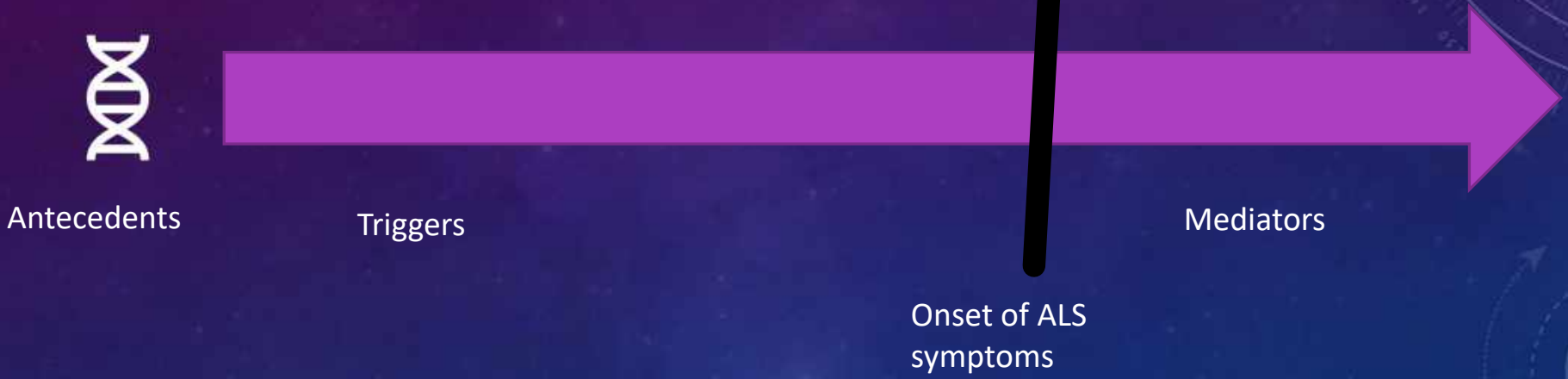
*These revised recommendations emphasize the equivalence of clinical and electrophysiological tests in establishing neurogenic changes in bodily regions.
Abbreviations: ALS, amyotrophic lateral sclerosis; NA, not applicable.

https://wiki.mcmaster.ca/LIFESCI_4M03/group_1_presentation_1_-_als

INVESTIGATE

- Functional medicine patient history/timeline (Antecedents, Triggers, and Mediators)
- Clues from the examination that suggest nutritional imbalances or environmental exposures
- Laboratory testing

What does your functional medicine timeline look like?



TRIGGERS AND MEDIATORS

- Smoking, especially among post-menopausal women.
- High level of physical fitness (not strength) or athleticism, and lower body mass index than average.
  - Increased risk among professional football and soccer players.
- Repeated head injuries
- Occupations in which exposure to chemicals, pesticides, metals, and EMF is more likely.
  - Pesticides: organochlorine compounds, pyrethroids, herbicides, and fungicides; Lead, aluminum, arsenic, cadmium
- Pre-existing autoimmune diseases.
- Diets with higher intake of carbs, glutamate, and certain fats and with lower intake of fruits, vegetables, vitamin E, carotenoids and omega-3 PUFAs.
- History of repeated antibiotic use (dysbiosis).
- Fungal contaminated grass and well-water, proximity to water contaminated with cyanobacteria (BMAA).

LABORATORY INVESTIGATIONS

- Inflammatory markers and antioxidants: HS-CRP, homocysteine, B12, folate, glutathione, vitamin C, vitamin D, vitamin E, omega fatty acid profile, fasting insulin, basic metabolic panel, hemoglobin A1c, advanced lipid profile (particle size study).
- Infections: Borrelia burgdorferi, mycoplasma species, enteroviruses, **cyanobacteria, HERV-K**.
- Toxins: Heavy metal testing, mycotoxins assay, toxic chemicals profile.
- Gut health: Stool testing, OAT. Future: Test for Cyanobacteria or BMAA levels.
- Minerals: RBC magnesium, copper, zinc, selenium, iodine.
- Hormones: Cortisol, testosterone, estradiol, progesterone, thyroid.

INTEGRATE: HOW TO PUT IT TOGETHER

SLEEP AND ALS

- Sleep disorders are extremely common among those suffering with ALS. One study of 40 patients found sleep disorders were observed in 70%
  - insomnia in 65% ALS patients.
  - sleep disordered breathing/hypoventilation in 52.5%.
  - restless legs syndrome in 5% patients.
  - nighttime awakenings attributable to symptoms associated with ALS were noted in 85%.
  - further exacerbating a disturbed sleep, anxiety and depression in 57.5% patients.
- Excessive daytime somnolence emerged as an independent predictor for the presence of sleep disorders in ALS patients

- Panda S, et al. *Neurol India*. 2018;66(3):700-708. doi:10.4103/0028-3886.232327
- Diaz-Abad, et al. Journal of Clinical Neuromuscular Disease 2018; (20): 60-68 doi: 10.1097/CND.0000000000000234

NUTRITION AND ALS

- High risk of malnutrition
  - Symptoms of dysphagia, depression, cognitive impairment, difficulty with self-feeding and meal preparation, hypermetabolism, anxiety, respiratory insufficiency, and fatigue with meals increase the risk of malnutrition.
- Energy expenditure/hypermetabolism – can influence the rate at which the disease progresses
- Diets higher in antioxidants and fiber-rich foods such as fruit and vegetables reduce the risk of ALS
- Consumption of foods high in ω-3 PUFAs may help prevent or delay the onset of ALS
- Evidence that gut microbial composition and function may be altered in people with ALS
  - In one study using an ALS mouse model disease was altered after the mice received certain strains of gut microbes - *Akkermansia muciniphila* ameliorated whereas *Ruminococcus torques* and *Parabacteroides distasonis* exacerbated the symptoms.

GUIDELINES FOR TUBE-FEEDING IN ALS

When nutrition status is compromised by dysphagia and weight loss (5%–10% of usual body weight) or body mass index <20 kg/m^2 without weight loss and when forced vital capacity is >50%, a percutaneous endoscopic gastrostomy placement is indicated.

When forced vital capacity is <50%, a radiologically inserted gastrostomy is the preferred means of enteral placement due to lessened aspiration and respiratory risk.

ENTERAL NUTRITION

DIET AND ALS

- Meet or exceed caloric (energy) demand!
  - Calorie-restricted SOD1 mice had shorter survival time than ad libitum SOD1 mice.
- Ketogenic diets *may* improve the survival and function of motor neurons
  - Enhance mitochondrial function (restore complex I activity).
  - Increases production of GABA/decreases production of glutamate.
  - Reduces neuroinflammation by reducing the activity of microglia, astrocytes, and T-cells that infiltrate the brain, reduces oxidative stress, lowering levels of ROS, and decreasing the glucose metabolism that activates pro-inflammatory pathways.
  - While animal studies promising, of the two human trials (NCT01016522 and NCT02306590) no results have been reported. Although unconfirmed, I am told that the former study was terminated due to increased death rate in the treatment group.

