NeuroDegenerative Conditions:

Toxic, Immunologic, and Endocrine Risk Factors

36th Annual Chiropractic Internists Symposium
Omaha, Nebraska
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Who is this guy?

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Opinion Leader – NuMedica, Inc.

Functional Medicine consultant

Alzheimer's Statistics

- 5.3 Million current Alzheimer's patients
- 6th Leading cause of death (currently)
- 1 new case in the US every 70 seconds
- $148 Billion annual costs due to Alzheimer's
- Average annual cost for an Alzheimer's Patient: $42, 641

- *Alzheimer's Association*

Where the Current Model Started

nature

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nature › letters › article

Letter | Published: 16 March 2006

A specific amyloid-β protein assembly in the brain impairs memory

Sylvain Lesné, Ming Teng Koh, Linda Kotilinek, Rakez Kayed, Charles G. Glabe, Austin Yang, Michela Gallagher & Karen H. Ashe ✉

Nature **440**, 352–357 (2006) | Cite this article

14 July 2022 Editor's Note: The editors of Nature have been alerted to concerns regarding some of the figures in this paper. Nature is investigating these concerns, and a further editorial response will follow as soon as possible. In the meantime, readers are advised to use caution when using results reported therein.

Where we are now...

"it looks like the original paper that established the amyloid plaque model as the foundation of Alzheimer's research over the last 16 years might not just be wrong, but a deliberate fraud."

https://wallstreetpro.com/2022/07/23/two-decades-of-alzheimers-research-was-based-on-deliberate-fraud-by-2-scientists-that-has-cost-billions-of-dollars-and-millions-of-lives/

> They concurred with his overall conclusions, which cast doubt on hundreds of images, including more than 70 in Lesné's papers. Some look like "shockingly blatant" examples of image tampering, says Donna Wilcock, an Alzheimer's expert at the University of Kentucky.

Science, Vol 377, Issue 6604, 2022

https://www.science.org/content/article/potential-fabrication-research-images-threatens-key-theory-alzheimers-disease

Alzheimer's disease (AD)
Pathology includes the accumulation of amyloid-β (Aβ) toxins, the formation of neuroprotofibrillary tangles (NFTs) by hyperphosphorylated tau proteins, and neurodegeneration resulting from the secretion of neurotoxins and inflammatory factors.
Molecular biomarkers, including APP, Tau, BACE1, ApoE, GLP1R, NGF, BDNF, GSK3B, CASP9, CLU, AGER, DPYSL2, and PNMT, play crucial roles in its pathogenesis.

Current Drug Targets:

Human GSK3B Protein (His Tag)
Mouse NGF Protein (No Tag)
Human NGF Protein (No Tag)
Human GLP1R Protein (hFc Tag)
Human Tau Protein (His Tag)
Human BACE1 Protein (His Tag)
Human RAGE Protein (No Tag)

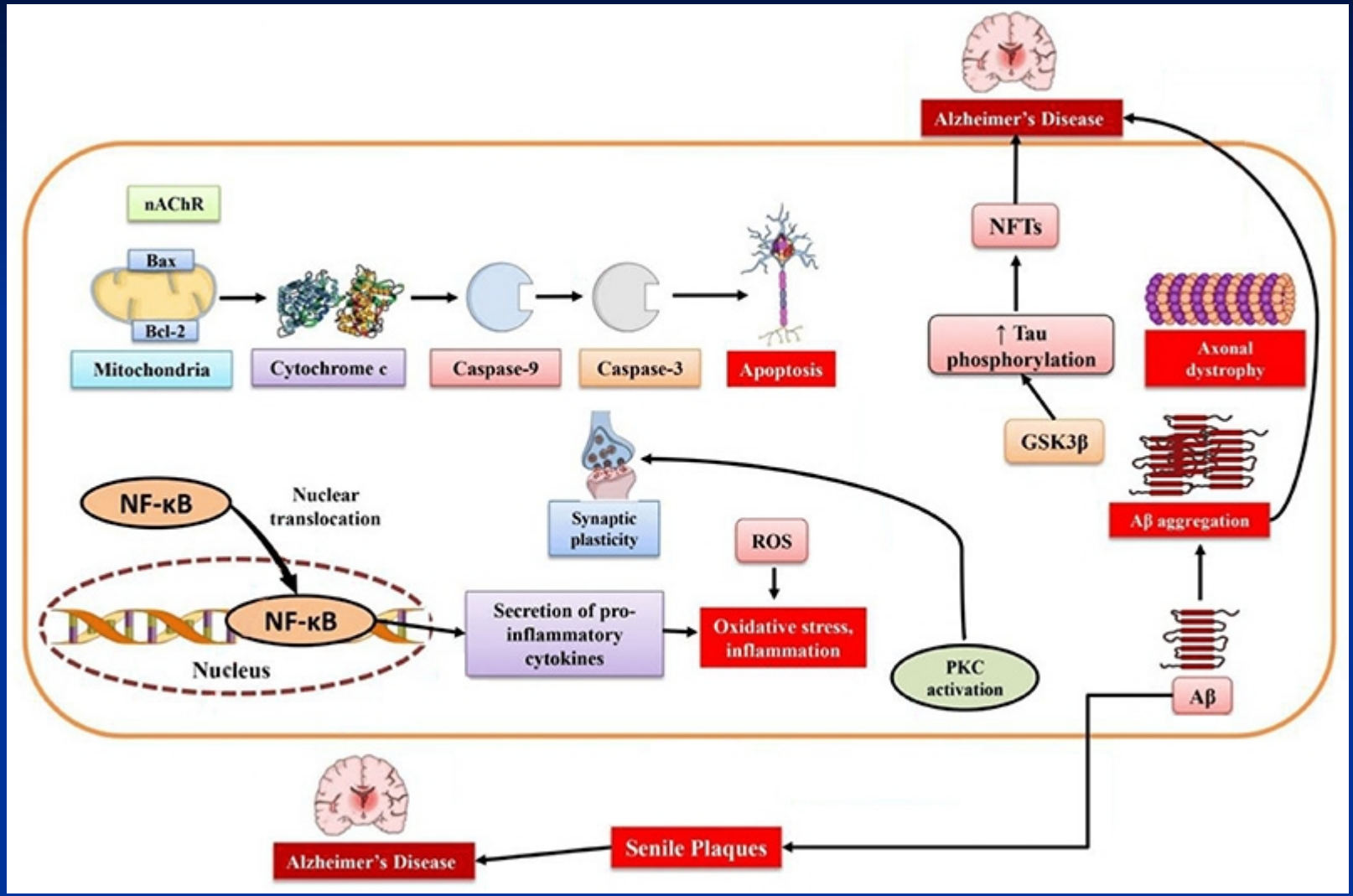
Human GLP1R Protein (His & AVI Tag)
Mouse RAGE Protein(His Tag)
Human APP Protein (hFc Tag)
Human Clusterin Protein (His Tag)
Mouse BDNF Protein (His Tag)
Human ApoE Protein (E3)(His & Trx Tag)
Human Beta-amyloid 40 (His & GST Tag)

Current Pharmaceutical trials for AD

Ongoing trials for novel AD therapeutics targeting Aβ, tau, neuroinflammation, and synaptic preservation.

- FDA approved anti- AB antibodies: aducanumab and lecanemab
- BACE inhibitors: Reduce Aβ production.
- NGF and BDNF: Enhance neuronal survival and synaptic plasticity.
- Targeting ApoE: Decreases AB deposition and enhances AB clearance.
- Targeting tau kinases: Prevents tau tangle formation.
- Targeting GLP-1R: Reduces neuroinflammation, attenuates oxidative stress, and neurotrophic effects.
- Targeting CASP9: Blocks the formation of NFTs

The conventional medical model for AD



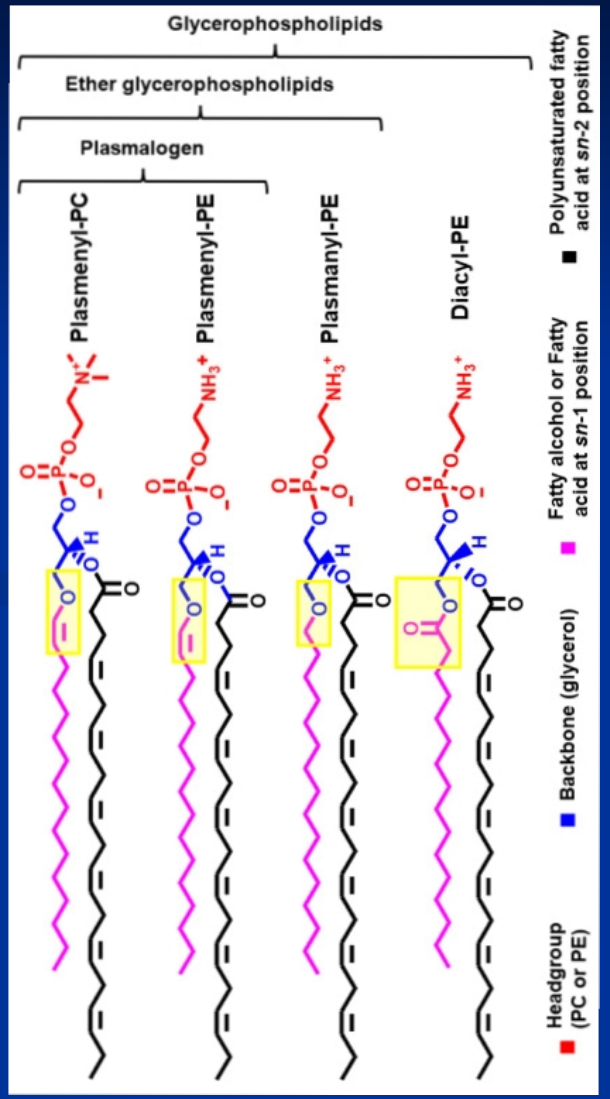
Sinobiological.com

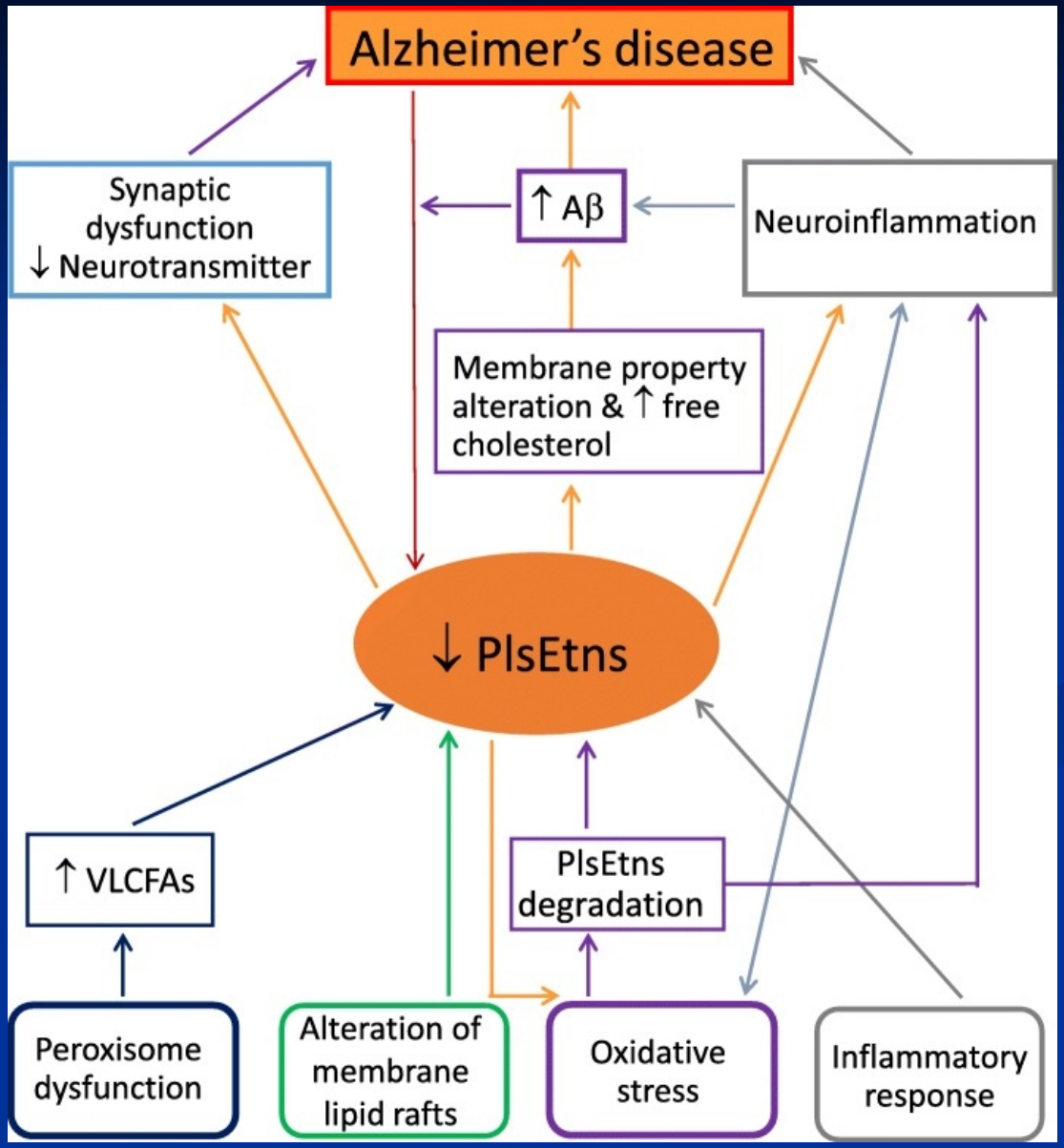
The Current Trend in Alternative Treatment:

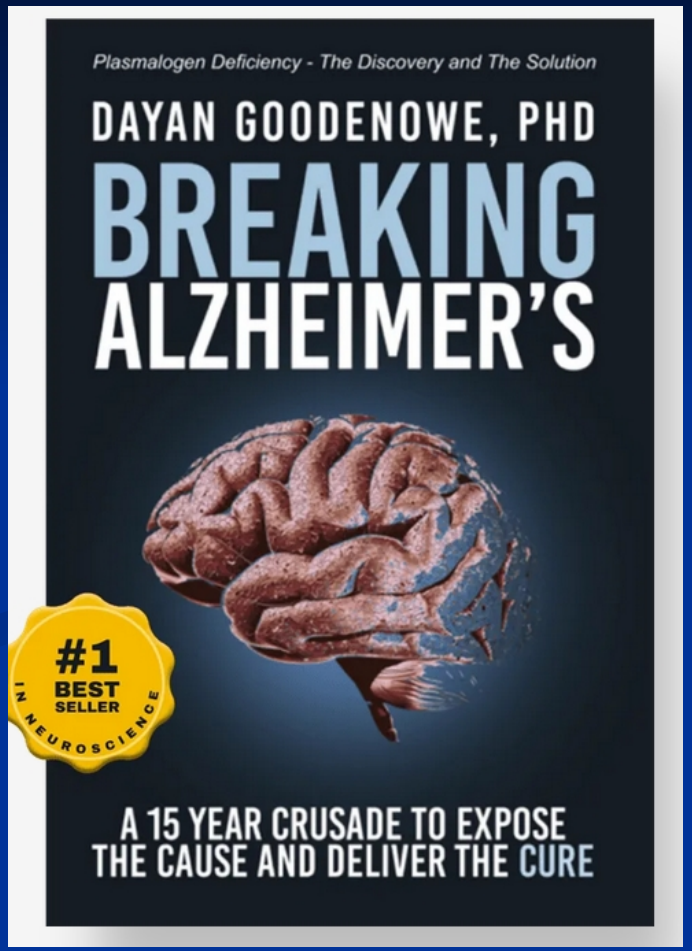
Plasmologens (Dr. Dayan Goodenowe)

- Glycerophosopholipids found in the cell membranes of the nervous, immune, and cardiovascular systems.
- Some initial evidence that plasmologen imbalance may cause membrane mediated abberations in inflammatory cascades, and may be involved in neurocognitive disorders such as Alzheimer's.
- Decreased levels of PlsEtns have been commonly found in AD patients, and were correlated with cognition deficit and severity of disease.
- Limited studies showed positive therapeutic outcomes with plasmalogens interventions in AD subjects and in rodents. Potential mechanisms may be related to the reduction of γ–secretase activity (catalyzes the synthesis of β-amyloid (Aβ))
- PlsEtns prevented neuronal cell death by enhancing phosphorylation of AKT and ERK signaling through the activation of orphan G-protein coupled receptor (GPCR) proteins.
- PlsEtns have been found to suppress the death of primary mouse hippocampal neuronal cells through the inhibition of caspase-9 and caspase-3 cleavages.