MOVEMENT AND ALS

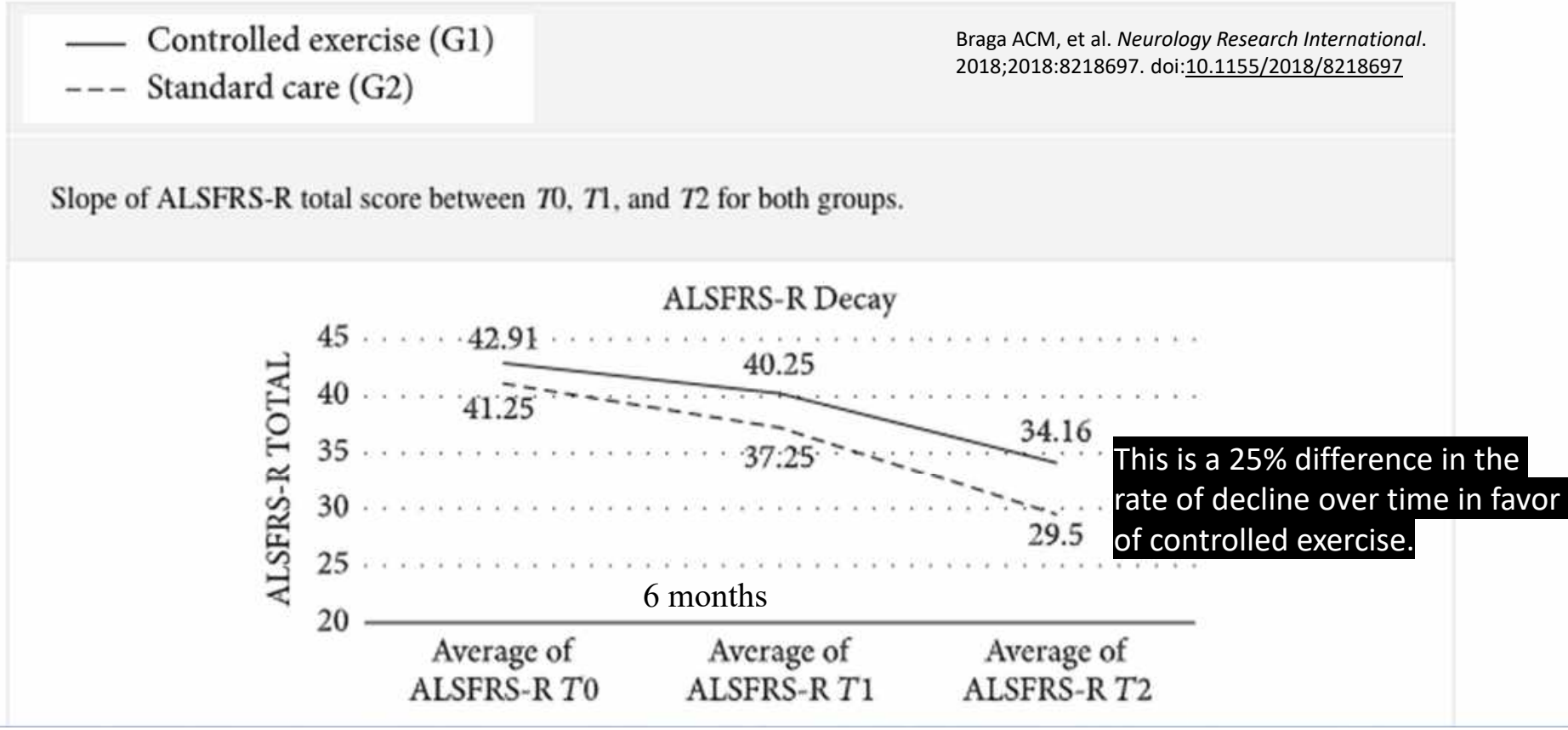
- Moderate exercise has been shown to improve strength and prolong survival in animal models of ALS
- Not to be avoided!
  - Sedentary behavior leads to deconditioning and weakness on top of the deconditioning and weakness caused by the disease itself, contributing to muscle and joint tightness, contractures, and pain.
- Benefits include appetite, digestion, mood, sleep, positive impact on hormones/trophic factors (including BDNF and IGF-1), and inflammatory markers.

EXERCISE AND ALS

- Emphasis on stretching, strength-building, range-of-motion, and *moderate* aerobic exercise
  - For aerobic conditioning – a cycle ergometer or a treadmill ramped up to about 70-75% maximal heart rate for about 10-20 minutes, three times per week.
  - For strengthening – muscles that can overcome gravity and provide some resistance can be strengthened safely with moderate weightlifting (3 sets of 10 repetitions that are not too intense to complete).
  - If a patient has fatigue or pain that lasts longer than 30 minutes after exercise, the program needs to be reduced and modified.
  - Stretching (yoga, tai chi) and aqua therapy are also good.
- Consider involving physical and occupational therapy
- Individualized program over group classes

The Role of Moderate Aerobic Exercise as Determined by Cardiopulmonary Exercise Testing in ALS

Braga ACM, et al. *Neurology Research International*. 2018;2018:8218697. doi:10.1155/2018/8218697



This is a 25% difference in the rate of decline over time in favor of controlled exercise.

MEDICAL MANAGEMENT AND ALS

- Pain
- Spasticity
- Speech and swallowing
- Mood/behavior
- Mobility issues/Durable Medical Equipment
- Disease-modifying therapy – riluzole, edaravone
- Treating root cause imbalances (functional labs)
- Tracking weight and BMI, Forced Vital Capacity, ALSFRS-R, and the areas of imbalance identified on functional medicine testing

FORCED VITAL CAPACITY

- FVC spirometry is performed as follows:
- The patient is seated in a chair and asked to breathe comfortably.
- A clip is placed over the nose.
- They are given a tube to breathe into.
- After sealing their lips tightly over the tube, they are asked to inhale as deeply as possible and exhale as forcefully as they can.
- The procedure is repeated at least three times to obtain a consistent and average value.
- The normal FVC range for an adult is between 3.0 and 5.0 L

THE ALSFRS-R

- Originally, a 10-item standardized questionnaire, revised(-R) to give greater weight to respiratory involvement and became the 12-item ALSFRS-R.
  - Assesses speech, salivation, swallow, and then functions mediated by cervical, trunk, lumbosacral, and respiratory muscles - each assessed by 3 items.
  - Each item is scored from 0-4, with 4 reflecting no involvement by the disease and 0 reflecting maximal involvement. The item scores are added to give a total (maximum score 48).
    - >40 (minimal to mild)
    - 39-30 (mild to moderate)
    - < 30 (moderate to severe)
    - < 20 (advanced disease)

Speech	Salivation	Swallowing
Handwriting	Cutting food	Climbing stairs
Turning in bed	Walking	Dressing and hygiene
Dypspnea (difficulty breathing)	Orthopnea (Shortness of breath while lying down)	Breathing insufficiency

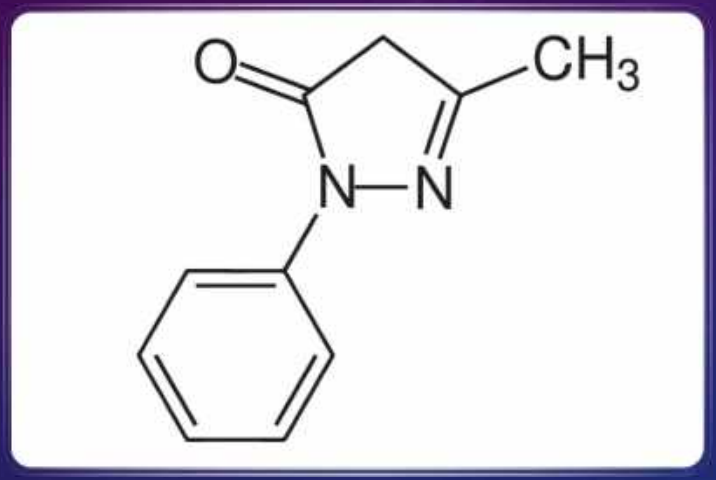
RILUZOLE (FDA APPROVED IN 1995) IMPROVES SURVIVAL BY 3 MONTHS

The mechanisms of riluzole includes:

- 1) an inhibitory effect on glutamate release
- 2) inactivation of voltage-dependent sodium channels
- 3) ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors
- 4) neuroprotective in various in vivo experimental models of neuronal injury involving excitotoxic mechanisms