- *Su XQ, Wang J, Sinclair AJ. Plasmalogens and Alzheimer's disease: a review. Lipids Health Dis. 2019 Apr 16;18(1):100. doi: 10.1186/s12944-019-1044-1. PMID: 30992016; PMCID: PMC6466717.*
- *Bozelli JC Jr, Epand RM. Plasmalogen Replacement Therapy. Membranes (Basel). 2021 Oct 29;11(11):838. doi: 10.3390/membranes11110838. PMID: 34832067; PMCID: PMC8620983.*
- *Messias, M.C.F., Mecatti, G.C., Priolli, D.G. et al. Plasmalogen lipids: functional mechanism and their involvement in gastrointestinal cancer. Lipids Health Dis 17, 41 (2018). https://doi.org/10.1186/s12944-018-0685-9*







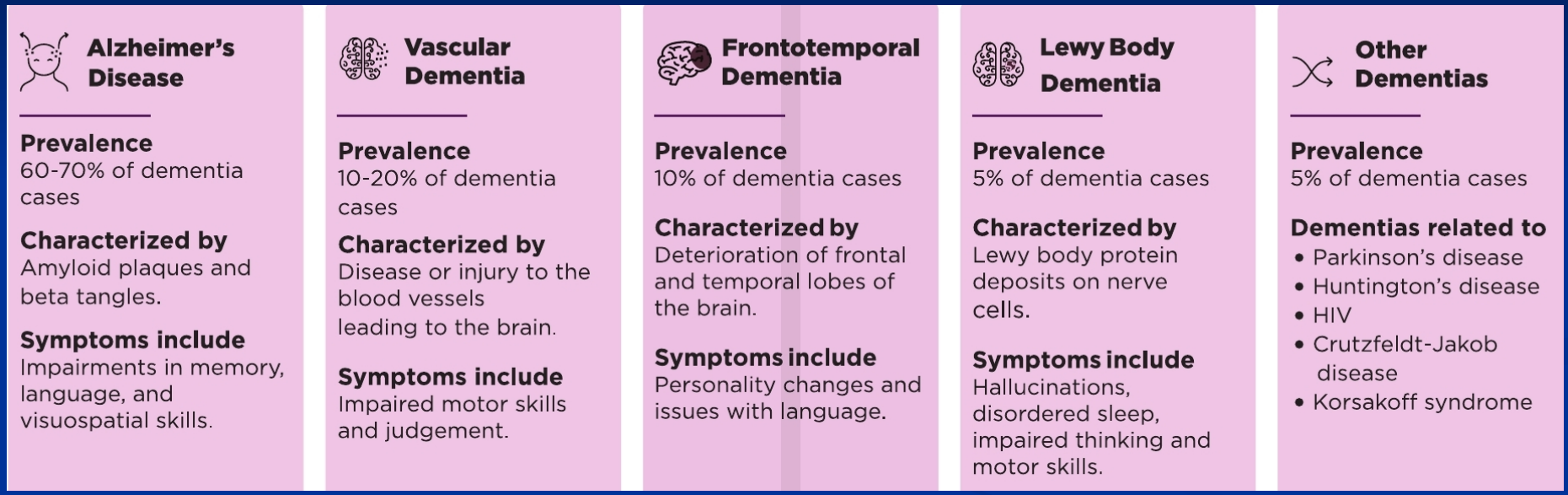
But the reality is that either neither conventional therapy nor alternative therapy will solve this with a single solution.

There is no Magic Pill

There are too many factors involved.

First Identify your patient through appropriate screening

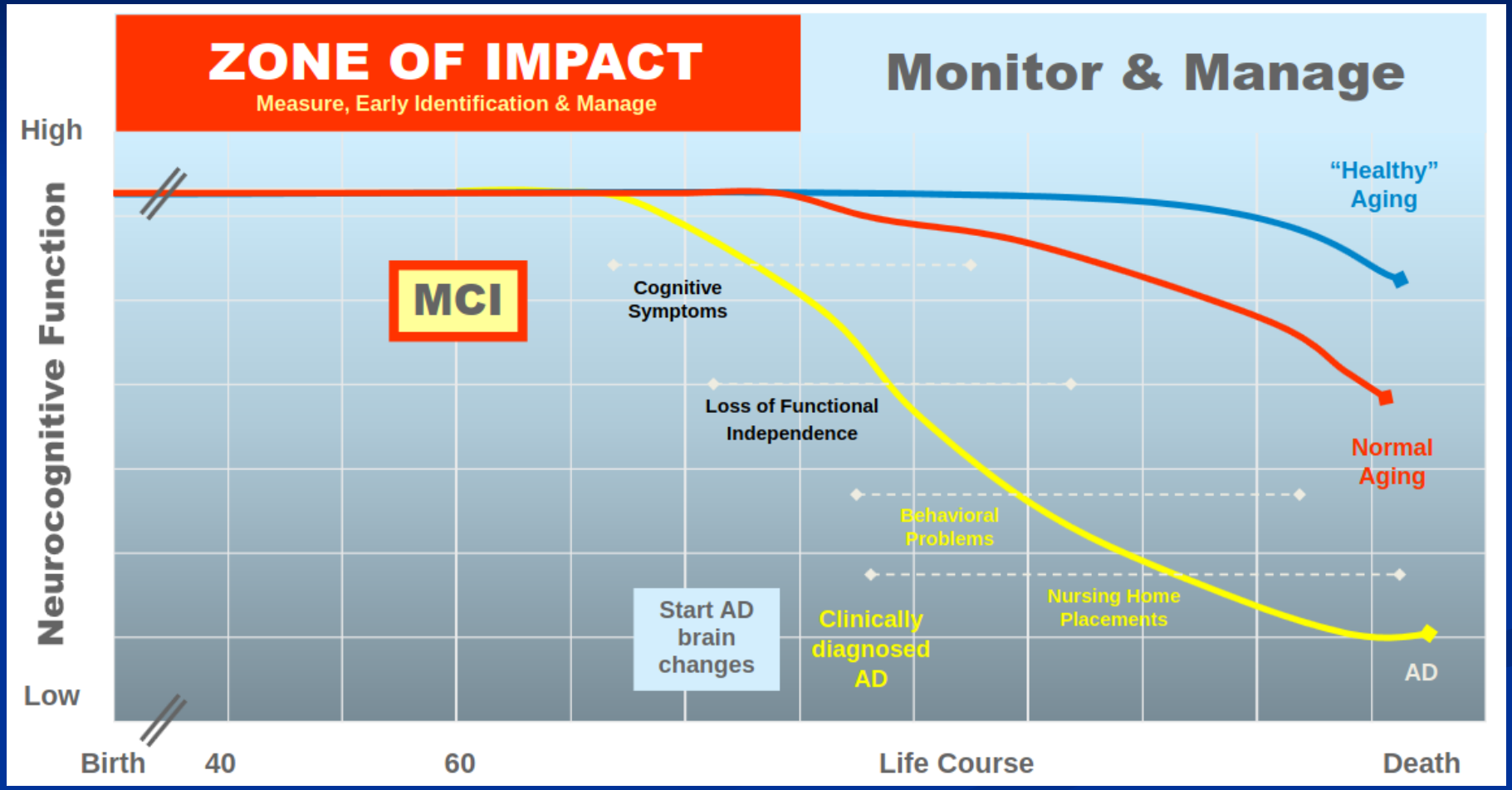
Identify subform of Dementia or other Neurocognitive disorder

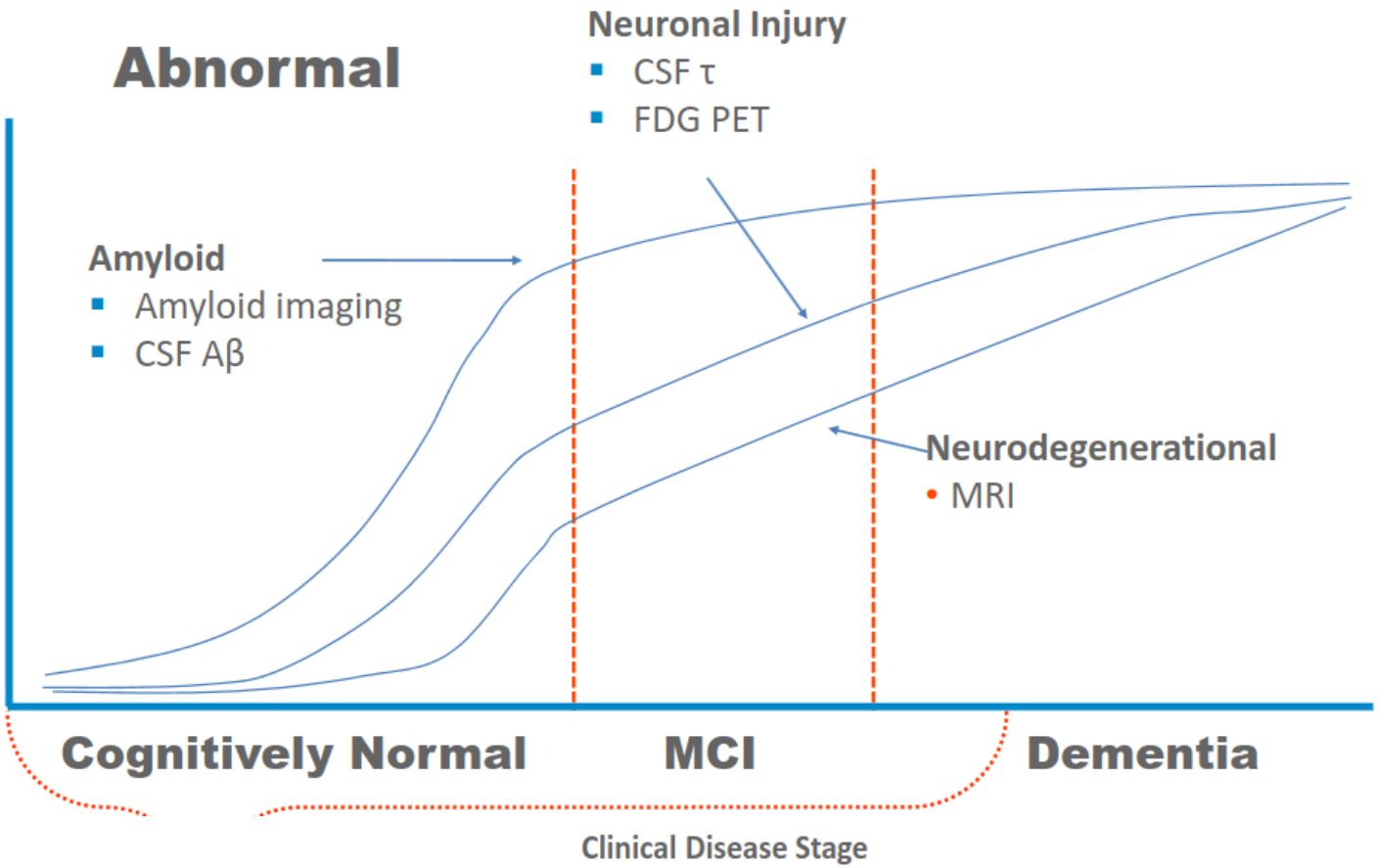


Initial Screening:

“How do you THINK you’re thinking” can get pretty subjective.

Quantify the subjective – Computerized, standardized testing





Adapted from: Mild Cognitive Impairment: *Ten Years Later; Ronald C. Petersen, PhD, MD;* ARCH NEUROL/VOL 66 (NO. 12), DEC 2009

Pathogenesis

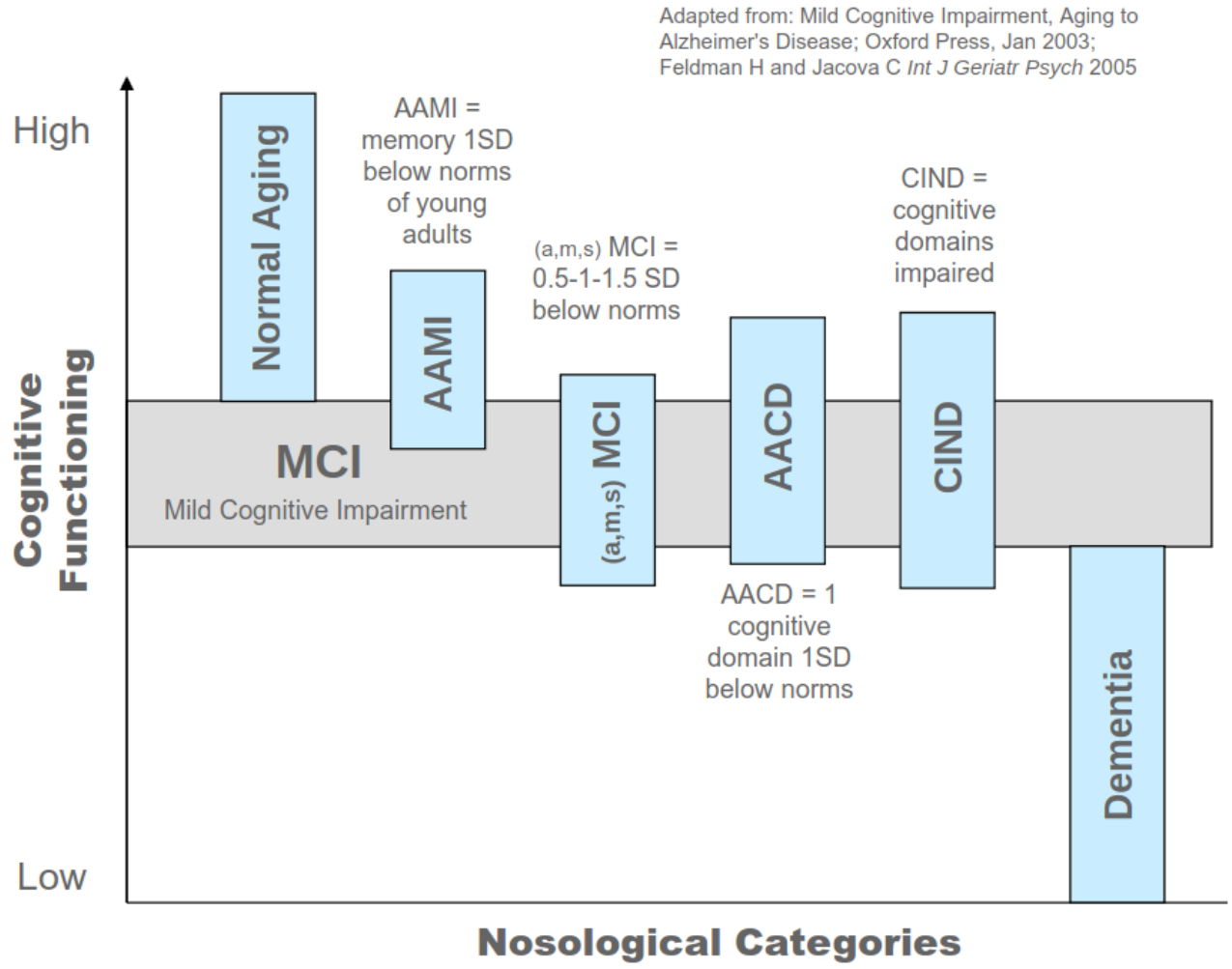
Clinical Classification

Clinical Classification		Degenerative	Vascular	Psychiatric	Medical Conditions
Nonamnestic MCI	Single Domain	FTD			
	Multiple Domain	DLB	VaD		
Amnestic MCI	Single Domain	AD		Depr	
	Multiple Domain	AD	VaD	Depr	

AD = indicates Alzheimer disease;
Depr = depression;
DLB = dementia with Lewy bodies;
FTD = frontotemporal dementia; and
VaD = vascular dementia.

Adapted from: Mild Cognitive Impairment: *Ten Years Later; Ronald C. Petersen, PhD, MD;* ARCH NEUROL/VOL 66 (NO. 12), DEC 2009

Memory Complaint… Condition Segmentation



aMCI = Amnesic MCI, memory complaint, memory impaired for age; usually of a degenerative nature; 1.5 SD below normal subjects—while other domains might be very mildly impaired at perhaps less than 0.5 SD below appropriate comparison subjects. …this is the most common, and most of the literature on the topic refers to this form of the disorder. In all likelihood, when this form of MCI is on a degenerative basis, the vast majority of cases will progress to AD.

mMCI = Multiple-domain MCI; two or more domains including memory; 0.5 to 1.0 SD level of impairment. The diagnosis of multiple-domain MCI is a clinical judgment on the part of the person evaluating the subject and cannot be made solely on the basis of neuro-psychological testing. Persons with multiple-domain MCI may progress to AD or perhaps to vascular dementia.

sMCI = Single non-memory impairment; characterized by a person having a relatively isolated impairment in a single non-memory domain such as executive function… These mild conditions could represent incipient forms of other dementias. For example, the executive symptoms may lead to frontotemporal dementia. (2001 Petersen et.al.)

CIND = Cognitive impairment, no dementia includes encephalopathy, delirium, MR, etc. (1997 Graham et.al.) Canadian Study of Health and Aging

AACD = Age associated cognitive decline. Objective cognitive decline (1994 Levy et.al.) International Psycogeriatric Association

AAMI = Age associated memory impairment. (1986 Crook et.al.) NIMH workgroup.
Benign senescent forgetfulness = (1962 Kral et.al.)

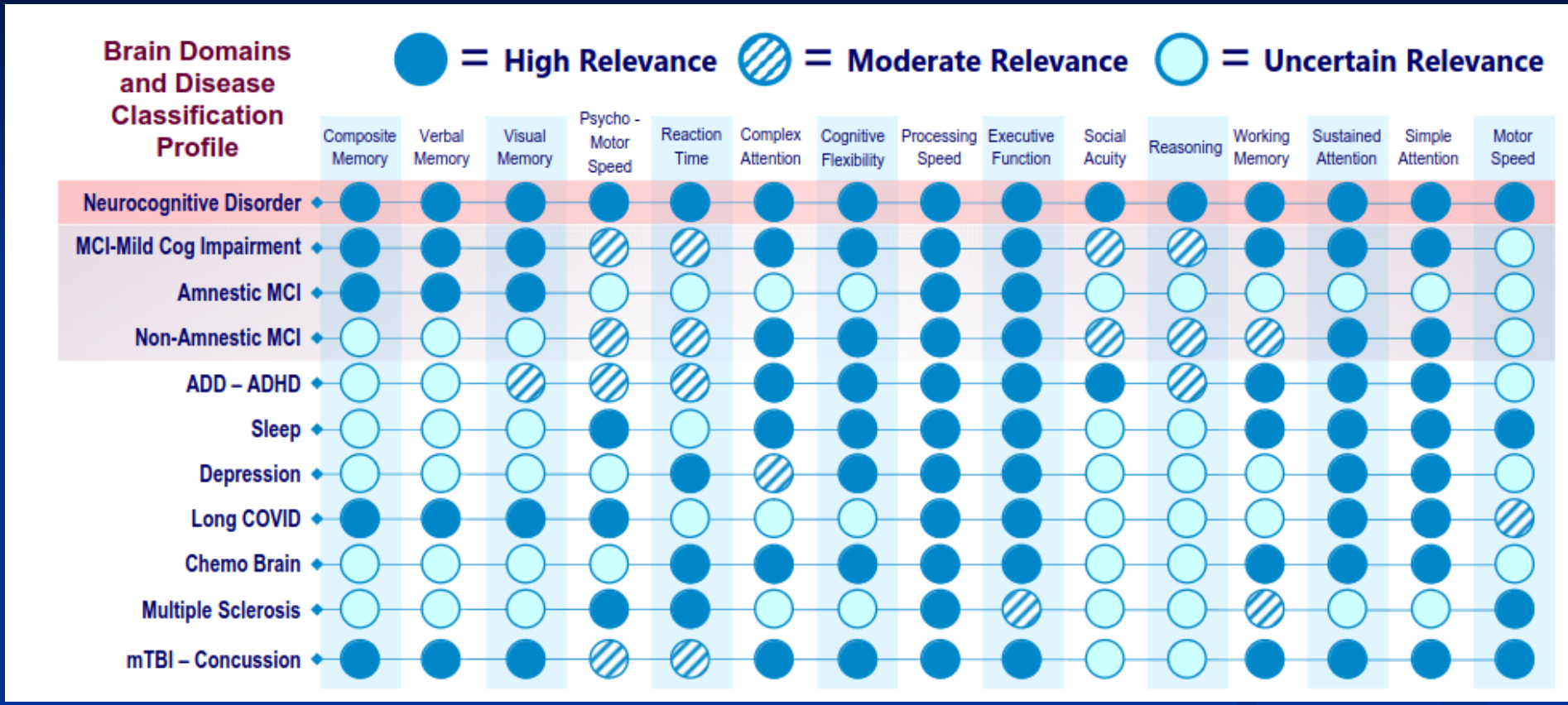
Patient Profile:	Percentile Range				> 74	25 - 74	9 - 24	2 - 8	< 2
	Standard Score Range				> 109	90 - 109	80 - 89	70 - 79	< 70
Domain Scores	Subject Score	Standard Score	Percentile	VI**	Above	Average	Low Average	Low	Very Low
Neurocognition Index (NCI)	NA	84	14	Yes			x		
Composite Memory	60	52	1	Yes					x
Verbal Memory	30	54	1	Yes					x
Visual Memory	30	68	1	Yes					x
Processing Speed	16	83	13	Yes			x		
Executive Function	8	91	27	Yes		x			
Psychomotor Speed	112	97	42	Yes		x			
Reaction Time*	938	92	30	Yes		x			
Complex Attention*	22	89	23	Yes			x		
Cognitive Flexibility	6	90	25	Yes		x			
Total Test Time (min: secs)	34:12				Total time taken to complete the tests shown.				

Amnestic MCI

Non-Amnestic MCI

Www.CNSVS.com

Patient Profile	Percentile Range				> 74	25 - 74	9 - 24	2 - 8	< 2
	Standard Score Range				> 109	90 - 109	80 - 89	70 - 79	< 70
Domain Scores	Patient Score	Standard Score	Percentile	VI**	Above	Average	Low Average	Low	Very Low
Neurocognition Index (NCI)	NA	75	5	Yes				X	
Composite Memory	85	75	5	Yes				X	
Verbal Memory	39	58	1	Yes					X
Visual Memory	46	103	58	Yes		X			
Psychomotor Speed	133	75	5	Yes				X	
Reaction Time*	811	78	7	Yes				X	
Complex Attention*	12	83	13	Yes			X		
Cognitive Flexibility	19	66	1	Yes					X
Processing Speed	39	81	10	Yes			X		
Executive Function	20	66	1	Yes					X
Simple Attention	40	107	68	Yes		X			
Motor Speed	92	78	7	Yes				X	



Next, apply the Functional Medicine model of Cause-Driven Multi-factorial Pathologies to a fundamentally interlinked model of NeuroCognitive Disorders.

For example, we *do not see autoimmune as being separate issues, but rather separate manifestations of a fundamentally interlinked core pathophysiology involving Food Allergies and Stealth Infections.*

Why are neurocognitive disorders different in this paradigm?

Systemic inflammation and disease progression in Alzheimer's Disease

Both acute and chronic systemic inflammation, associated with increases in TNF-a; is associated with an increase in cognitive decline in Alzheimer's disease.

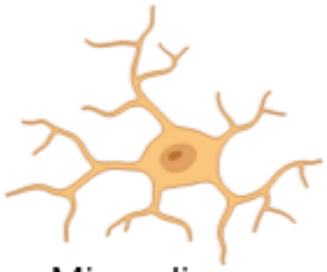
Twice the rate of decline over a 6 month period . High baseline levels of TNF-a were associated with a 4x increase in the rate of cognitive decline.

C. Holmes, et al. Neurology, Sept 2009; 73; 768-774

Great – this merely narrows down any possible etiology to any and all intrinsic and extrinsic inflammatory factors.

No big deal.

Activation of Microglial Toxicity



Microglia

Stimulus Factor

Activated Microglia

- Genetic predisposition
- Infections
- Toxic exposures
- Oxidative Stress
- Mitochondrial dysfunction
- Physical trauma
- Food intolerance
- Dysbiosis
- Nutritional deficit
- Metabolic imbalances

Neurotrophic Factors: BDNF, NGF, GDNF, NT 3/4

Growth Factors: bFGF, HGF

Excitatory amino acids: Glutamate, histamine

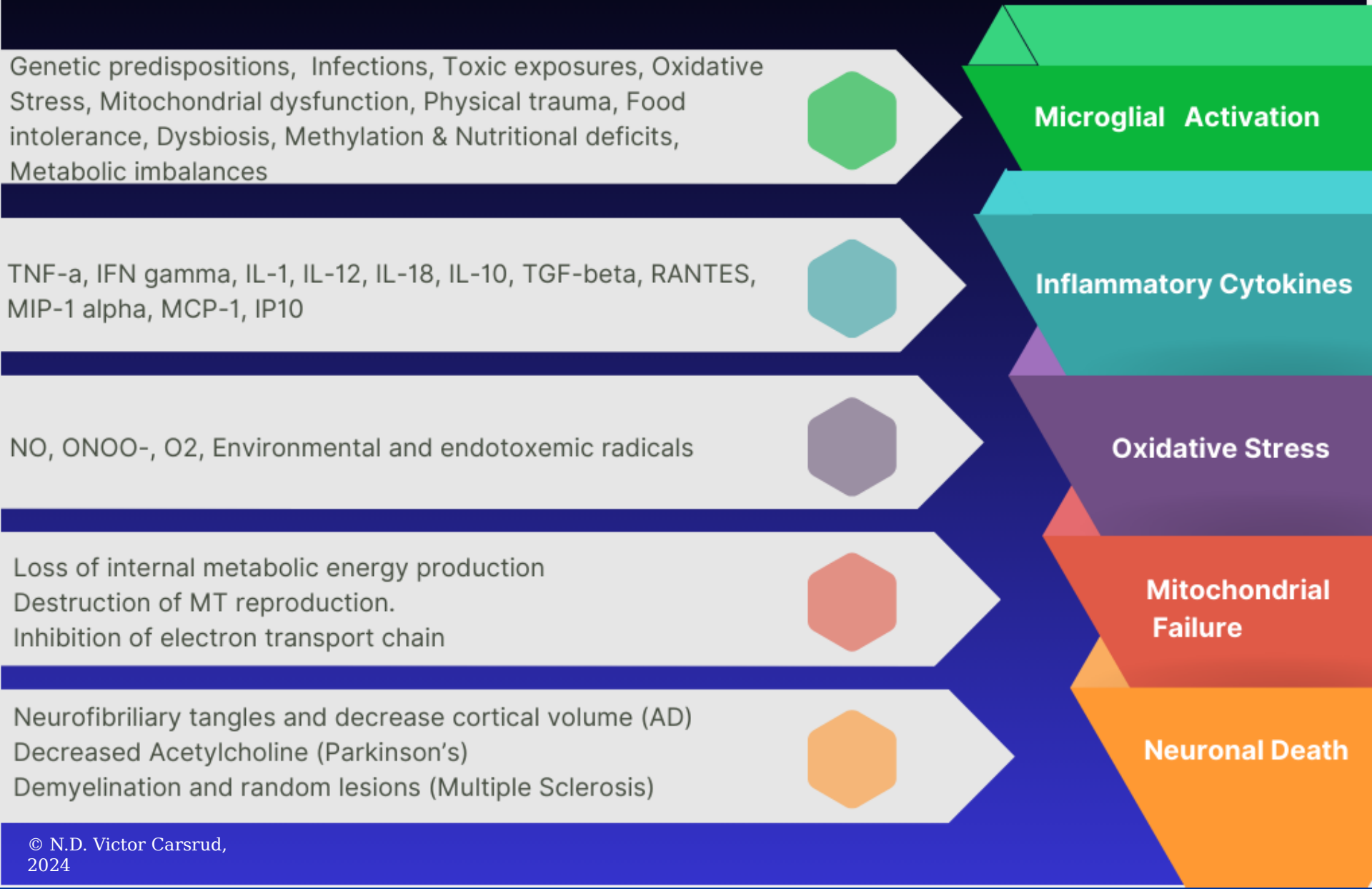
Reactive Oxidative Species: NO, ONOO-, O_2-

Proteases: MMP, Cathepsin

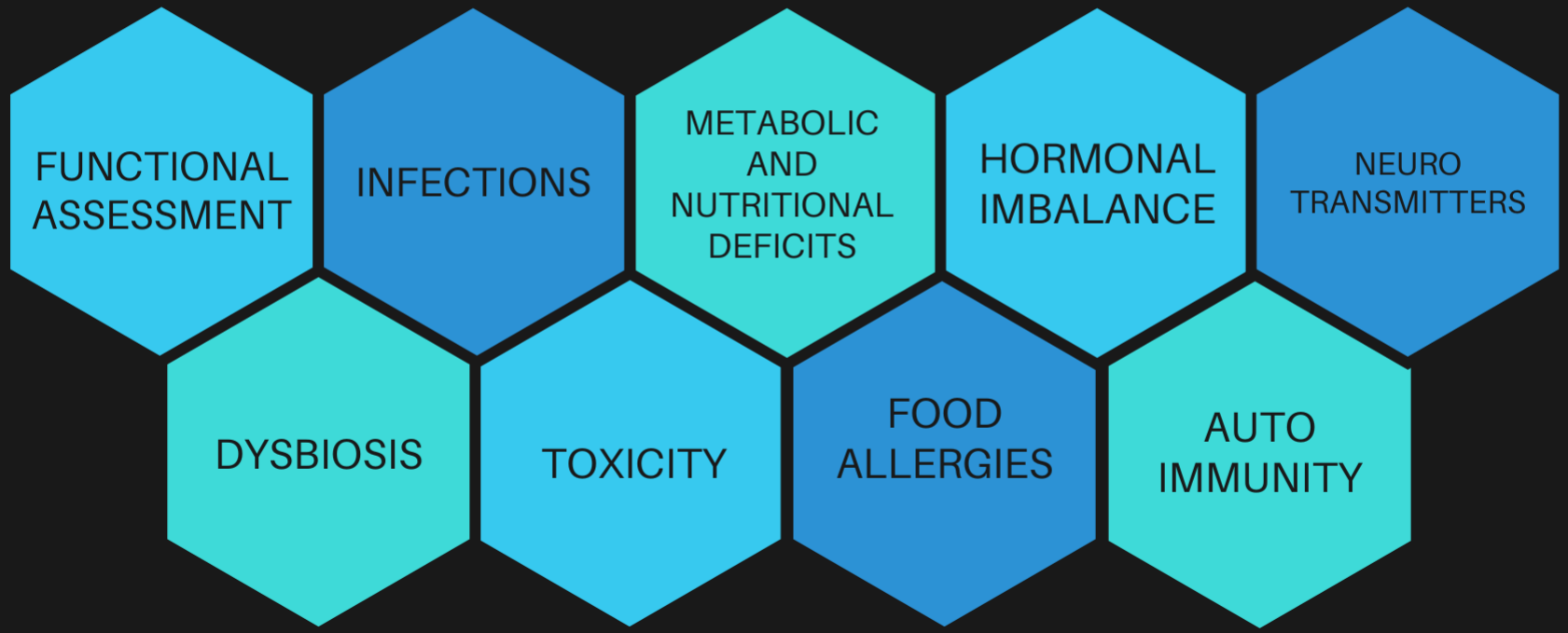
Nucleic Acid disruption: ATP, UDP

Cytokine/Chemokine regulation: TNFα, IFN-γ, IL-1, IL-6, IL-12, IL-18, IL-10, TGF-β, RANTES, MIP-1α, MCP-1, IP10

A Functional Medicine Model of Neurocognitive Decline



Functional Medicine Assessment of Neurocognitive Disorders



Neurocognitive Assessment - Overview

Metabolic assessment

- Insulin, blood sugar, HbA1c, homocysteine, lipids, inflammatory markers
- Thyroid and hormonal imbalances

Genetic factors

- Apo E, COMT, MTHFR, MTR/MTRR, CBS, AHCY

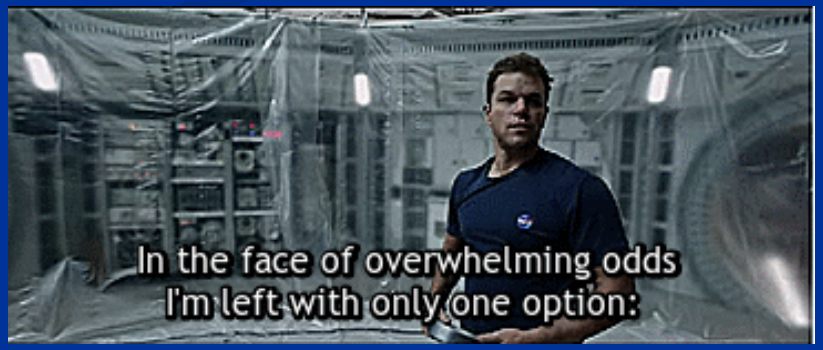
Food Allergies

Neurotransmitters – especially excitatory ie. Glutamate

Toxins – environmental, heavy metals, mycotoxins, PFA's.

Autoimmune factors

- TPO/TG Ab
- Anti-neuronal antibodies
- Anti-receptor antibodies
- Cytokine analysis

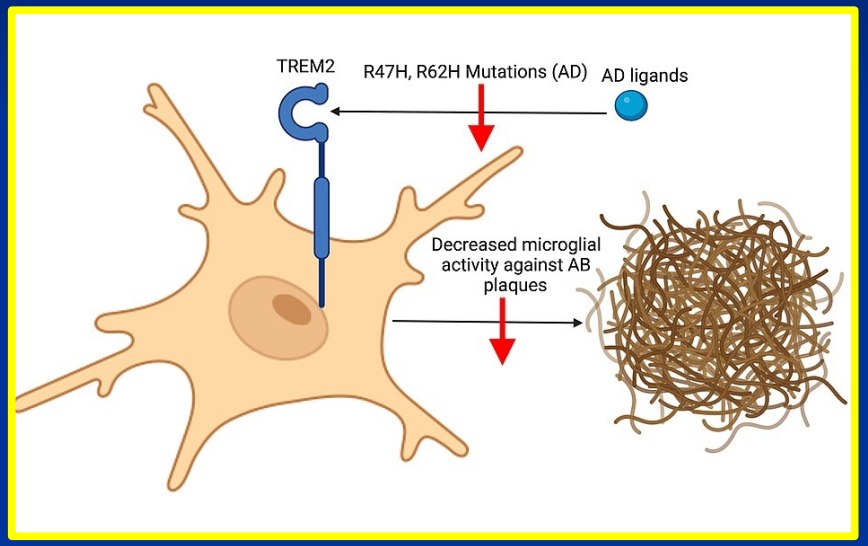


Infections

- HSV, CMV, Lyme, Strep, Yersina, C. pneumoniae

Genetics

- Apo E 4/4 – *principle cholesterol transporter in the brain, and inhibitor of the classical complement pathway (C1q)*
- TREM2 – *reduces microglial response to the formation of plaques*
- CD33 – *myeloid and lymphoid cell transmembrane receptor associated with expression of TREM2. Reduces phagocytosis in microglia against plaques.*



NeuroCognitive Patient Examples

Look at the Trends

- Genetic predisposition – Apo E4
- Infections – HSV 1, EBV, Lyme
- Toxic exposures – environmental, mycotoxins
- Oxidative Stress
- Mitochondrial dysfunction
- Physical trauma - TBI
- Food intolerance – gluten, dairy, etc.
- Dysbiosis - endotoxemia
- Methylation defects.
- Nutritional deficit – Amino acids, Magnesium, iodine, methylation
- Metabolic imbalances – blood sugar, homocysteine, uric acid, hormones

Patient One Summary
The Basics

- FBS – 240, HbA1c – 8.9
- Food allergy: IgG positives to Gluten, Dairy, and Egg
- Tot chol 274, LDL 174, HDL 35, Trig 326
- Homocysteine – 13
- Toxins: Nickel, Thallium, Arsenic, Glyphosate, Tiglylclycine, Ochratoxin A, Aflatoxin B1Atrazine, DMDTP, misc PFA’s

Patient 2 Summary
A Little More Data

Vit D 19.2 L *

FT3 - 2.3 L *

Total testosterone - 383

Prolactin 10.1

PSA 0.6

Food allergy: GLUTEN, EGG

IgE high (159 H)

Infections: EBV, Strep A, CMV, Lyme

Auto-antibodies:

Anti-Purkinje, Anti-dopamine

ACh - 8.78 H
5HTP - 8.93 L
low trending PEA
Phosphatidylcholine
Tiglyglycine

MOLD and Hvy metals
Atrazine, Glyphosate

Chaetoglobosin
(induces neural apoptosis)

Low level PFAs

Patient 3 Summary

(The Whole Diagnostic Enchilada)

Food Allergies:DAIRY (cow), GLUTENApple, Apricot, black pepper, cauliflower, carrot, cucumber, orange, peach, lemon, raspberry, potato

EGG, Goat milk, almond, cataloupe, celery, clam, coffee, green bean, cabbage, mustard, hops, oyster, spinach, tomato, watermelon, peanut

Anti- LPS - dysbiosis

Infection:EBV, HSV1 and 2, Streptococcus A

Anti-tubulin (dymylenation)

Anti Neuro Specific endolase (autonomic NS)

Anti-Voltage gated calcium channels and AntiTinin (MSK)

Anti-RAGE pepited and anti-Endothelian A receptor (Autoimmunity)

Anti-dopamine receptor and anti-dipeptidylaminopepdiase protein 6 (inflammation)

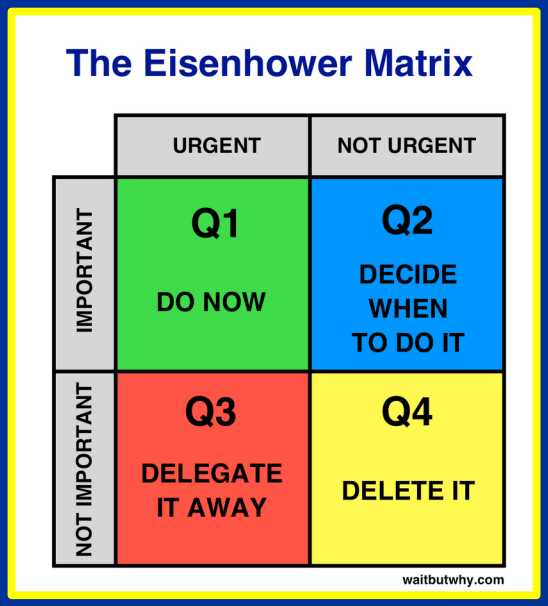
Organic Acids:
Adipic Acid 10.9 H (junk food - needs l-carnitine)
Malic Acid <0.2 L (MT need)
Vit B5 33.38 H
phenyllactic acid 0.31 H (dysbiosis)
Citramalic Acid 11.28 H (yeast indicator)
HPHPA 670 HH (clostridial species)

Neurotransmitters:
Glutamate 4501.13 H
5-HTP 9.07 L
(serotonin low normal)

Toxins:
Mycotoxins: aflatoxin G1, G2, M1, Fumosins B3, Satratoxin, T-2 Toxin (DON, Citrinin)

Metals:
Aluminum, Tin*, tellurium (antimony, barium, cadmium)
Chemicals
Glyphosate **
BPA **

Where to Start?