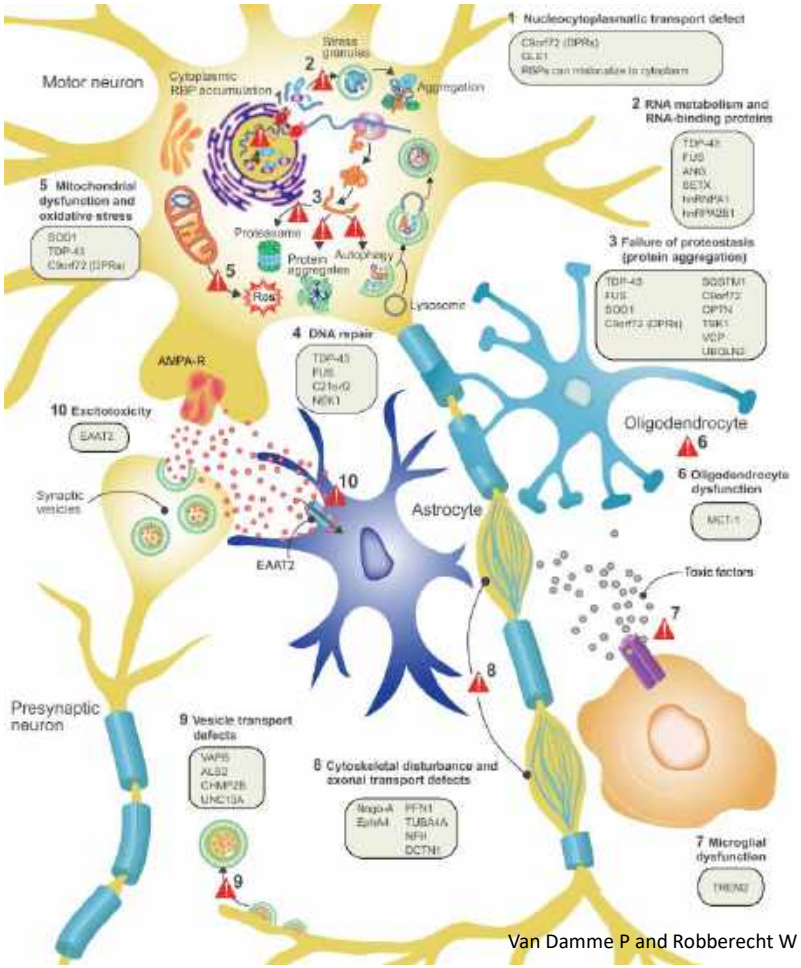
Shown to delay median time to death in a transgenic mouse model of ALS (mice carrying the superoxide dismutase mutation), and similar findings in human clinical trials was the basis for its approval by the FDA.

EDAVARONE – A FREE RADICAL SCAVENGER



- Exact mechanism of action in ALS unknown. However, it probably acts as a free radical scavenger countering oxidative tissue injury in the CNS.
- Approved in the U.S. in May 2017 based on two randomized clinical trials that took place in Japan.
- 60 mg IV qDay x 10 days within a 14-day period, then off 14 days (repeat cycle).

1. Nucleocytoplasmic transport defect
2. RNA metabolism and RNA-binding proteins
3. Failure of proteostasis (protein aggregation)
4. DNA repair abnormalities
5. Mitochondrial dysfunction and oxidative stress
6. Oligodendrocyte dysfunction
7. Microglial dysfunction
8. Cytoskeletal disturbances and axonal transport defects
9. Vesicle transport defects
10. Excitotoxicity



Van Damme P and Robberecht W et al. Dis Model Mech. 2017; 10(5): 537–549.

Mechanisms Implicated in ALS

RESTORE: HORMONES AND ALS

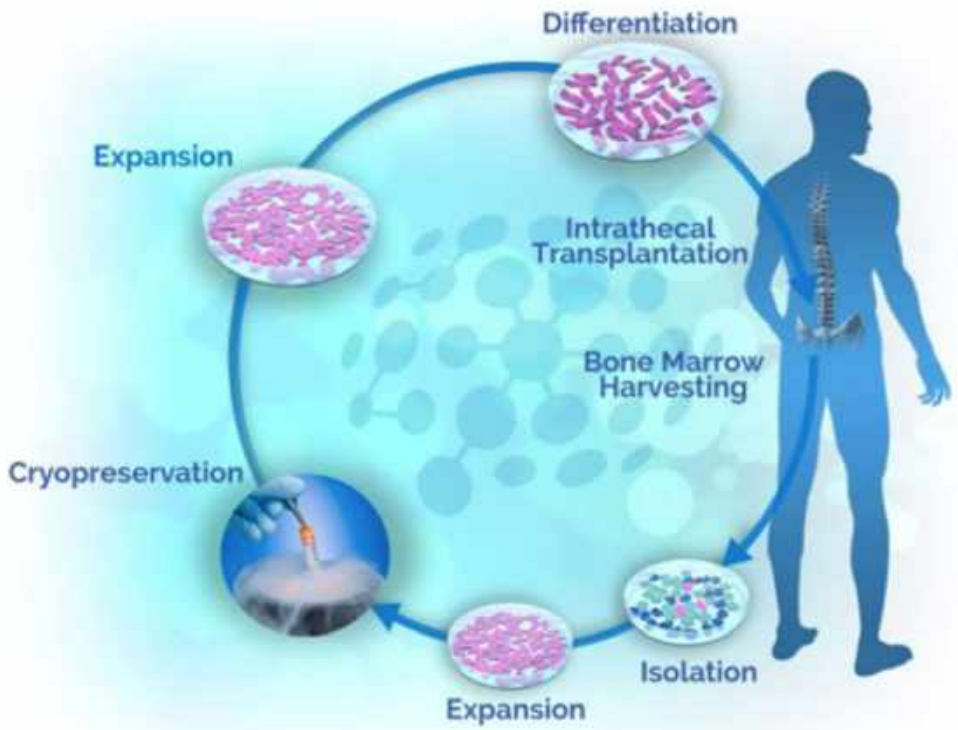
- Cortisol: Circadian cortisol dysregulation has been observed in ALS patients and should be addressed.
- Estrogen and progesterone: A large case-control study of 653 patients and 1,217 controls demonstrated hormone replacement therapy (HRT) was associated with a reduced risk of ALS in women living in the Netherlands (OR = 0.57, 95% CI 0.37–0.85).
  - Estradiol has been reported to exert neuroprotection in the brain from excitotoxic insults, and in primary culture of rat spinal cord motor neurons in vitro.
- Testosterone: Free testosterone has been identified as significantly decreased in ALS compared to controls. Because testosterone crosses the blood-brain barrier only as unbound form, this observation suggest a possible involvement of this sex hormone in the pathophysiology of this severe motor neuron disease.

- Rooney JPK, et al. Neurology 2017; 89 (12): 1283-1290.
- Nakamizo T, et al. Neuroreport 2000;11(16):3493-7.

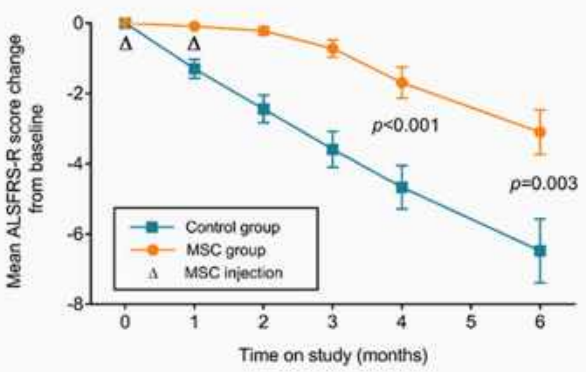
REGENERATE

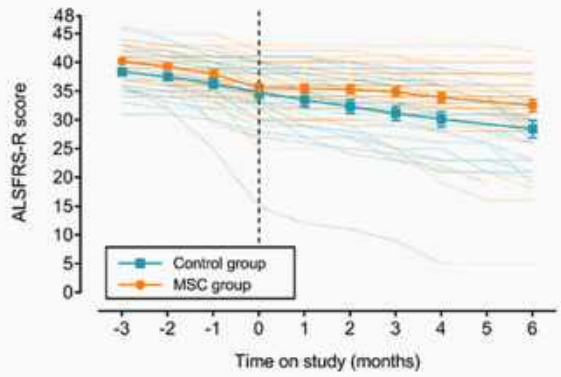
- “Regenerate” focuses on inflammatory aspects of neurodegeneration to tip the balance linking inflammation to neuronal cell death
- Provides growth factors that facilitate nerve cell growth, repair, and survival (VEGF, NGF, BDNF)
- Address disordered T- and B-cell regulatory function
- Increases microglial M2 phenotype by suppressing TNF-α and IL-1β
    - Under stress, **microglial cells** are induced into the **M1** type, releasing inflammatory factors and causing neuroinflammatory responses. After the inflammation fades away, **microglia** shift into the alternative activated **M2 phenotypes** that play a role in neuroprotection.
- increase anti-inflammatory cytokines (IL-4, IL-10, and TGF-beta)
- Deliver micro-RNA that regulate a wide variety of processes involved in immunomodulation and neuroprotection
- Reduce Caspase-3 and thereby reduce apoptosis

1. Bone marrow is harvested and MSCs are isolated from the total bone marrow population
2. MSCs are expanded *ex-vivo* and cryopreserved
3. MSCs are thawed and induced to differentiate
4. MSC-NTF cells are transplanted back into the patient by intrathecal administration



Phase 2 Trial of Intrathecal administration of Lenzumestrocel: two injections with 4-week interval concomitant with riluzole.





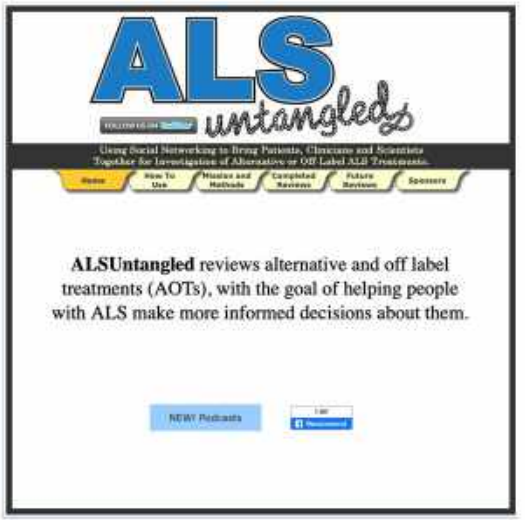
- Improvement in Deteriorating Physiological Function

	MSC group		Control group	
The mean changes in the ALSFRS-R total scores (+4 months)	-1.69 (SD 2.51)	vs	-4.67 (SD 3.25)	
Functional stability based on the responder analysis (+4 months)	69%	vs	19%	P=0.0002
Functional stability based on the responder analysis (+6 months)	62.5%	vs	22.2%	P=0.0019

- Compare the control group, the MSCs group has significant improvement in retardation in their symptom.
- In the initial 1 to 4 month period. the regression is reduced by almost 50%, it slow down almost 50%

Oh KW, et al. Ann Neurol 2018 Sep;84(3):361-373.

RICHARD BEDLACK, M.D., PH.D. AND ALS UNTANGLED

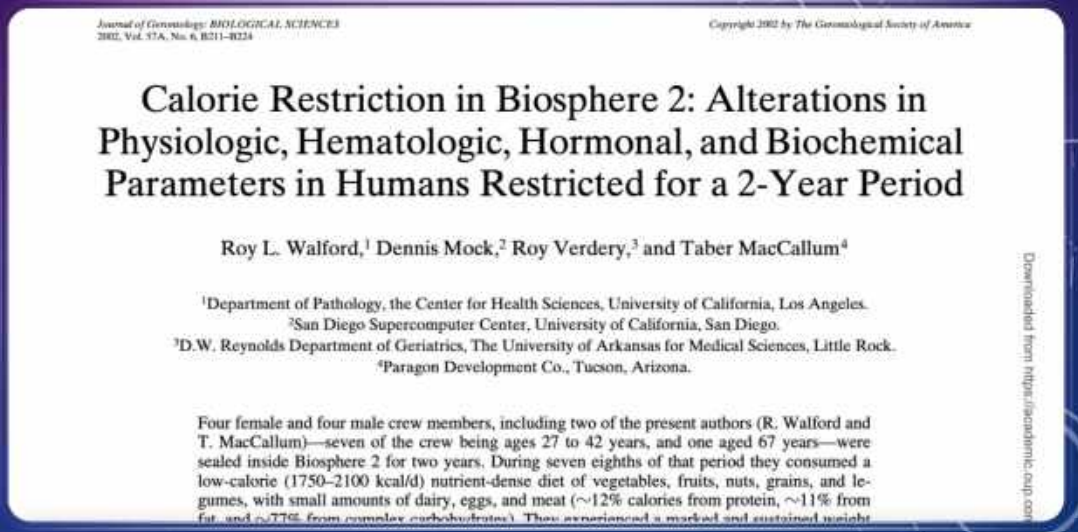



BIOS2


BIOS2

CALORIE RESTRICTION IN BIOSPHERE 2

- 50 variables on each crew member compared outside and inside the Biosphere 2
- BMI decreased 19% for men, 13 % for women
- Blood pressure decreased (25% systolic and 22% diastolic)
- WBC count decreased 31%
- Insulin decreased 42%
- T3 decreased 19%
- Glucose decreased 21%
- Cholesterol decreased 30%
- ”The results resembled those of rodents or monkeys maintained on a calorie-restricted regime.”



Journal of Gerontology: BIOLOGICAL SCIENCES
2002, Vol. 57A, No. 6, B211–B224

Calorie Restriction in Biosphere 2: Alterations in Physiologic, Hematologic, Hormonal, and Biochemical Parameters in Humans Restricted for a 2-Year Period

Roy L. Walford,[1] Dennis Mock,[2] Roy Verdery,[3] and Taber MacCallum[4]

[1]Department of Pathology, the Center for Health Sciences, University of California, Los Angeles.
[2]San Diego Supercomputer Center, University of California, San Diego.
[3]D.W. Reynolds Department of Geriatrics, The University of Arkansas for Medical Sciences, Little Rock.
[4]Paragon Development Co., Tucson, Arizona.

Four female and four male crew members, including two of the present authors (R. Walford and T. MacCallum)—seven of the crew being ages 27 to 42 years, and one aged 67 years—were sealed inside Biosphere 2 for two years. During seven eighths of that period they consumed a low-calorie (1750–2100 kcal/d) nutrient-dense diet of vegetables, fruits, nuts, grains, and legumes, with small amounts of dairy, eggs, and meat (~12% calories from protein, ~11% from

BUT ALL WAS NOT GREAT INSIDE THE BIOSPHERE 2

- Hypoxia - During the first 18 months of the mission oxygen levels gradually dropped from 21 percent to 14 percent. The low levels of oxygen triggered sleep apnea among several Biospherians.
- Hypercapnia - The bacteria in the Biosphere soil consumed the oxygen and released a large amount of carbon dioxide which became bound up in the cement of the structure, break the cycle of respiration and photosynthesis. Carbon dioxide reached levels as high as 4,500 ppm.
- Nitrous oxide levels in the air rose to 79 parts per million.
- Of the Biosphere's 25 small-animal species, 19 became extinct.
- Trees and most food plants struggled, but weedy vines, particularly morning glories, flourished in the carbon dioxide-rich atmosphere. The vines overgrew other plants, choking out food crops.
- Nutrients leached from soil polluted the water systems.
- Most of the introduced insects went extinct, leaving Crazy Ants running everywhere, together with scattered cockroaches and katydids.

WALFORD'S TIMELINE: "ATYPICAL" PARKINSONISM AND MOTOR NEURON SYNDROME

- 1993: after leaving the Biosphere, unable to walk more than a block due to back pain.
- 1994: he underwent lumbar spine surgery with improvement in pain, but gait continued to deteriorate.
- 1996: he had trouble initiating his gait ("freezing") and began falling frequently. He had increased difficulty arising from a chair. He was diagnosed with possible Parkinson's disease and given a trial of levodopa therapy. But the regimen failed to improve his gait and made him depressed.
- He stopped his levodopa therapy after 3 months and began taking coenzyme q10 that was associated with a marked but transient (2-4 months) improvement in his gait and he was able to resume his gym activity.
- 1997: had to depend on a walker
- 1999: trouble swallowing food and coughed often during meals.
- 2001: mild dysarthria, no cognitive deficit.
- 2002: clear progression in his neck flexion because of weakness of neck extensors. His exam showed brisk deep tendon reflexes with ankle clonus (an upper motor neuron sign); his sensory examination was intact as was his cerebellar exam. About this time, he was started on riluzole.
- April 27, 2004: Roy Walford died of ALS

Lassinger BK, et al. Movement Disorders 2004;19(4):465-469.

Atypical Parkinsonism and Motor Neuron Syndrome in a Biosphere 2 Participant:
A Possible Complication of Chronic Hypoxia and Carbon Monoxide Toxicity?