- Diet and Exercise
- Metabolism
- Hormones
- Food Allergies
- Dysbiosis
- Mitochondria and Methylation
- Detox
- Autoimmune
- Stimulate nerve growth

The Basics:
Diet and Exercise

Exercise and AD

Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer's Disease
Assessment of on ADAS cog scal over 18 months, n=138, t - 24 weeks at avg 142 min exercise/wk.
Significantly increased cognitive results in exercisers vs non-exercisers.
Nicola T Lautenschlager; Kay Cox, Leon Flicker, JAMA, Sept 3, 2008; Vol 300, No 9

Walking 6 mi/wk maintains cognitive function and brain volume, compared to 5 point MMSE decrease over same time period in non-exercisers
Neurology Reviews, Jan 2011

Exercise and AD

Exercise training increases size of hippocampus and improves memory, N=120, T - 1 yr, measurement of BDNF, hippocampal volume, and cognitive function at 6 months and 1 year.

Aerobic exercise group showed increases in hippocamal volume and increases in performance.. Greater increases in BDNF associated with greater increases in hippocampal volume. Annual increase in hippocampal volume of 1-2%. Compared to decrease of 1-2% decrease annually.

Physical activity similar in extent to being 3 years younger in age and were associated with a 20% lower risk of cognitive impairment.

Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. JAMA. 2004 Sep 22;292(12):1454-61. doi: 10.1001/jama.292.12.1454. PMID: 15383516.

What’s the best exercise?

The one they’ll do.

Fasting

Day 1: Drop in blood sugar and insulin, continues throughout
Day 2: Weight loss begins as body passes into ketosis
Day 3: Peak in Autophagy and induced HGH levels
Day 4: Plateau of Intestinal, musculoskeletal, and Immune stem cells

- Fasting is easier when already in a ketogenic state.
- Milder effects can be seen with Intermittent Fasting.
- Similar effects can be had with a guided Fasting Mimicking Diet for 3-5 days once a month.

- Wilhelmi de Toledo F, Grundler F, Bergouignan A, Drinda S, Michalsen A. Safety, health improvement and well-being during a 4 to 21-day fasting period in an observational study including 1422 subjects. PLoS One. 2019 Jan 2;14(1):e0209353. doi: 10.1371/journal.pone.0209353. PMID: 30601864; PMCID: PMC6314618. https://pubmed.ncbi.nlm.nih.gov/30601864/
- Antunes F, Erustes AG, Costa AJ, Nascimento AC, Bincoletto C, Ureshino RP, Pereira GJS, Smaili SS. Autophagy and intermittent fasting: the connection for cancer therapy? Clinics (Sao Paulo). 2018 Dec 10;73(suppl 1):e814s. doi: 10.6061/clinics/2018/e814s. PMID: 30540126; PMCID: PMC6257056. https://pubmed.ncbi.nlm.nih.gov/30540126/

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CLINICAL AND TRANSLATIONAL REPORT

A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan

Sebastian Brandhorst[15], In Young Choi[15], Min Wei, Chia Wei Cheng, Sargis Sedrakyan, Gerardo Navarrete, Louis Dubeau, Li Peng Yap, Ryan Park, Manlio Vinciguerra, Stefano Di Biase, Hamed Mirzaei, Mario G. Mirisola, Patra Childress, Lingyun Ji, Susan Groshen, Fabio Penna, Patrizio Odetti, Laura Perin, Peter S. Conti, Yuji Ikeno, Brian K. Kennedy, Pinchas Cohen, Todd E. Morgan, Tanya B. Dorff, Valter D. Longo

[15] Co-first author

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DOI: https://doi.org/10.1016/j.cmet.2015.05.012 | CrossMark

Article Info

Highlights

- FMD rejuvenates the immune system and reduces cancer incidence in C57BL/6 mice
- FMD promotes hippocampal neurogenesis and improves cognitive performance in mice
- FMD causes beneficial changes in risk factors of age-related diseases in humans

Summary

Prolonged fasting (PF) promotes stress resistance, but its effects on longevity are poorly understood. We show that alternating PF and nutrient-rich medium extended yeast lifespan independently of established pro-longevity genes. In mice, 4 days of a diet that mimics fasting (FMD), developed to minimize the burden of PF, decreased the size of multiple organs/systems, an effect followed upon re-feeding by an elevated number of progenitor and stem cells and regeneration. Bi-monthly FMD cycles started at middle age extended longevity, lowered visceral fat, reduced cancer incidence and skin lesions, rejuvenated the immune system, and retarded bone mineral density loss. In old mice, FMD cycles promoted hippocampal neurogenesis, lowered IGF-1 levels and PKA activity, elevated NeuroD1, and improved cognitive performance. In a pilot clinical trial, three FMD cycles decreased risk factors/biomarkers for aging, diabetes, cardiovascular disease, and cancer without major adverse effects, providing support for the use of FMDs to promote healthspan.

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Images/Data

Figure 1 View all Images/Data

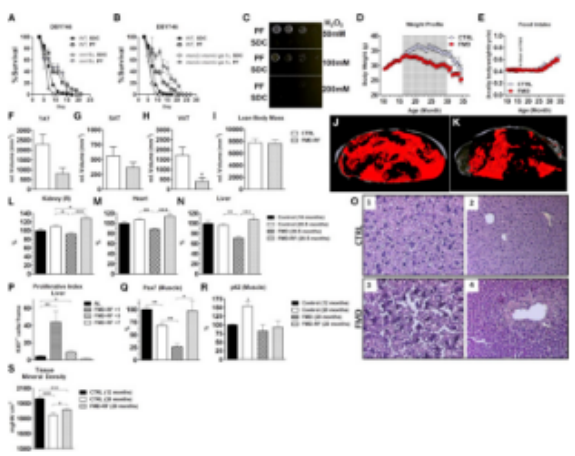
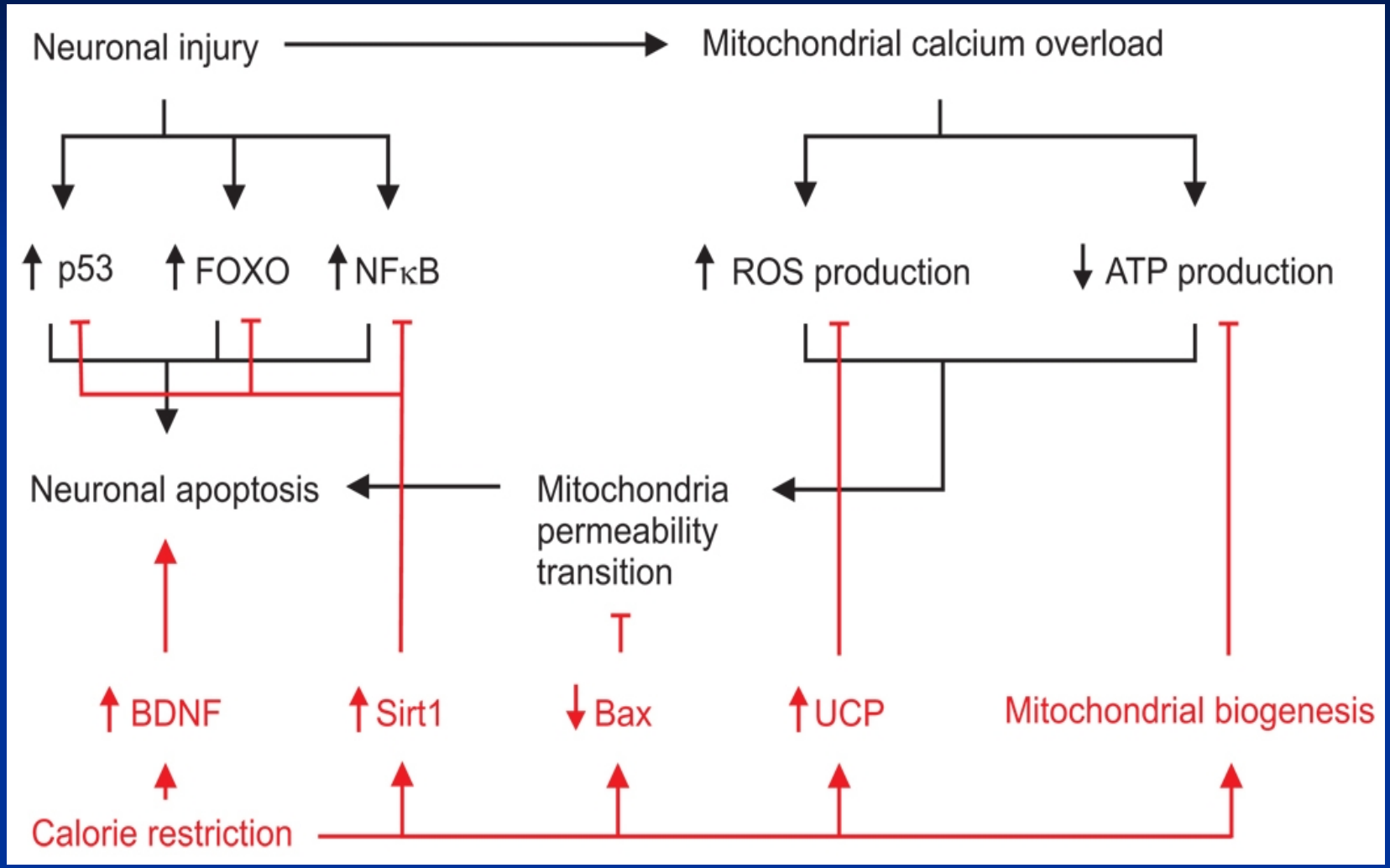


Figure 1

Periodic FMD Promotes a Lean Bodyweight, Improves Healthspan, and Promotes Tissue Regeneration

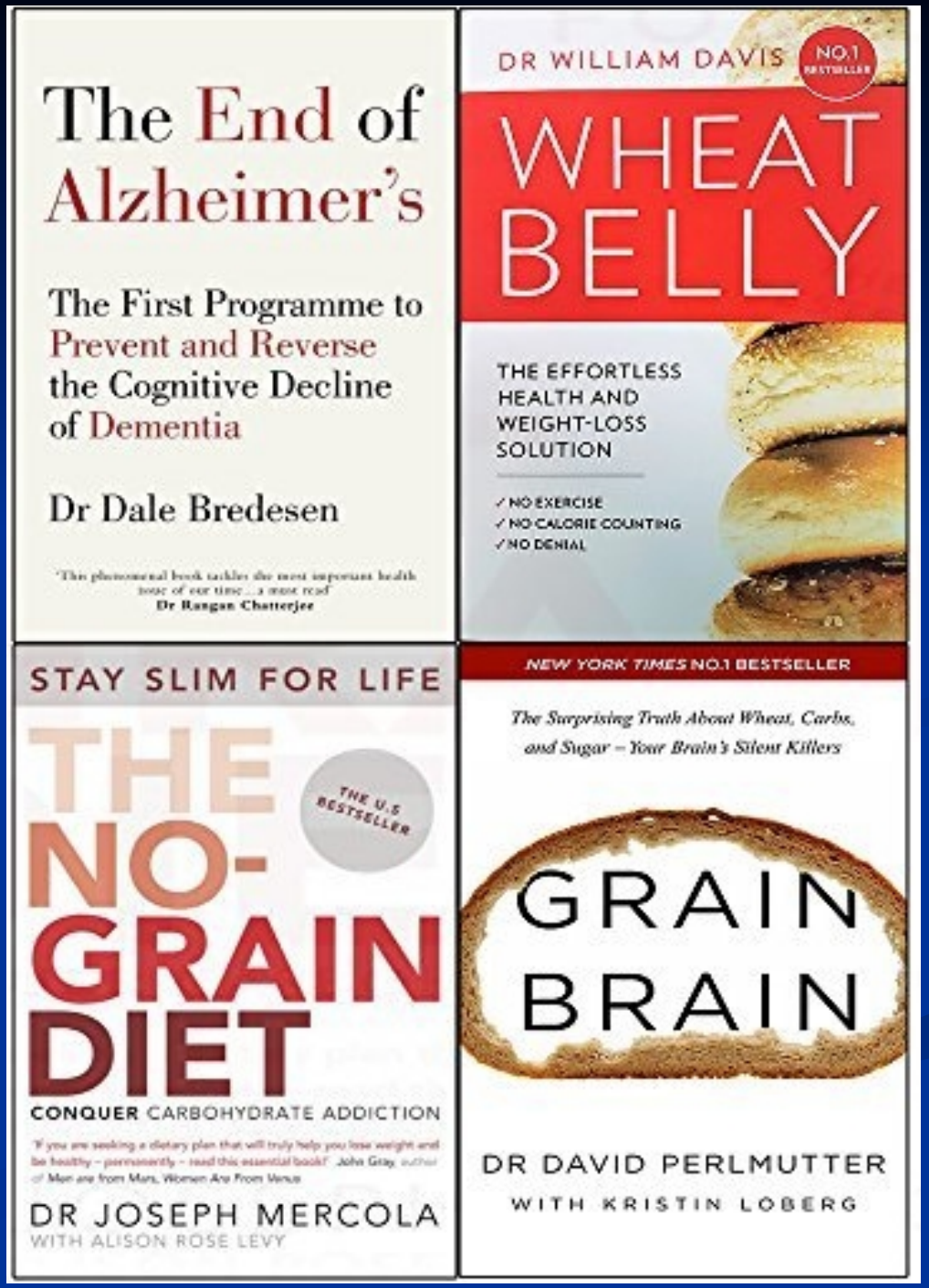
Caloric Restriction and Neuronal Protection (as in Intermittent Fasting)



Next:

Food Allergies

(Yes, Jack, I listened in class)



Celiac and AD

A possible association exists between progressive cognitive impairment and celiac disease, given the temporal relationship and the relatively high frequency of ataxia and peripheral neuropathy, more commonly associated with celiac disease.

Hu WT, et al, Archives of Neurology 63: 1440-1446, October 2006

But….

Gluten-free diet failed to improve the neurologic disability except in 1 patient.