Brian K Lassinger; Carolyn Kwak;
Roy L Walford; Joseph Jankovic

Movement Disorders
Vol. 19

UNTANGLING WALFORD'S ALS

- Did conditions of Biosphere 2 trigger Walford's ALS?
  - Studies show that combined intermittent hypoxia leads to oxidative stress, mitochondrial dysfunction, and a marked increase in apoptosis in the cerebral cortex of mice.
  - Hypercapnia causes modification of membrane-bound proteins and lipids in the brain and the generation of ROS with resultant cellular oxidation.
  - Nitrous oxide interacts with vitamin B12 resulting in selective inhibition of methionine synthase leading to hyperhomocysteinemia which, in turn, aggravates ROS-induced depression of neurotransmitter release from motor nerve terminals.

OR, BY CONTRAST, DID THE ANTI-INFLAMMATORY CALORIE-RESTRICTED OPTIMAL NUTRITION DIET AND HAVE A PROTECTIVE EFFECT AGAINST ALS PROGRESSION?

POTENTIAL BENEFITS OF CALORIE RESTRICTION

CR increases bioavailability of NO

CR decreases vascular ROS generation

CR activates the Nrf2/Antioxidant Response Element pathway inducing ROS detoxification system

CR acts as a master switch controlling the activity of several genes involved in immunity, inflammation, and lipid metabolism

CR increases autophagy while repressing apoptosis

CR has hormonal and metabolic impacts

THE HEART BEATS 3,363,840,000 TIMES IN 80 YEARS

“The purpose of life, after all, is to live it, to taste experience to the utmost, to reach out eagerly and without fear for newer and richer experience.”

– Eleanor Roosevelt

CASES

THE FUNCTIONAL NEUROLOGY TOOLBOX

THIS IS CHRISTINE

Wife, Clinical Psychologist, MS Sufferer

Christine's Timeline

- Born by cesarean section
- Early exposure to antibiotics
- Lactose intolerance
- "Be a high achiever"
- Sexual assault
- History of mononucleosis
- Birth of first child
- **Diagnosed with MS**
- Standard American Diet
- Poor sleep habits
- No regular exercise
- Low stress resistance

Initial Laboratory Findings

LOW VITAMIN B12

LOW MAGNESIUM

LOW VITAMIN D

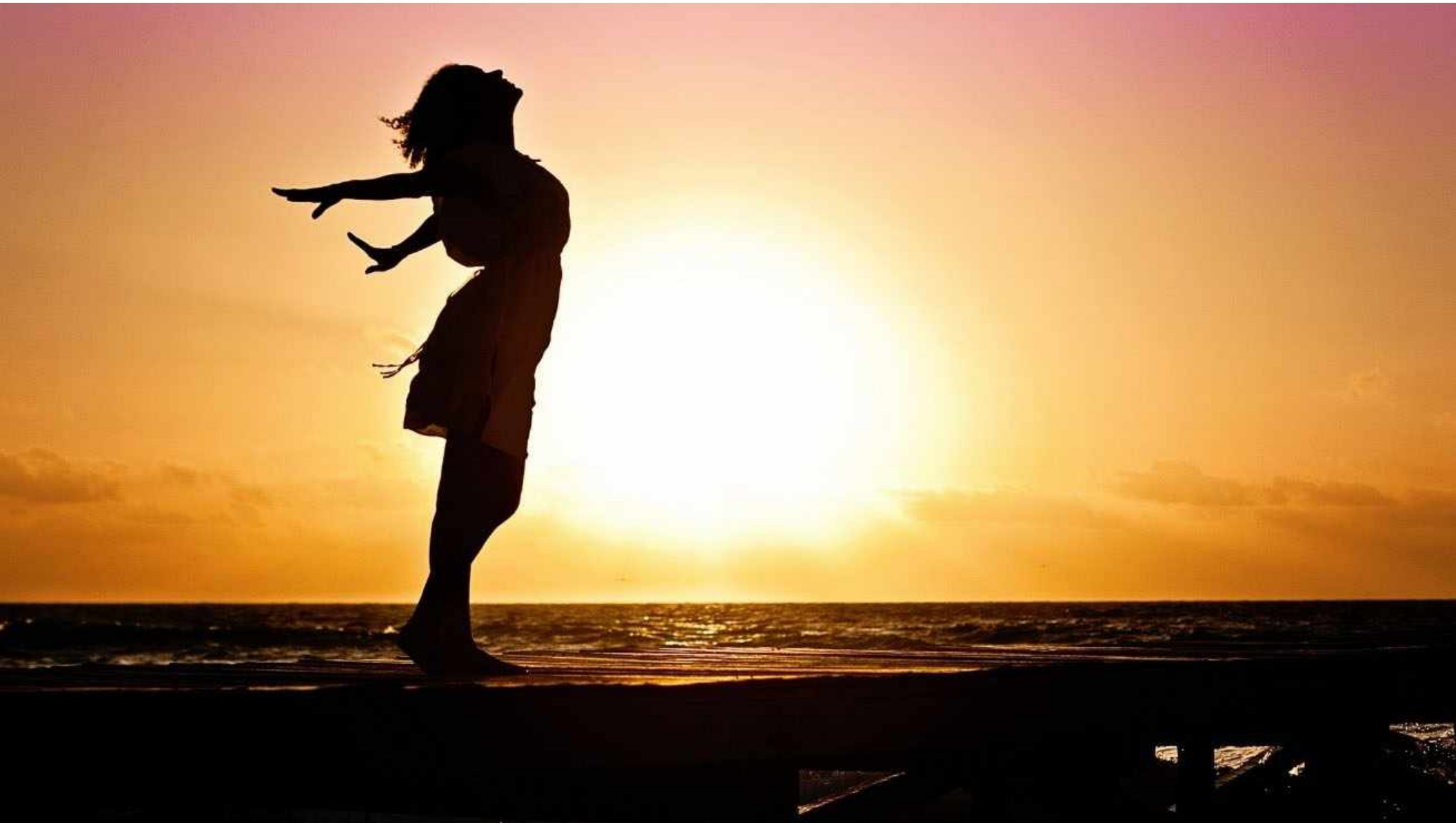
LOW SERUM ZINC

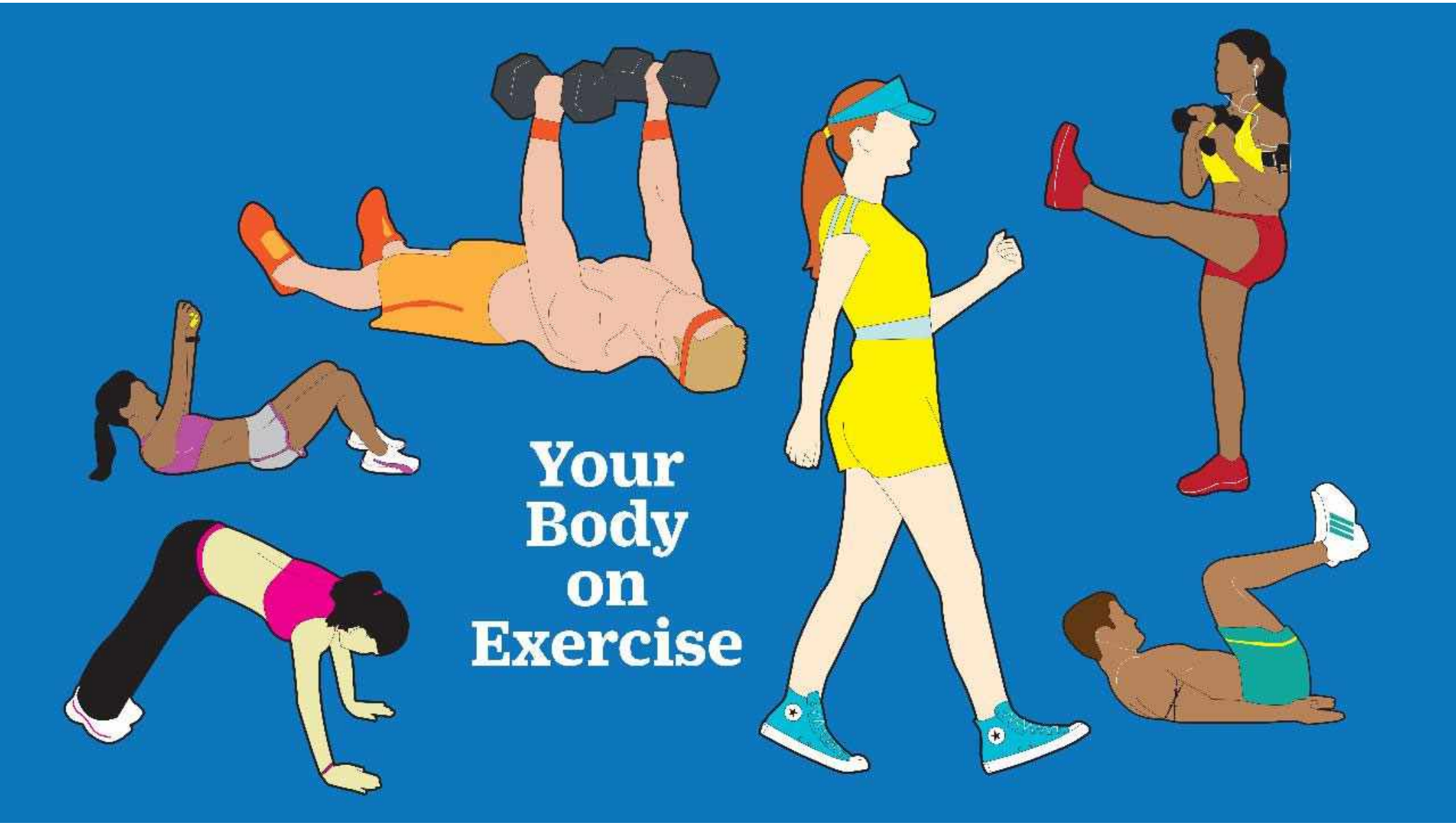
HIGH OMEGA 6:3 RATIO

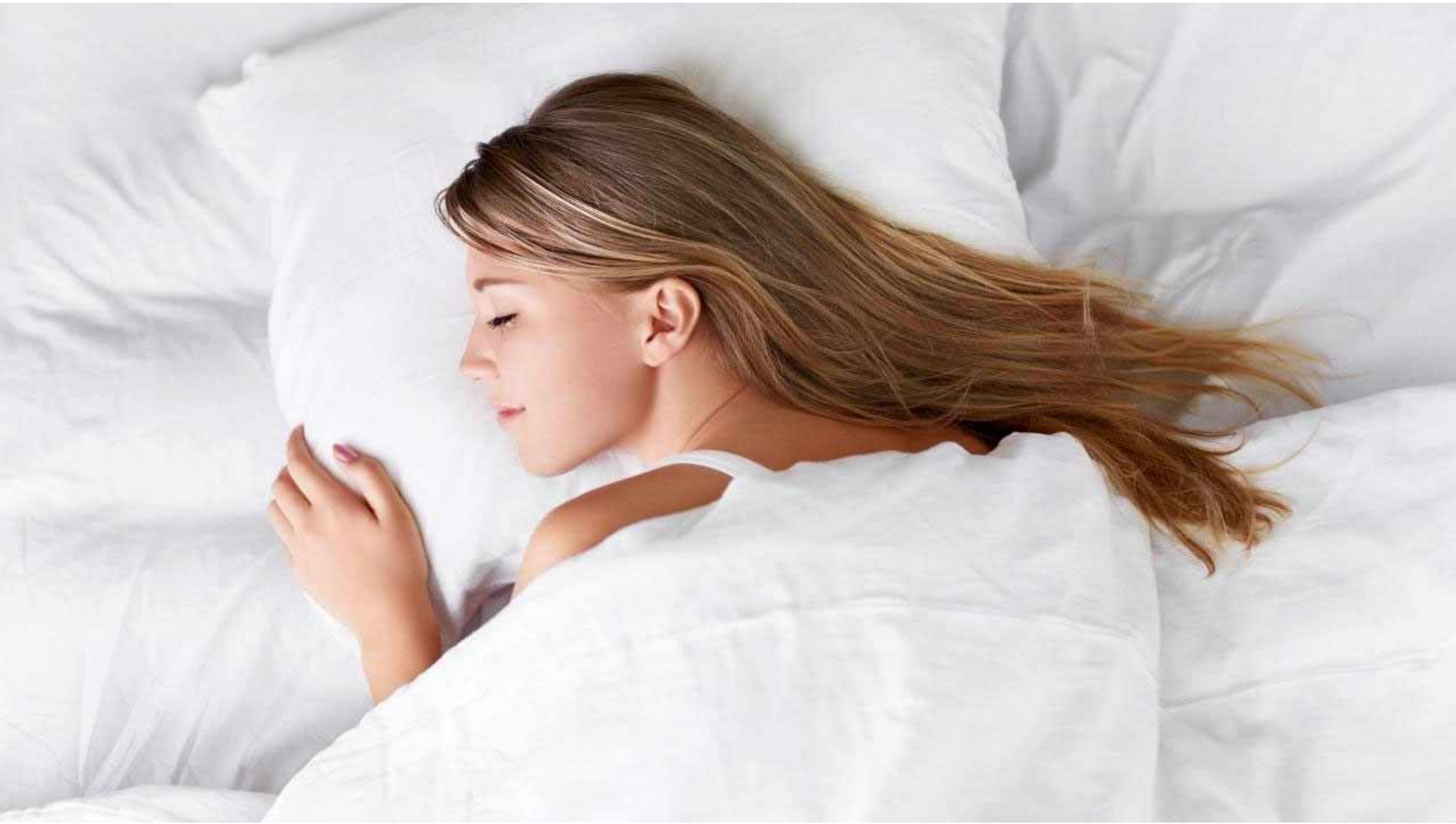
LOW THYROID HORMONES (T3 AND T4)

THYROID ANTIBODIES (HASHIMOTO'S)