CD is a multisystem disorder and may play a role in some cases of presenile dementia

Collin, P. et al, Neurology, 41: 372-375; March 199 1

Wahl's Protocol

Modified Paleo Diet removing possible antigens, used in MS and other immune driven neurocognitive disorders

Bresden ReCode

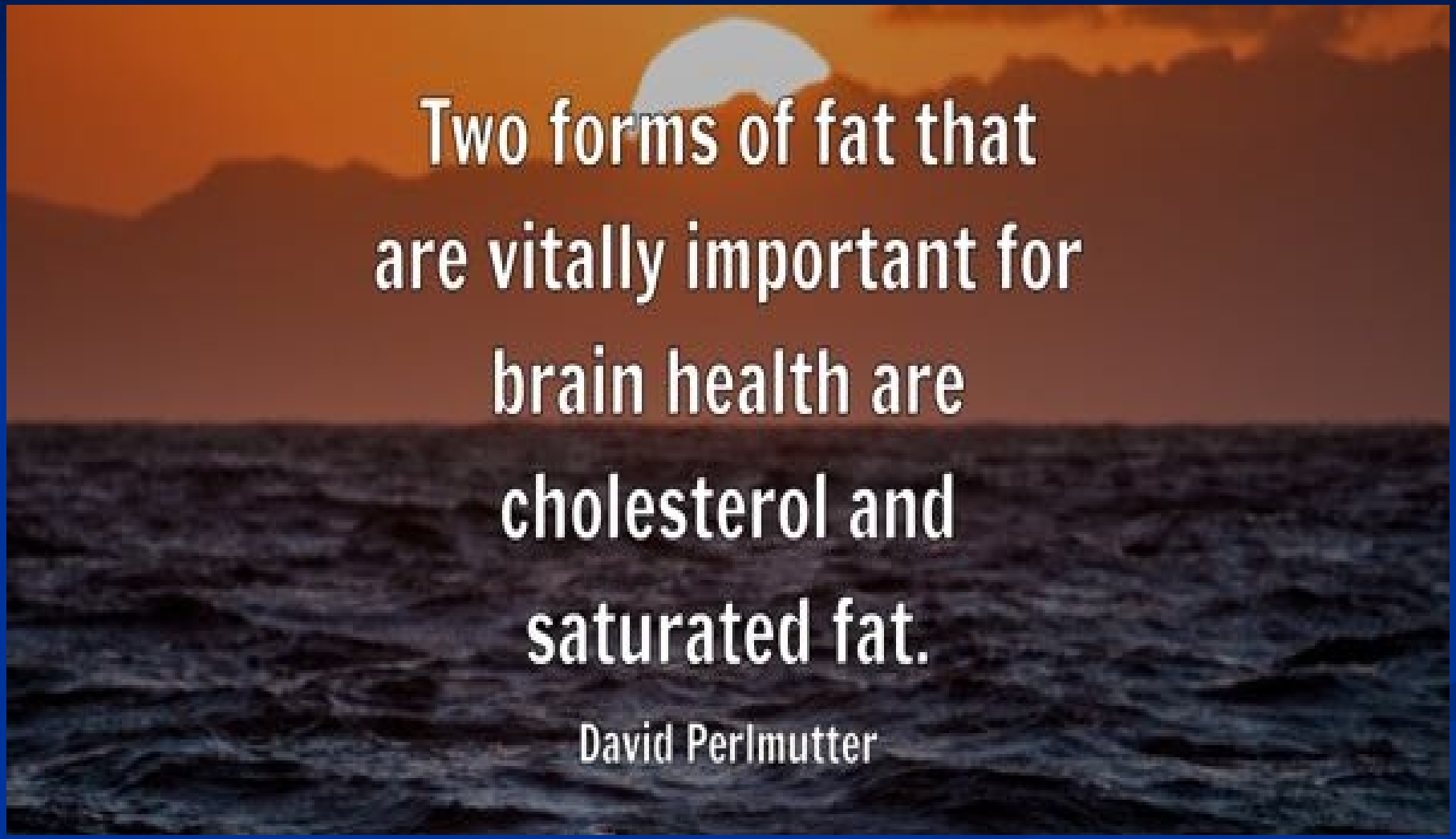
THE "ALZHEIMER'S DIET"

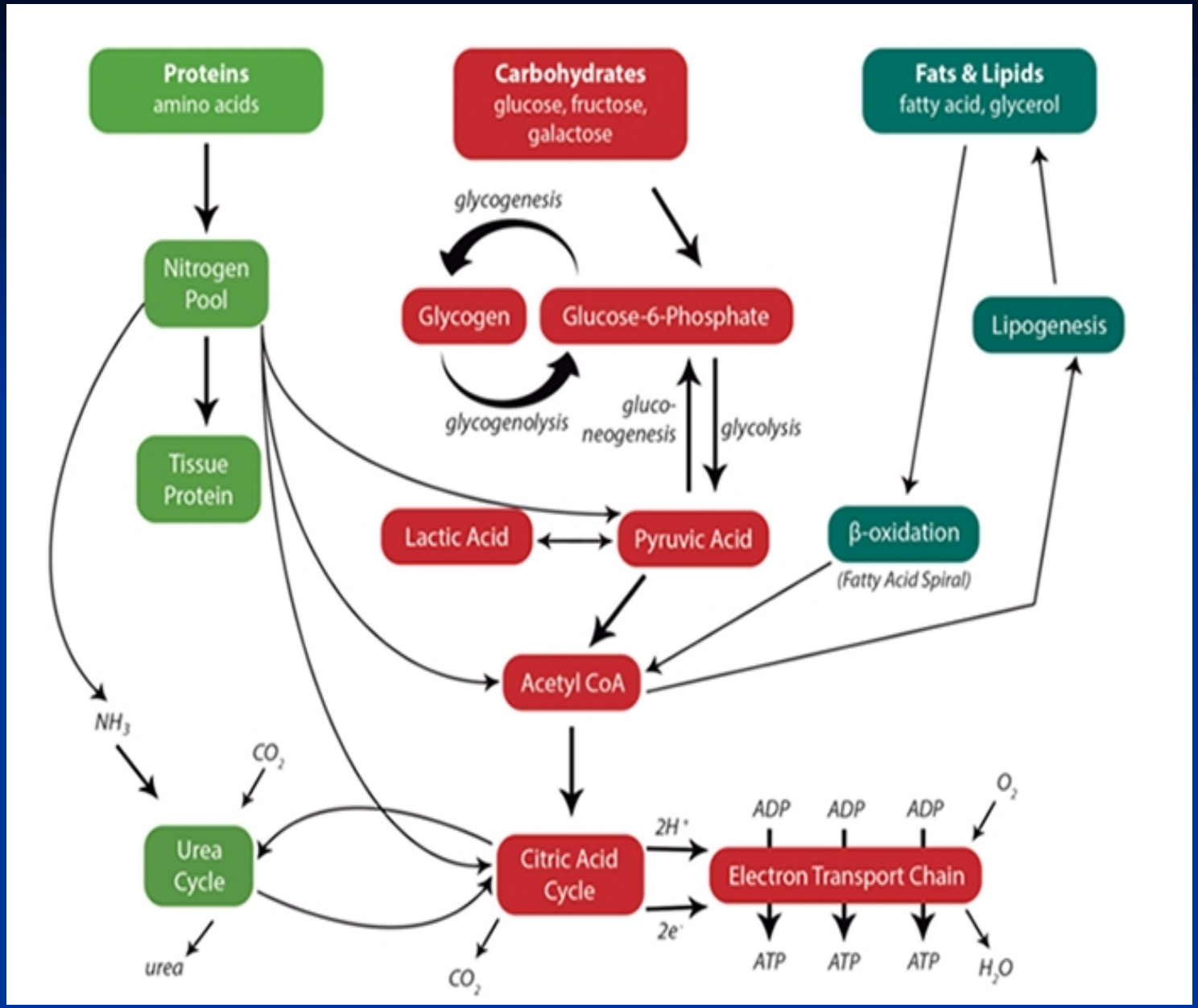
HOW TO IMPLEMENT "THE BREDESEN PROTOCOL" TO SLOW + REVERSE COGNITIVE DECLINE

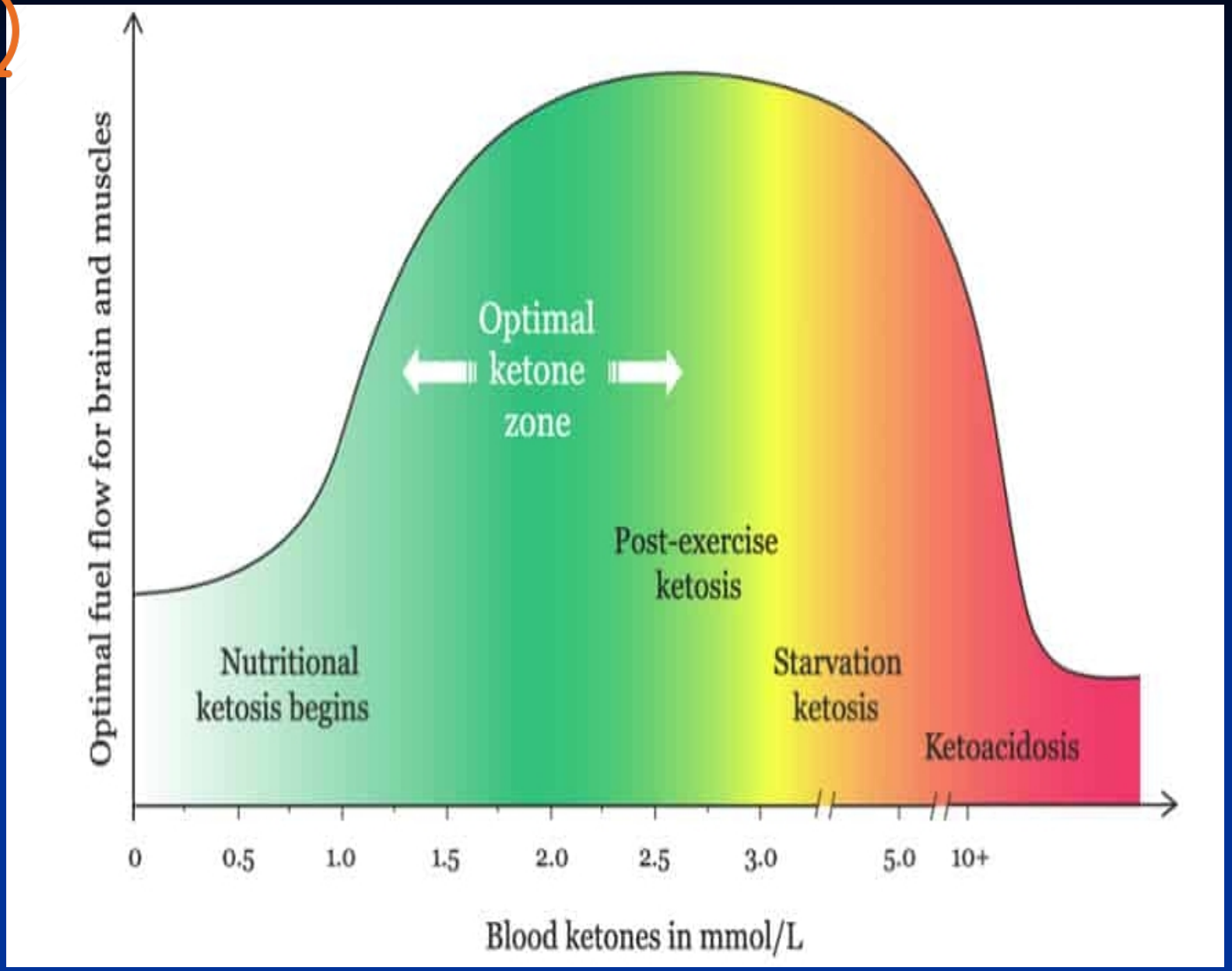
How can you have a ketogenic diet while being plant based and avoiding animal products?

EAT	AVOID
	
Whole, Predominantly Plant-Based Food	Highly-Processed, Meat/Animal-Product-Heavy Foods
Aim for "mild ketosis"	Avoid refined carbohydrates and simple sugar
10-15 servings of non-starchy vegetables per day	Avoid "non-nutritive sweetners" such as Splenda, Sweet N' Low, etc.
Fast for 12 hours between dinner and breakfast + 3 hours before bedtime	Avoid late-night snacking

But hang on....

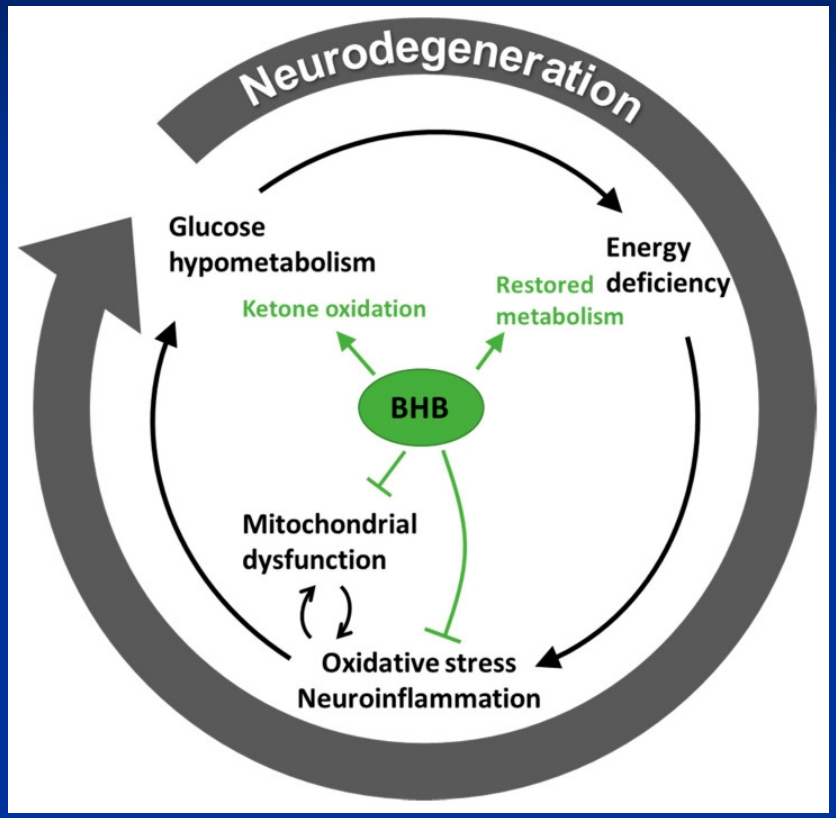






Spritzler, F. RD, CDE & Scher, B., MD. (2020 March 23). *The Complete Guide to Ketosis.* Diet Doctor.

Ketogenic Diet



- Reduces NFKB activity/inflammation
- Enhances mitochondrial numbers
- Enhances ATP production and cellular energy
- Reduces Reactive Oxidative Stress
- Reduces programmed cell death (apoptosis)

- <u>Enhanced with:</u>
- MCT oil
- Restricted carbohydrates
- Increased dietary fat
- Exercise
- Good salt
- Intermittent fasting
- Regular exercise
- Good sleep

Int J Mol Sci. 2020 Nov; 21(22): 8767.
Published online 2020 Nov 20. doi: 10.3390/ijms21228767
PMCID: PMC7699472
PMID: 33233502

Effects of Ketone Bodies on Brain Metabolism and Function in Neurodegenerative Diseases

Nicole Jacqueline Jensen,[1,*] Helena Zander Wodschow,[1] Malin Nilsson,[1] and Jørgen Rungby[1,2]

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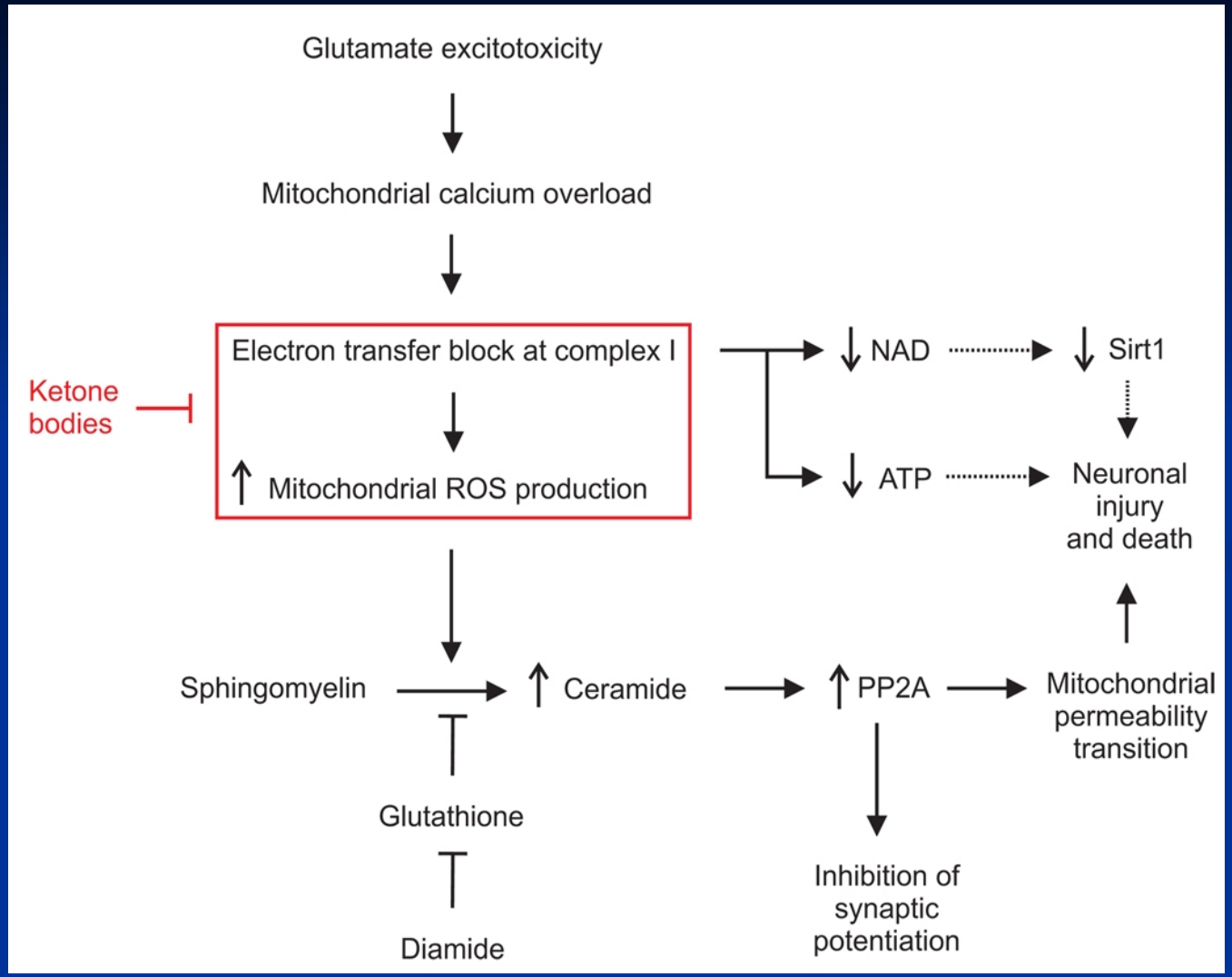
Abstract

Go to: ▸

Under normal physiological conditions the brain primarily utilizes glucose for ATP generation. However, in situations where glucose is sparse, e.g., during prolonged fasting, ketone bodies become an important energy source for the brain. The brain's utilization of ketones seems to depend mainly on the concentration in the blood, thus many dietary approaches such as ketogenic diets, ingestion of ketogenic medium-chain fatty acids or exogenous ketones, facilitate significant changes in the brain's metabolism. Therefore, these approaches may ameliorate the energy crisis in neurodegenerative diseases, which are characterized by a deterioration of the brain's glucose metabolism, providing a therapeutic advantage in these diseases. Most clinical studies examining the neuroprotective role of ketone bodies have been conducted in patients with Alzheimer's disease, where brain imaging studies support the notion of enhancing brain energy metabolism with ketones. Likewise, a few studies show modest functional improvements in patients with Parkinson's disease and cognitive benefits in patients with—or at risk of—Alzheimer's disease after ketogenic interventions. Here, we summarize current knowledge on how ketogenic interventions support brain metabolism and discuss the therapeutic role of ketones in neurodegenerative disease, emphasizing clinical data.