Eat this Every Day

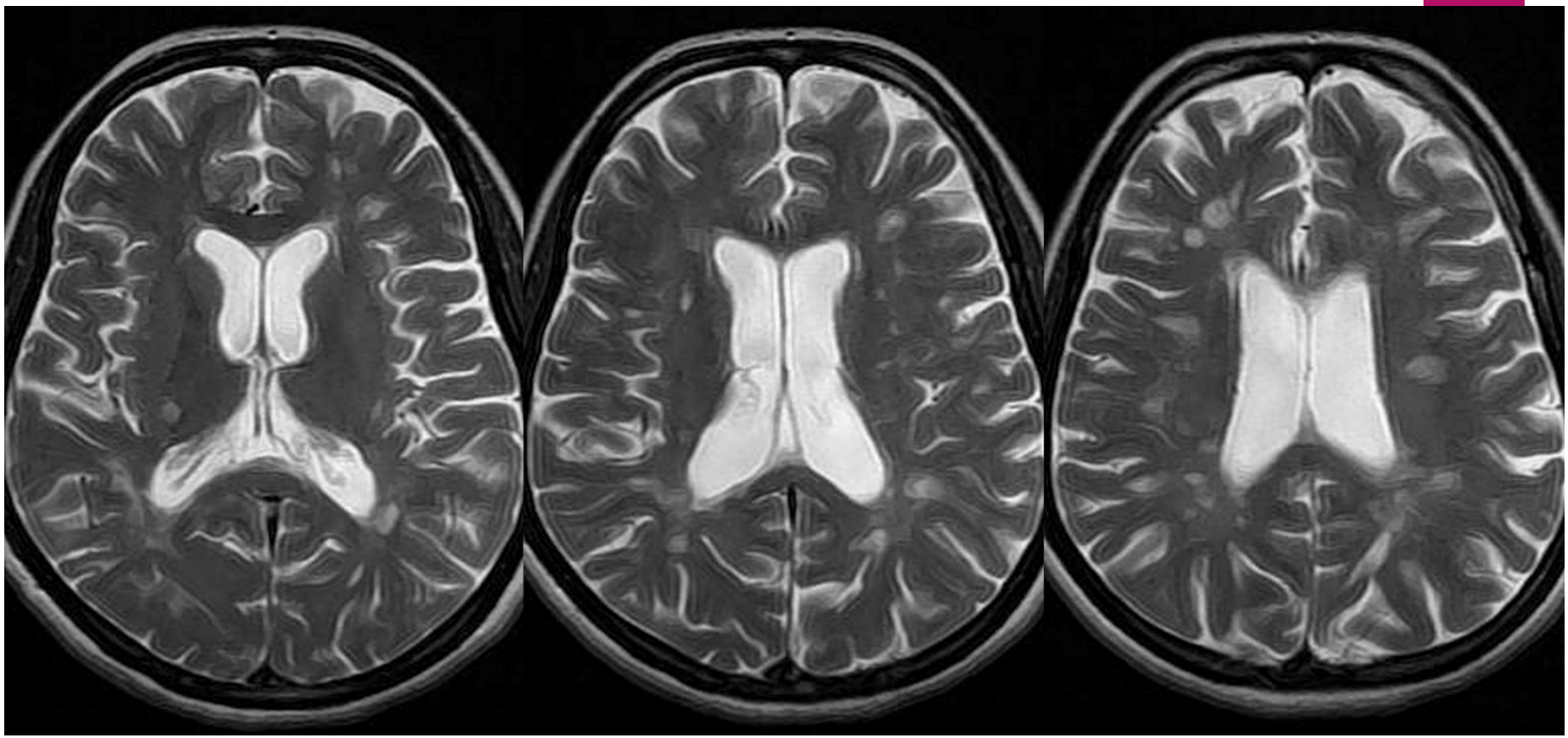



Your
Body
on
Exercise



Targeted Supplementation

Results



and counting

THIS IS Robert

Businessman, husband, father, and Alzheimer's sufferer

Robert's Clinical History and Findings

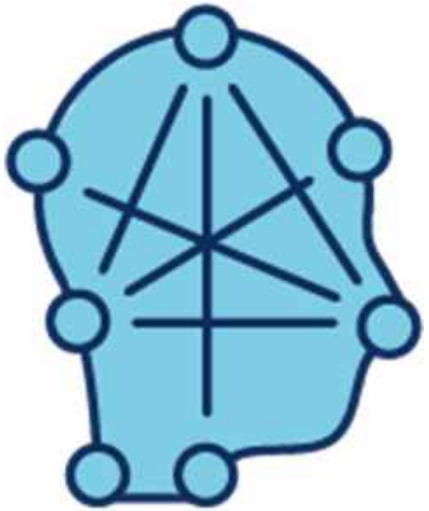
- 67-year-old male, small business owner, with a chief complaint of "memory loss"
- Difficulty with memory when working with clients and contracts
  - Would forget contracts he had previously discussed and names of clients he had known for years.
- Montreal Cognitive Assessment (MoCA) 19/30 - normal is 26 to 30.
  - Weakness with delayed recall (1/5 correct), sentence repetition, word fluency, visuo-spatial skills, executive functioning.
- MRI of the Brain – loss of brain volume, including the hippocampus, and iron deposits in the brain.
- CSF – findings consistent with Alzheimer's disease (low ATI and high P-tau).

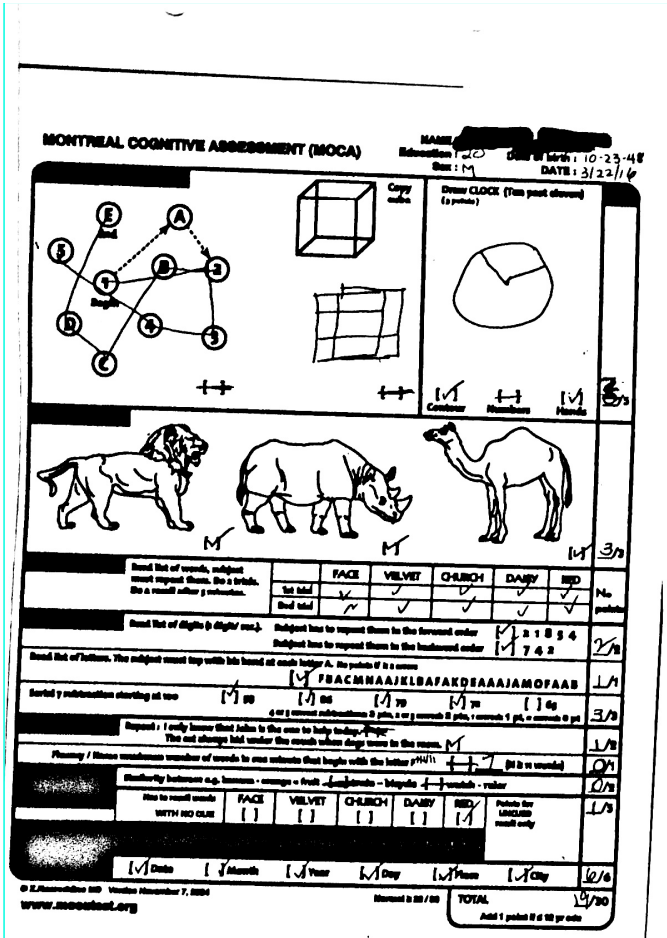
Robert's Timeline

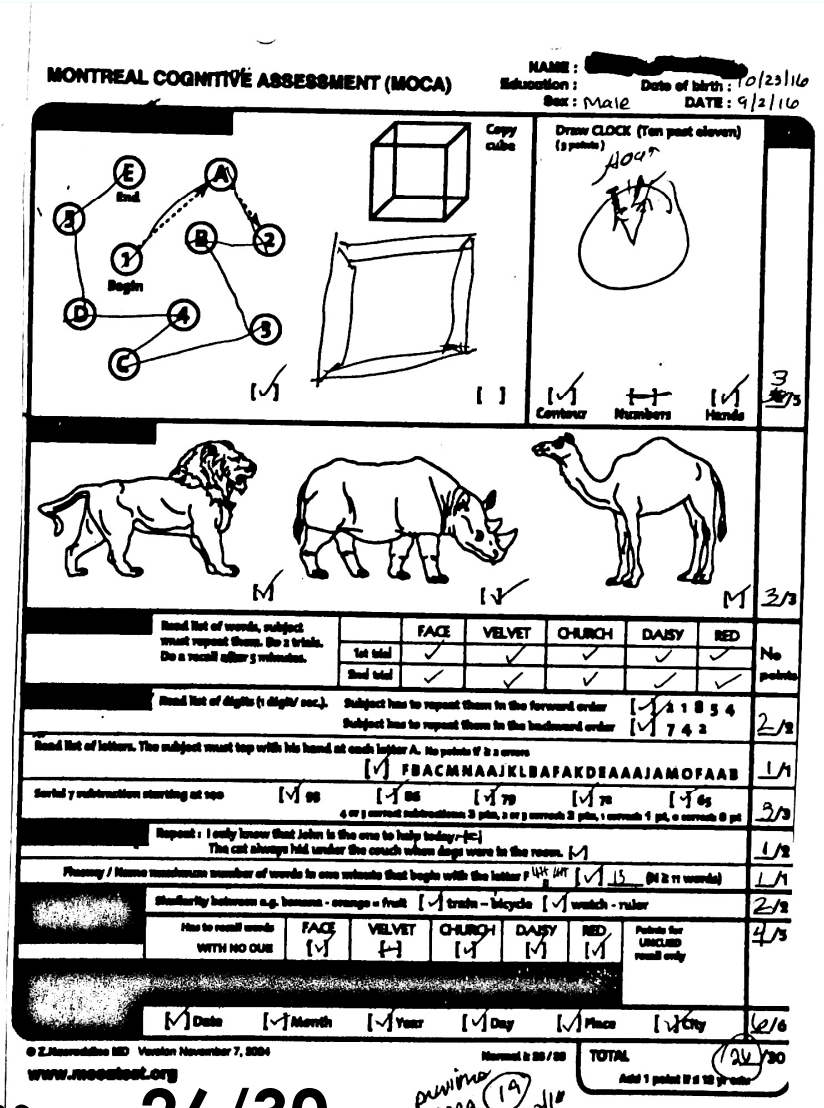
Laboratory Testing

- Increased Homocysteine
- Increased High-Sensitivity C-Reactive Protein
- Low Vitamin D
- Low Zinc
- Low Thyroid Hormone
- Low Magnesium
- High Omega 6:3 Fatty Acid Ratio

THE TRANSFORMATION







19/30 ⟶ 6 months ⟶ **26/30**

Journal of
Alzheimer's Disease & Parkinsonism

Bredesen et al., J Alzheimers Dis Parkinsonism 2018, 8:5
DOI: 10.4172/2161-0460.1000450