Neuroprotective effects of Ketogenic Diets



Mechanisms underlying the neuroprotective effects of a ketogenic diet

Maalouf M, Rho JM, Mattson MP. The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. Brain Res Rev. 2009 Mar;59(2):293-315. doi: 10.1016/j.brainresrev.2008.09.002. Epub 2008 Sep 25. PMID: 18845187; PMCID: PMC2649682.

Time-restricted ketogenic diet in amyotrophic lateral sclerosis: a case study


Matthew C. L. Phillips[1*] Samuel E. Johnston[2] Pat Simpson[3] David K. Chang[4]

Danielle Mather[4] Rognvald J. Dick[2]

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[4] Department of Speech Language Therapy, Waikato Hospital, Hamilton, New Zealand

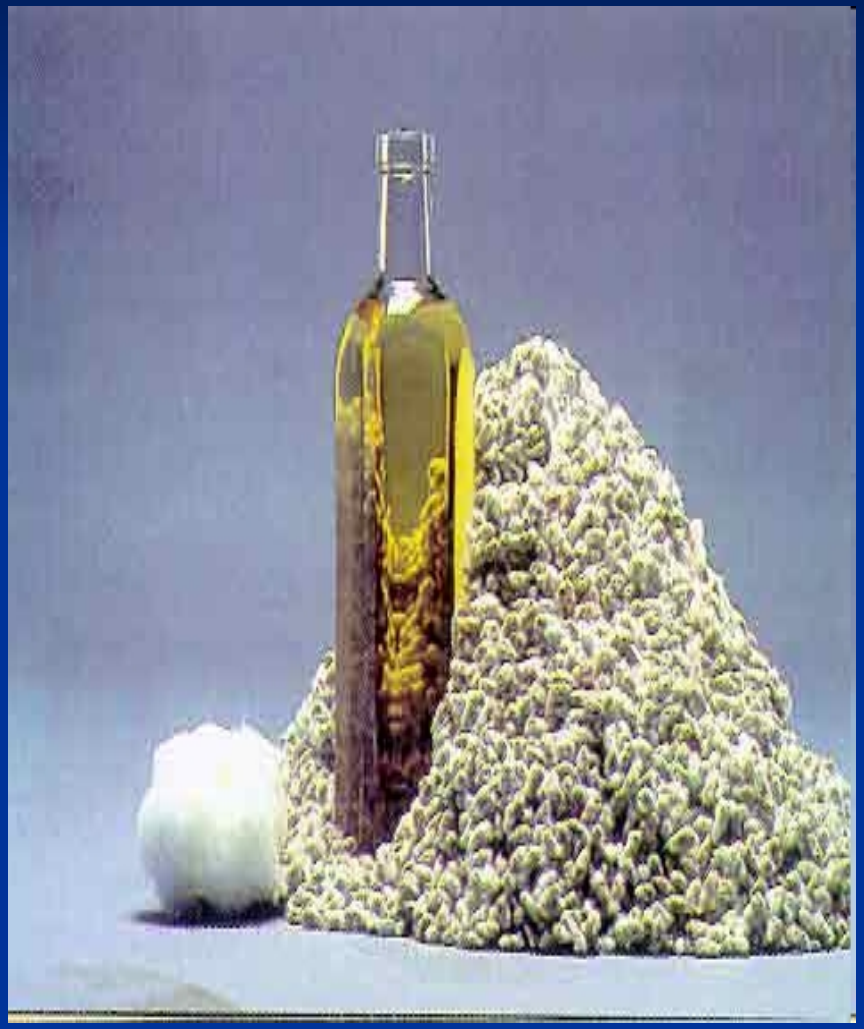
Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disorder. The most devastating variant is bulbar-onset ALS, which portends a median survival of 24 months from the onset of symptoms. Abundant evidence indicates that neuron metabolism and mitochondrial function are impaired in ALS. Metabolic strategies, particularly fasting and ketogenic diet protocols, alter neuron metabolism and mitochondria function in a manner that may mitigate the symptoms of this disorder. We report the case of a 64-year-old man with a 21-month history of progressive, deteriorating bulbar-onset ALS, with an associated pseudobulbar affect, who implemented a time-restricted ketogenic diet (TRKD) for 18 months. During this time, he improved in ALS-related function (7% improvement from baseline), forced expiratory volume (17% improvement), forced vital capacity (13% improvement), depression (normalized), stress levels (normalized), and quality of life (19% improvement), particularly fatigue (23% improvement). His swallowing impairment and neurocognitive status remained stable. Declines were measured in physical function, maximal inspiratory pressure, and maximal expiratory pressure. Weight loss was attenuated and no significant adverse effects occurred. This case study represents the first documented occurrence of a patient with ALS managed with either a fasting or ketogenic diet protocol, co-administered as a TRKD. We measured improved or stabilized ALS-related function, forced expiratory volume, forced vital capacity, swallowing, neurocognitive status, mood, and quality of life. Measurable declines were restricted to physical function, maximal inspiratory pressure, and maximal expiratory pressure. Now over 45 months since symptom onset, our patient remains functionally independent and dedicated to his TRKD.

Front. Neurol., 17 January 2024
Sec. Neuromuscular Disorders and Peripheral Neuropathies
Volume 14 - 2023 | https://doi.org/10.3389/fneur.2023.1329541

CARNIVORE

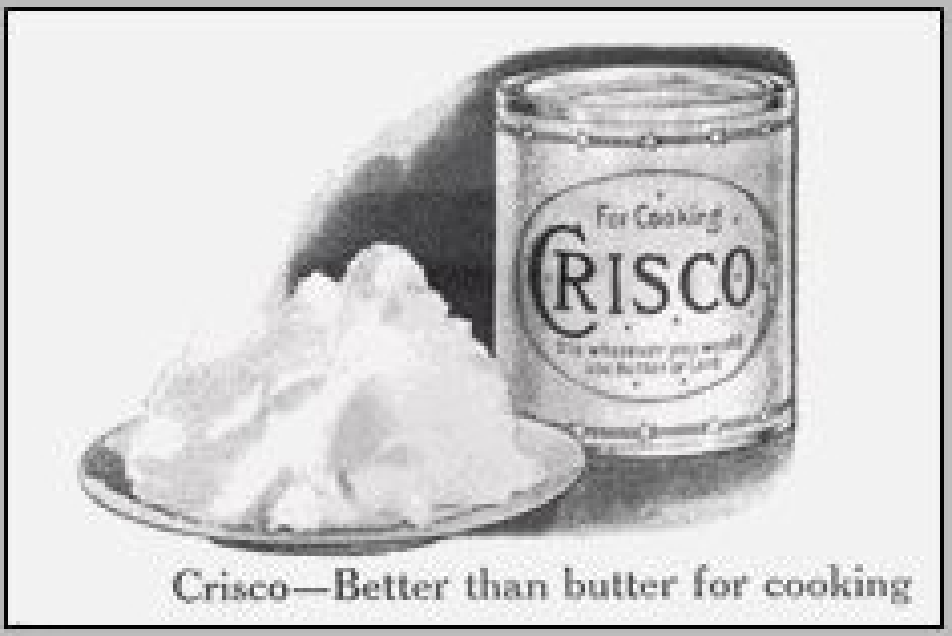
- A ketogenic, carnivorous diet is what allows lengthy, natural fasting and naturally stimulates an intermittent fasting habit with good functioning and little to no hunger.
- Carnivore support:
  - Vitamin C
  - Magnesium glycinate
  - Whey based protein
  - Adrenal glandular support
- AVOID SEED OILS

Cotton Seed Oil



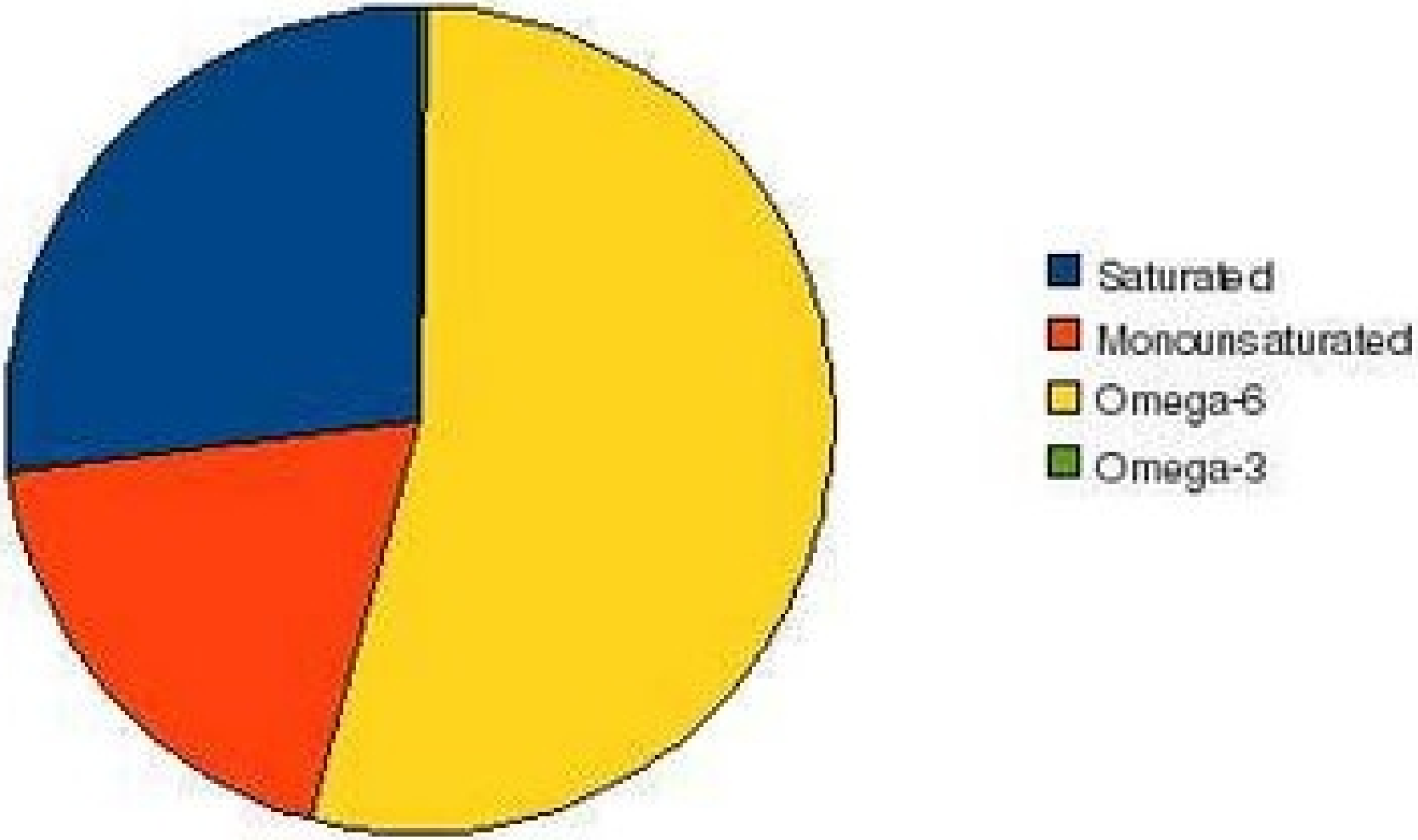
- Gossypol and 20 other toxic side products.
- Been linked to neurotransmitter binding and implicated in both autism and Alzheimer's disease progresion.
- Raises LDL's and CVD extremely quickly in laboratory rat models.

Procter and Gamble Introduced Crisco (*CRYS*alized *C*ottonseed *O*il) to the Public in 1911



Two 1912 advertisements for Crisco in the *Ladies Home Journal*

Fat Composition of Cottonseed Oil



Carnivore

ORIGINAL RESEARCH

CURRENT DEVELOPMENTS IN NUTRITION

Nutritional Requirements and Status

Behavioral Characteristics and Self-Reported Health Status among 2029 Adults Consuming a "Carnivore Diet"

Belinda S Lennerz,[1,2,3] Jacob T Mey,[4] Owen H Henn,[1,2] and David S Ludwig[1,2,3]

[1]New Balance Foundation Obesity Prevention Center, Boston Children's Hospital, Boston, MA, USA; [2]Division of Endocrinology, Boston Children's Hospital, Boston, MA, USA; [3]Department of Pediatrics, Harvard Medical School, Boston, MA, USA; and [4]Integrated Physiology and Molecular Medicine, Pennington Biomedical Research Center, Baton Rouge, LA, USA

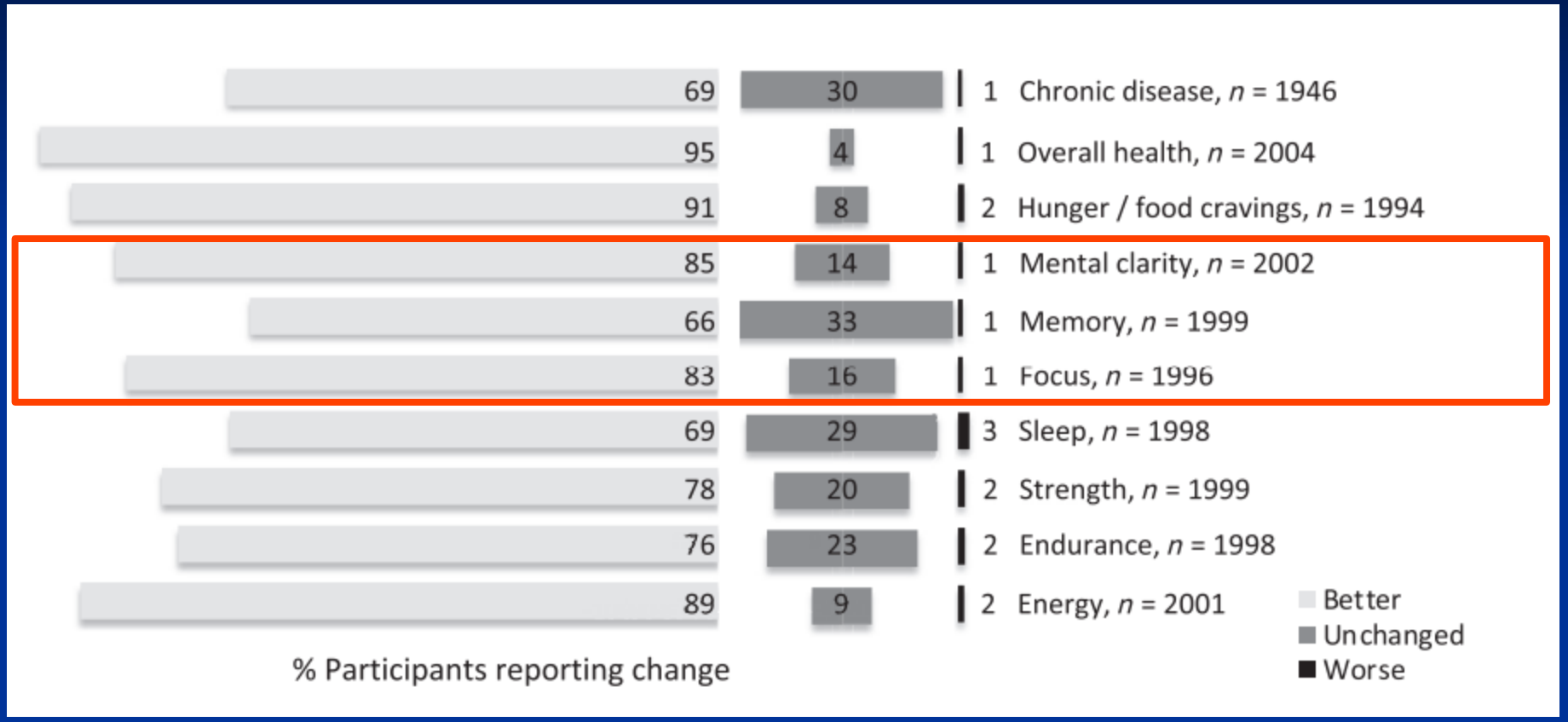
ABSTRACT

Background: The "carnivore diet," based on animal foods and excluding most or all plant foods, has attracted recent popular attention. However, little is known about the health effects and tolerability of this diet, and concerns for nutrient deficiencies and cardiovascular disease risk have been raised.

Objectives: We obtained descriptive data on the nutritional practices and health status of a large group of carnivore diet consumers.

Methods: A social media survey was conducted 30 March–24 June, 2020 among adults self-identifying as consuming a carnivore diet for ≥6 mo. Survey questions interrogated motivation, dietary intake patterns, symptoms suggestive of nutritional deficiencies or other adverse effects, satisfaction, prior and current health conditions, anthropometrics, and laboratory data.

Results: A total of 2029 respondents (median age: 44 y, 67% male) reported consuming a carnivore diet for 14 mo (IQR: 9–20 mo), motivated primarily by health reasons (93%). Red meat consumption was reported as daily or more often by 85%. Under 10% reported consuming vegetables, fruits, or grains more often than monthly, and 37% denied vitamin supplement use. Prevalence of adverse symptoms was low (<1% to 5.5%). Symptoms included gastrointestinal (3.1%–5.5%), muscular (0.3%–4.0%), and dermatologic (0.1%–1.9%). Participants reported high levels of



Chronic condition	Prevalence, *n* (%)	Changes when following diet, %				
		Resolved	Improved	Unchanged	Worsened	New
Obesity/overweight	928 (46)	52	41	5	1	0.2
Underweight	100 (5)	52	28	14	5	1
Lipid abnormalities	429 (21)	27	29	18	19	8
Hypertension	374 (18)	61	32	7	0.3	0.0
Cardiovascular	126 (6)	41	43	15	0.8	0.8
Diabetes/insulin resistance	402 (20)	74	24	1	0.0	0.0
Gastrointestinal	531 (26)	59	38	1	1	0.2
Endocrinologic	191 (9)	40	48	12	0.5	0.0
Autoimmune	369 (18)	36	53	11	0.0	0.0
Musculoskeletal	502 (25)	42	54	4	0.0	0.2
Neurological	89 (4)	42	42	16	1	0.0
Cognitive	100 (5)	42	54	4	0.0	0.0
Psychiatric	479 (24)	48	48	4	0.0	0.0
Respiratory	354 (17)	51	34	14	0.0	0.0
Urologic	181 (9)	76	16	8	0.0	0.6
Dermatologic	690 (34)	44	48	7	0.6	0.1
Ophthalmologic	327 (16)	12	36	51	0.6	0.6
Hematologic	127 (6)	66	18	14	0.0	2
Oncologic	75 (4)	41	12	47	0.0	0.0
Other	208 (10)	42	45	13	0.0	1
Diabetes medications		**Discontinued**	**Decreased**	**Unchanged**	**Increased**	**New**
Insulin	29 (1)	52[2]	38	3	0.0	7
Insulin (T2DM only)	13 (0.6)	92	0.0	0.0	0.0	8
Diabetes injectables, other	16 (0.8)	100	0.0	0.0	0.0	0.0
Oral diabetes medications	82 (4)	84	14	2	0.0	0.0

[1]Participants were asked if they had ever suffered from or taken any of the listed conditions or medications. *n* (%) of positive responses is given in the first column (prevalence) and is the denominator for percentages in the subsequent columns. Positive respondents were then asked to rate the severity of each condition relative to the time before starting the carnivore diet on a 5-point scale. For visualization, response frequencies are color-coded dark gray if ≥70%, and in increasing brightness if 40%–69%, 20%–39%, 10%–19%, 5%–9%, 1%–4%, and <1%. T2DM, type 2 diabetes mellitus.

[2]Includes people with type 1 diabetes mellitus and T2DM.

For those still worrying:

Self Reported
(outed on Social Media)

5 years strict Carnivore

CAC results:

Zero

RAYUS RADIOLOGY

6243 South Redwood Rd
Taylorsville 84123
USA

Phone: 801-563-0333
Fax: 801-563-0335
WWW.RAYUSRADIOLOGY.COM

Patient Name
Patient ID
Date of Birth (40 years)
Gender male

Series: CaScore spiral
Study: Cardiac^CALCIUM_SCORE (Adult)
Referring Physician: Referral^Self^^^

Series No.: 3
Study Date: 15-Feb-2024

Report

High-resolution, ECG synchronized Computed Tomography of the heart with attention to the coronary arteries was performed using Siemens HeartView CT. The average heartrate of the patient during the examination was 82BpM. Coronary calcification was analyzed using Siemens calcium scoring software. These are the results of the evaluation:

Artery	Number of Lesions	Volume [mm³]	Equiv. Mass *) [mg CaHA]	Calcium Score
LM	0	0.0	0.00	0.0
LAD	0	0.0	0.00	0.0
CX	0	0.0	0.00	0.0
RCA	0	0.0	0.00	0.0
Total	**0**	**0.0**	**0.00**	**0.0**

Threshold: 130HU (93.5 mg/cm³ CaHA)
*) Calibration factor: 0.719 mg/(HU·cm³) CaHA

The Computed Tomography of the coronary arteries detected no coronary calcifications. According to the current state of knowledge (O´Rourke, Circulation 2000; 102:126) a coronary atherosclerosis including unstable plaque is very unlikely when no calcifications are present. A significant luminal obstructive disease is also very unlikely. Most patients without coronary calcifications have angiographically normal coronary arteries. There is only a low risk of a cardiac event in the next 2 to 5 years.

Reference Norms of Calcium Score

No Identifiable Calcification	Minimal Identifiable Calcification	Mild Calcification	Moderate Calcification	Significant Calcification
0	1-10	11-100	101-400	401 and above

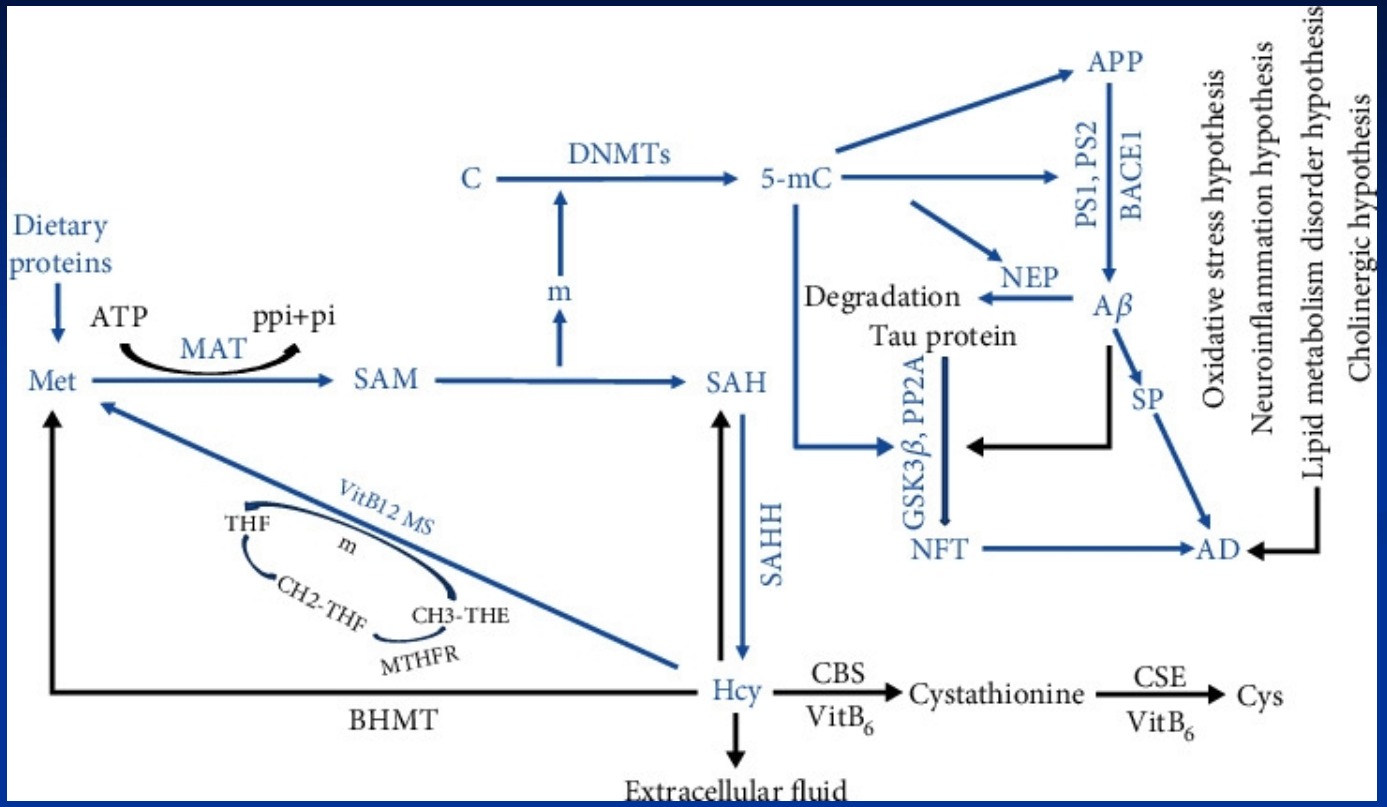
(Following Mayo Clin Proc. 1999;74(3):243-252)

Baseline GI and Blood Brain Barrier Protocol

- Combination digestive enzymes
- Glutamine
- Tumeric based anti-inflammatory or SGS
- 50 bil cfu + Probiotic
- Omega 3 FA
- Vitamin D
- Colostrum or SBI

Metabolic Factors

Homocysteine and AD



Both direct and indirect linkages to AD via aberations in DNA and methylation, but also through strokes and microvascular disease.

- Morris MS. Homocysteine and Alzheimer's disease. Lancet Neurol. 2003 Jul;2(7):425-8. doi: 10.1016/s1474-4422(03)00438-1. PMID: 12849121.
- Pi T, Liu B, Shi J. Abnormal Homocysteine Metabolism: An Insight of Alzheimer's Disease from DNA Methylation. Behav Neurol. 2020 Sep 8;2020:8438602. doi: 10.1155/2020/8438602. PMID: 32963633; PMCID: PMC7495165.
- Miller JW. Homocysteine and Alzheimer's disease. Nutr Rev. 1999 Apr;57(4):126-9. doi: 10.1111/j.1753-4887.1999.tb06936.x. PMID: 10228350.

Brain Atrophy and blood sugar

- Higher normal fasting plasma glucose associated with hippocampal atrophy
- N=226 cognitively healthy adults.
  - Baseline fasting glucose and baseline volumetric MRI of hippocampus and amygdala
    - PATH Study, Neurology 2012; 79: 1019-1026

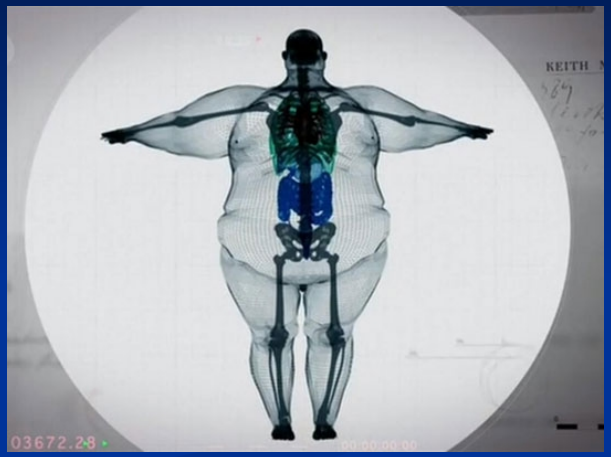
DMII and Dementia

- N=2067, mean age 76 years, median followup 6.8 years
- Baseline glucose and cognitive assessment every 2 years
- “We found the that increased risk was associated with higher glucose levels even at the lowest end of the glucose spectrum among people who had not received a diagnosis of diabetes. In conclusion, our data provided evidence that higher glucose levels are associated with an increased risk of dementia.
    - NEJM 369;6, Aug 8, 2013

Central Obesity and the Aging Brain

Volumetric decrease in hippocampal volume with increasing waist-hip ratios.

Jagust W, et al, Arch Neurology 62: 1545-48; Oct 2005



Insulin resistance in Cognitive Impairment. N: 523, 70-90 yo with early insulin resistance.

Geroldi, C et al., Arch Neurol 62; July, 2005;, 1067-72

Glucose tolerance status and risk of dementia in the community. (The Hisayama Study)

- Mild association between elevated post prandial glucose levels, but not fasting glucose levels, and AD.

Ohara, T et al, Neurology, Sept 20, 2011, Vol 77, No 12, 1126-1134

Diabetes mellitus and the risk of dementia

Rotterdam Study
6370 Patients,
Risk ratio of AD with diabetes - 1.9X
Risk ratio of dementia if using Insulin - 4.3X
The diabetes attributable risk for dementia of 8.8% suggests that diabetes may have contributed to the clinical syndrome in a substantial proportion of all dementia patients

Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology. 1999 Dec 10;53(9):1937-42. doi: 10.1212/wnl.53.9.1937. PMID: 10599761.

Increased blood sugar increases glycation of proteins. Advanced Glycosylation End Products (AGE) Post translational modification of proteins as amino groups of proteins react with monosaccharides.

Yaffe K, Lindquist K, Schwartz AV, Vitartas C, Vittinghoff E, Satterfield S, Simonsick EM, Launer L, Rosano C, Cauley JA, Harris T. Advanced glycation end product level, diabetes, and accelerated cognitive aging. Neurology. 2011 Oct 4;77(14):1351-6. doi: 10.1212/WNL.0b013e3182315a56. Epub 2011 Sep 7. PMID: 21900628; PMCID: PMC3182758.

Decrease in brain volume relative to increase in HbA1c

Enzinger, C et al, Neurology 64: 1704-11, May 24, 2005

Alzheimer's Diesase - Synergistic Effects of Glucose Deficit, Oxidative Stress and Advanced Glycation End Products.
AGE's more than markers. They exert adverse effects including activation of intracellular signal transduction pathways, upregulation of inflammatory cytokines and free radical production leading ot oxidative stress.

Munch, G et al, Journal of Neural Transmission 105 (4-5): 439-461, July 1998

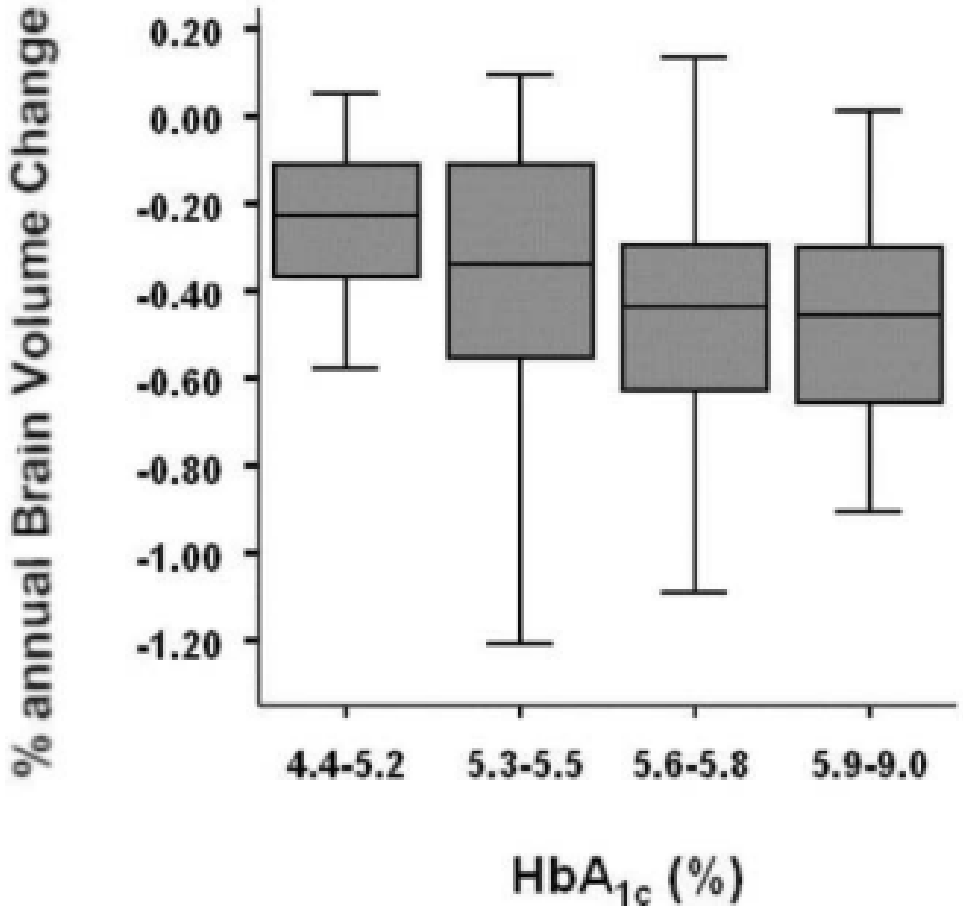


Figure 2. Association between glycated hemoglobin A (HbA_{1c}) and rate of brain atrophy. Box plots demonstrate significant differences in brain atrophy rates between subjects within different quartiles of HbA_{1c} levels (p = 0.0001). Boxes represent values from the 25th to the 75th percentiles, inner lines represent the median, and whiskers show the minimal and maximal values. Significant differences become evident in subjects exceeding the median of HbA_{1c} (5.6%), but there is also considerable overlap between groups.