Case Report Open Access

Reversal of Cognitive Decline: 100 Patients

Dale E Bredesen[1*], Kenneth Sharlin[2], David Jenkins[3], Miki Okuno[3], Wes Youngberg[4], Sharon Hausman Cohen[5], Anne Stefani[5], Ronald L Brown[6], Seth Conger[6], Craig Tanio[7], Ann Hathaway[8], Mikhail Kogan[9], David Hagedorn[10], Edwin Amos[11], Amylee Amos[12], Nathaniel Bergman[13], Carol Diamond[14], Jean Lawrence[15], Ilene Naomi Rusk[16], Patricia Henry[16] and Mary Braud[16]

[1]Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA
[2]Sharlin Health and Neurology/Functional Medicine, Ozark, MO, USA
[3]NeuroHub, Sydney, Australia
[4]Youngberg Lifestyle Medicine Clinic, Temecula, CA, USA
[5]Resilient Health, Austin, TX, USA
[6]Carolina Healthspan Institute, Charlotte, NC, USA
[7]Rezilir Health, Hollywood, FL, USA
[8]Integrative Functional Medicine, San Rafael, CA, USA
[9]GW Center for Integrative Medicine, George Washington University, Washington, DC, USA
[10]Coastal Integrative Medicine, Jacksonville, NC, USA
[11]Department of Neurology, University of California, Los Angeles, Los Angeles, CA, USA
[12]Amos Institute, Los Angeles, CA, USA
[13]Center for Functional Medicine, Cleveland Clinic, Cleveland, OH, USA
[14]Mount Sinai Hospital, New York, NY, USA
[15]Lawrence Health and Wellness, Toccoa, GA, USA
[16]Brain and Behavior Clinic, Boulder, CO, USA

Abstract

The first examples of reversal of cognitive decline in Alzheimer's disease and the pre-Alzheimer's disease conditions MCI (Mild Cognitive Impairment) and SCI (Subjective Cognitive Impairment) have recently been published.

THIS IS Ed

Corporate executive, family man, and ALS sufferer

Clinical History

- 58-year-old male executive in the mining industry presented with a 12-month history of left leg weakness, "leg would drag when jogging."
- Healthy, no family history of ALS, only medication was ASA 81 mg daily, a B-complex, and fish oil.
- Initial EMG and C-spine MRI normal. Initial outside impression: lumbar radiculopathy, surgery considered (not performed).
- Second opinion: mild left leg weakness, rare gastrocnemius fasciculations, slightly spastic tone in left leg, brisk LE reflexes L>R. Normal sensory exam. Routine blood work (including B12) normal. Spinal fluid: elevated protein.
- Repeat EMG - "probable" ALS. FVC 5.19L (105% of predicted) and ALSFRS-R 47.

Sought Out Integrative Practitioners

- Outside Environmental Medicine practitioner – Diagnosed with mold toxin-related illness and MARCoNS. (Exposure 2 years prior discovered in a humidification unit in his home – unit replaced – but no specific home inspection or remediation done.) Treated with cholestyramine and BEG.
- However, over the next 7 months FVC went down to 100% and then 99%. ALSFRS-R stable at 47.
- Learned about The Wahls Protocol, contacted Dr. Terry Wahls who referred the patient to me.
- Labs: Homocysteine 11.7, MTHFR homozygous c677t, Omega 6:3 8.9, iodine 28, Free T4 1.0, Free T3 2.9, low total T3 74, vitamin D 42, normal H/H and B12 but MCV 101, elevated RBC mercury 0.0131 mcg/g, Cyrex Array 2 (intestinal antigenic permeability) ↑ actomyosin IgA, but occludin/zonulin and LPS IgG, IgA, and IgM were negative.

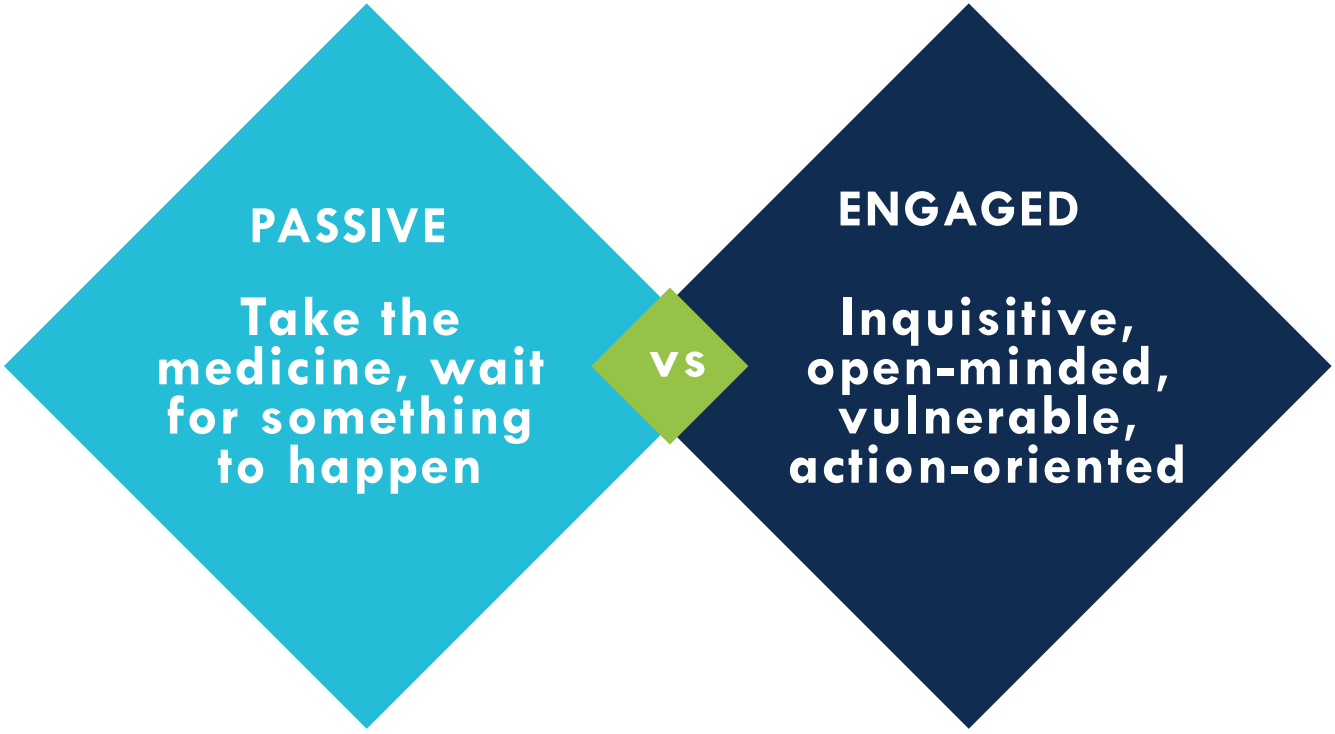
Diet, Lifestyle, and Targeted Supplementation

- Low carb, high fat, moderate protein anti-inflammatory "Wahls style" diet. Monitor weight.
- Omega 3 supplementation
- Probiotic 30 Billion CFU daily
- Detox nutritional support – NAC, broccoli sprout extract, milk thistle
- Methylation support
- Exercise evaluation including biometric analysis – personalized neuro fitness program emphasizing functional strength and balance.
- Stress resilience program utilizing patterned breathing linked to HRV and affirmations.

Follow up

- Returned to research medical center
  - Increased FVC up to 113% of predicted.
  - ALSFRS-R decreased by 1 point only over 9 months (expected rate is 1-point decrease per month).
  - Lower Extremity Functional Scale decreased only 2 points from 50 in 10/2016 to 48 in 5/2017.
- When last seen 2.5 years from the onset of symptoms patient reported feeling "stable…if not improved strength and function for day-to-day activities."
- At 5 years since diagnosis: "My health remains good and being quarantined allows me to stay very focused on executing my protocol. Perhaps the most enjoyable part is spending time with the grandsons including nine holes … every Sunday. It's just another reminder that life is good." July 26, 2020

THE ENGAGED APPROACH



Joseph Campbell

George Lucas

Thank you