HOMA -IR

- HOMA1 IR = fasting insulin (microU/L) x fasting glucose (nmol/L)/22.5
  - Insulin: pmol/L to uIU/mL, divide by (÷) 6
  - Glucose: mmol/L to mg/dL, multiply by (x) 18

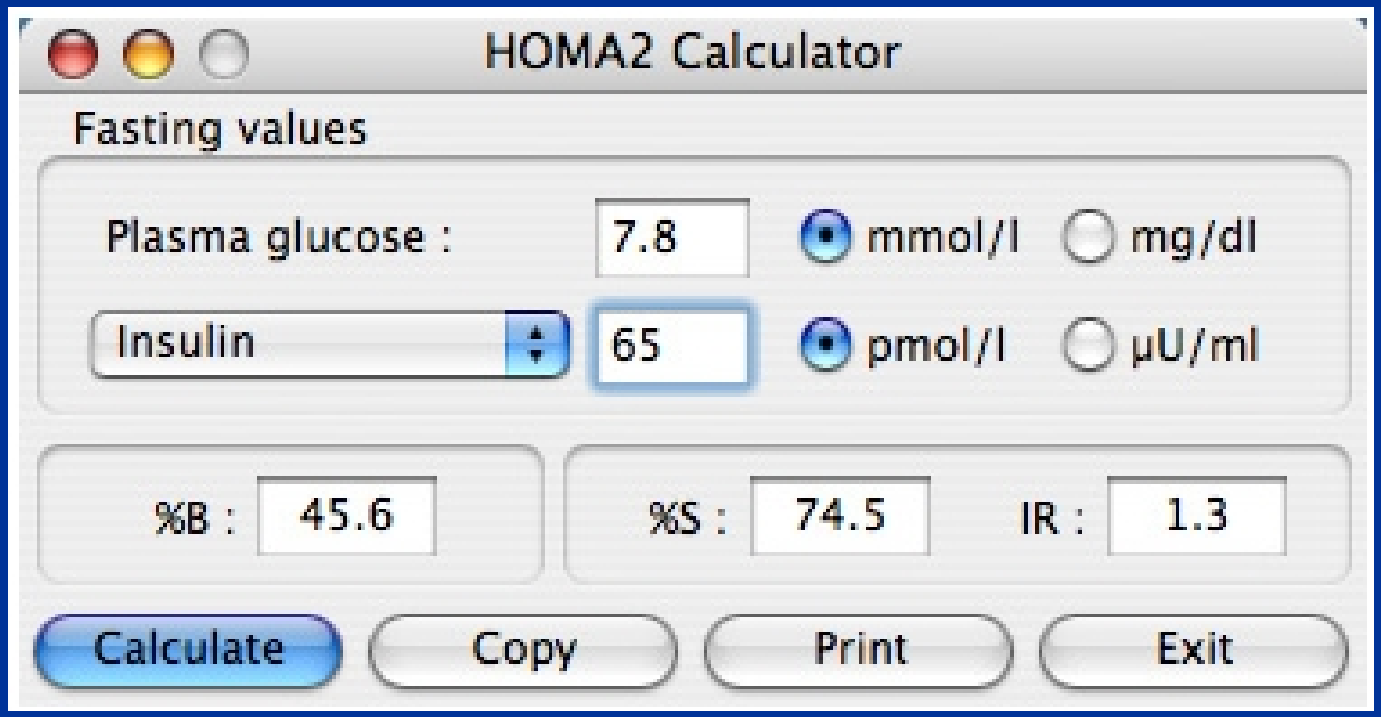
- Healthy Range: 1.0 (0.5–1.4)
  - Less than 1.0 means you are insulin-sensitive which is optimal.
  - Above 1.9 indicates early insulin resistance.
  - Above 2.9 indicates significant insulin resistance.

- https://www.dtu.ox.ac.uk/homacalculator/

UNIVERSITY OF OXFORD

DIABETES TRIALS UNIT
The Oxford Centre for Diabetes, Endocrinology and Metabolism

Radcliffe Department of Medicine



Blood Sugar Support Summary

1. White kidney bean extract – *"Carb blocker"*
2. Gymnema/Bitter melon/fenugreek – *Mild insulin resistance*
3. Cinnamon – *Moderate insulin resistance*
4. Berberine – *Heavy insulin resistance*
5. Alpha Lipoic Acid – *Heavy insulin resistance (* interaction with thyroid)*

- Liposomal Vit C – *Every patient, seriously.*
- Chromium – *"Willpower in a bottle"*
- Hormone Support– *check levels, then do it anyway*
- Intermittent Fasting/Ketogenic diet– *kickstart for everybody*
- Exercise – *No really.*

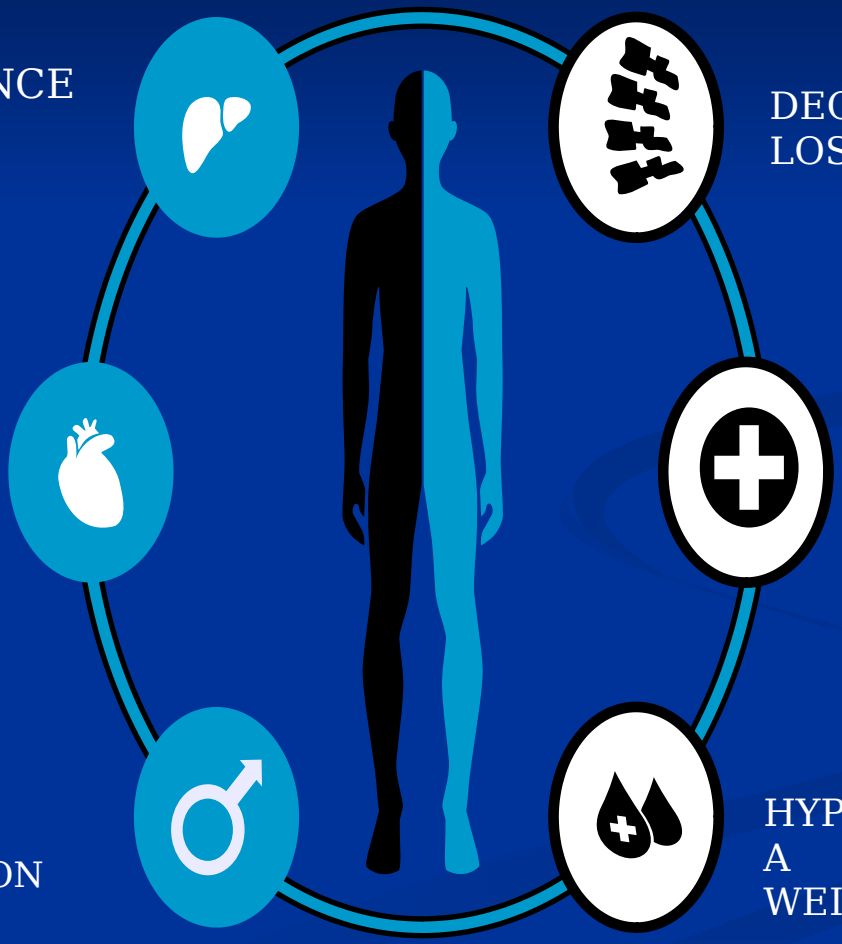
Andropause

Roughly defined as Low testosterone =250 ngm/dl or less

INSULIN RESISTANCE
DIABETES

HYPERTENSION
CARDIOVASCULAR
DISEASE

REDUCED LIBIDO
BURNED OUT FEELING
ERECTILE DYSFUNCTION



DECREASED FLEXIBILITY
LOSS OF MUSCLE MASS

NIGHT SWEATS
HOT FLASHES

HYPERCHOLESTEROLEMI
A
WEIGHT GAIN-WAIST

- Potential contribution of low testosterone values to the increasing rates of metabolic syndrome and diabetes have been noted across the literature.
  - *Testosterone deficiency induced by progressive stages of diabetes mellitus impairs glucose metabolism and favors glycogenesis in mature rat Sertoli cells. Rato L1, Alves MG1, Duarte AI2, Santos MS3, Moreira PI4, Cavaco JE1, Oliveira PF5. Int J Biochem Cell Biol. 2015 Sep;66:1-10. doi: 10.1016/j.biocel.2015.07.001. Epub 2015 Jul 3.*
  - *Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Muraleedharan V1, Marsh H, Kapoor D, Channer KS, Jones TH. Eur J Endocrinol. 2013 Oct 21;169(6):725-33. doi: 10.1530/EJE-13-0321. Print 2013 Dec.*
  - *Is a Previously or Currently Reduced Testosterone Level in Male Patients with Type 2 Diabetes Mellitus a Risk Factor for the Development of Coronary Artery Disease? A Systematic Review and Meta-analysis. Huang F, Diabetes Ther. 2018 Apr 4. doi: 10.1007/s13300-018-0415-3. [Epub ahead of print]*
  - *Testosterone and All-Cause Mortality in Older Men: The Role of Metabolic Syndrome. Laouali N1, Brailly-Tabard S2,3,4, Helmer C5,6, Ancelin ML7, Tzourio C5,6, Singh-Manoux A1, Dugravot A1, Elbaz A1, Guiochon-Mantel A2,3,4, Canonico M1., J Endocr Soc. 2018 Feb 26;2(4):322-335. doi: 10.1210/js.2018-00005. eCollection 2018 Apr 1.*

- In men, multiple studies have supported increasing relatively circulating levels of testosterone to around the 500 ng/dl level to reduce both Diabetes Mellitus and Metabolic syndrome.
  - *Tibblin G. Diabetes 1996;45(11):1605-9*
  - *Kapoor D et al. Euro J Endocrin 2006;154:899-906*
  - *Brikeland KI. J CEM 1993;76(2):275-8*
  - *Chang, Gerontology 1994;40(5):260-7*
  - *Haffner S., Metabol 1994;43(5):599-3*

Androgens and Alzheimer's Disease

- T therapy for AD patients may represent an essential clinical therapy to reduce dementia incidence and AD progression
  - *Bianchi VE. Impact of Testosterone on Alzheimer's Disease. World J Mens Health. 2022 Apr;40(2):243-256. doi: 10.5534/wjmh.210175. Epub 2022 Jan 2. PMID: 35021306; PMCID: PMC8987133.*
- Administration improves cognitive performance and memory, treatment should be started at an early stage of the disease. In men and women with AD, androgens improve mental state and slow the progression of the disease, providing a protective effect
  - *Kuznetsov KO, Khaidarova RR, Khabibullina RH, Stytsenko ES, Filosofova VI, Nuriakhmetova IR, Hisameeva EM, Vazhorov GS, Khaibullin FR, Ivanova EA, Gorbatova KV. [Testosterone and Alzheimer's disease]. Probl Endokrinol (Mosk). 2022 Jun 24;68(5):97-107. Russian. doi: 10.14341/probl13136. PMID: 36337024; PMCID: PMC9762454.*
- Higher total testosterone may reduce the risk of paternal Alzheimer's disease (odds ratio (OR) 0.86, 95% confidence interval (CI) 0.76 to 0.97, per SD increase in testosterone) and in meta-analysis for women (OR 0.92, 95% CI 0.87, 0.98)
  - *Yeung CHC, Au Yeung SL, Kwok MK, Zhao JV, Schooling CM. The influence of growth and sex hormones on risk of alzheimer's disease: a mendelian randomization study. Eur J Epidemiol. 2023 Jul;38(7):745-755. doi: 10.1007/s10654-023-01015-2. Epub 2023 May 31. PMID: 37253999.*
- Low plasma testosterone level was significantly associated with an increased risk of Alzheimer's disease in elderly men (random RR = 1.48, 95% CI 1.12-1.96, P = 0.006). Meta-analysis supports that low plasma testosterone level is significantly associated with increased risk of Alzheimer's disease in the elderly men. Low testosterone level is a risk factor of worse cognitive function in the elderly men.
  - *Lv W, Du N, Liu Y, Fan X, Wang Y, Jia X, Hou X, Wang B. Low Testosterone Level and Risk of Alzheimer's Disease in the Elderly Men: a Systematic Review and Meta-Analysis. Mol Neurobiol. 2016 May;53(4):2679-84. doi: 10.1007/s12035-015-9315-y. Epub 2015 Jul 8. PMID: 26154489.*

Male and Female induction of steroidogenesis

Jim Meyer, PharmD,
Super Genius

Zinc (as zinc bisglycinate chelate)- 10 mg
To increase Zinc-finger domain activity in testosterone metabolism

Longjack (Eurycoma longifolia; Tongkat Ali) (root) - 300 mg
To enhance endogenous production of testosterone

Ashwagandha (Withania somnifera)(root) (4.5% withanolides) - 250 mg
An adrenal adaptogen to reduce conversion of testosterone to cortisol

Tribulus terrestris (fruit) extract (60% saponins) - 200 mg
To enhance endogenous production of testosterone.

Ginseng (Panax) (rhizome) extract (4% ginsenosides) - 200 mg
An adrenal adaptogen to reduce conversion of testosterone to cortisol

Nettle (Urtica dioica) (root) extract (4:1) - 100 mg
To reduce the binding strength and efficacy of SHBG

Velvet bean (Mucuna pruriens) (seed) extract (99% L-Dopa) - 100 mg
To increase dopamine concentration and by association,

Grape seed extract (Vitis vinifera)(95% proanthocyanidins) - 10 mg

Dosage: 2 capsules , 2x/day

Progesterone

- And Cancer:
  - 500% increase in breast cancer in progesterone deficient women.
    - 1000% increase in all forms of cancer in progesterone deficient women
    - *Am J Epidem, 114 (1981): 209, Cowan et al*
- And Brain Injury:
  - 100 Trauma patients randomly treated with progesterone within 11 hours of injury.
  - Treated PG group had a 30 day mortality rate 57% lower than controls, with more likely moderate to good outcome compared to controls.
    - *Annal Emerg Med, 49, Apr 2007, 391*
  - Apparently works by down regulating aquaporins in injured brain tissue, but upregulating aquaporin activity in the cerebral ventricles.
  - Also upregulates genes inhibiting apoptosis in brain tissue.
- In men, low doses reasonable for effect, such as 5mg/day topical.

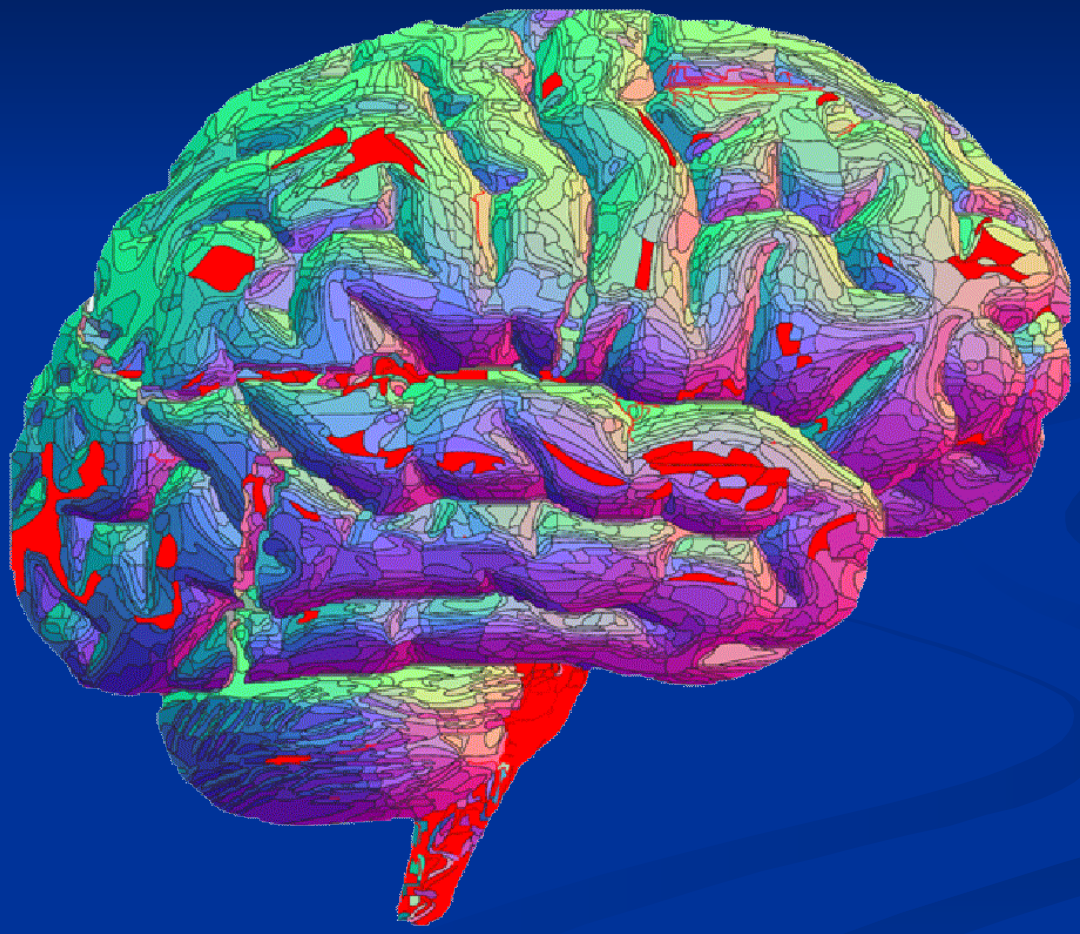
Progesterone and AD

- Along with DHEA, Progesterone used as a neurosteroids in neuroinflammation in the context of MS, AD, PD and TBI
  - *Yilmaz C, Karali K, Fodelianaki G, Gravanis A, Chavakis T, Charalampopoulos I, Alexaki VI. Neurosteroids as regulators of neuroinflammation. Front Neuroendocrinol. 2019 Oct;55:100788. doi: 10.1016/j.yfrne.2019.100788. Epub 2019 Sep 9. PMID: 31513776.*
- Progesterone suppresses Cholesterol Esterification in APP/PS1 mice and a cell model of Alzheimer's Disease generated from dysfunctional mitochondrial membrane function
  - *Shi W, Wu H, Liu S, Wu Z, Wu H, Liu J, Hou Y. Progesterone Suppresses Cholesterol Esterification in APP/PS1 mice and a cell model of Alzheimer's Disease. Brain Res Bull. 2021 Aug;173:162-173. doi: 10.1016/j.brainresbull.2021.05.020. Epub 2021 May 25. PMID: 34044033.*
- Progesterone improves glucose uptake in neurons in AD animal and cell line models
  - *Wu H, Wu ZG, Shi WJ, Gao H, Wu HH, Bian F, Jia PP, Hou YN. Effects of progesterone on glucose uptake in neurons of Alzheimer's disease animals and cell models. Life Sci. 2019 Dec 1;238:116979. doi: 10.1016/j.lfs.2019.116979. Epub 2019 Oct 21. PMID: 31647947.*
- Progesterone promotes survival of microvascular endothelial cells in AD patients
  - *Xu X, Ruan X, Ju R, Wang Z, Yang Y, Cheng J, Gu M, Mueck AO. Progesterone Receptor Membrane Component-1 May Promote Survival of Human Brain Microvascular Endothelial Cells in Alzheimer's Disease. Am J Alzheimers Dis Other Demen. 2022 Jan-Dec;37:15333175221109749. doi: 10.1177/15333175221109749. PMID: 35730360.*
- Synergistic effect with estrogen in neuroprotection
  - *Singh M, Su C. Progesterone and neuroprotection. Horm Behav. 2013 Feb;63(2):284-90. doi: 10.1016/j.yhbeh.2012.06.003. Epub 2012 Jun 23. PMID: 22732134; PMCID: PMC3467329.*

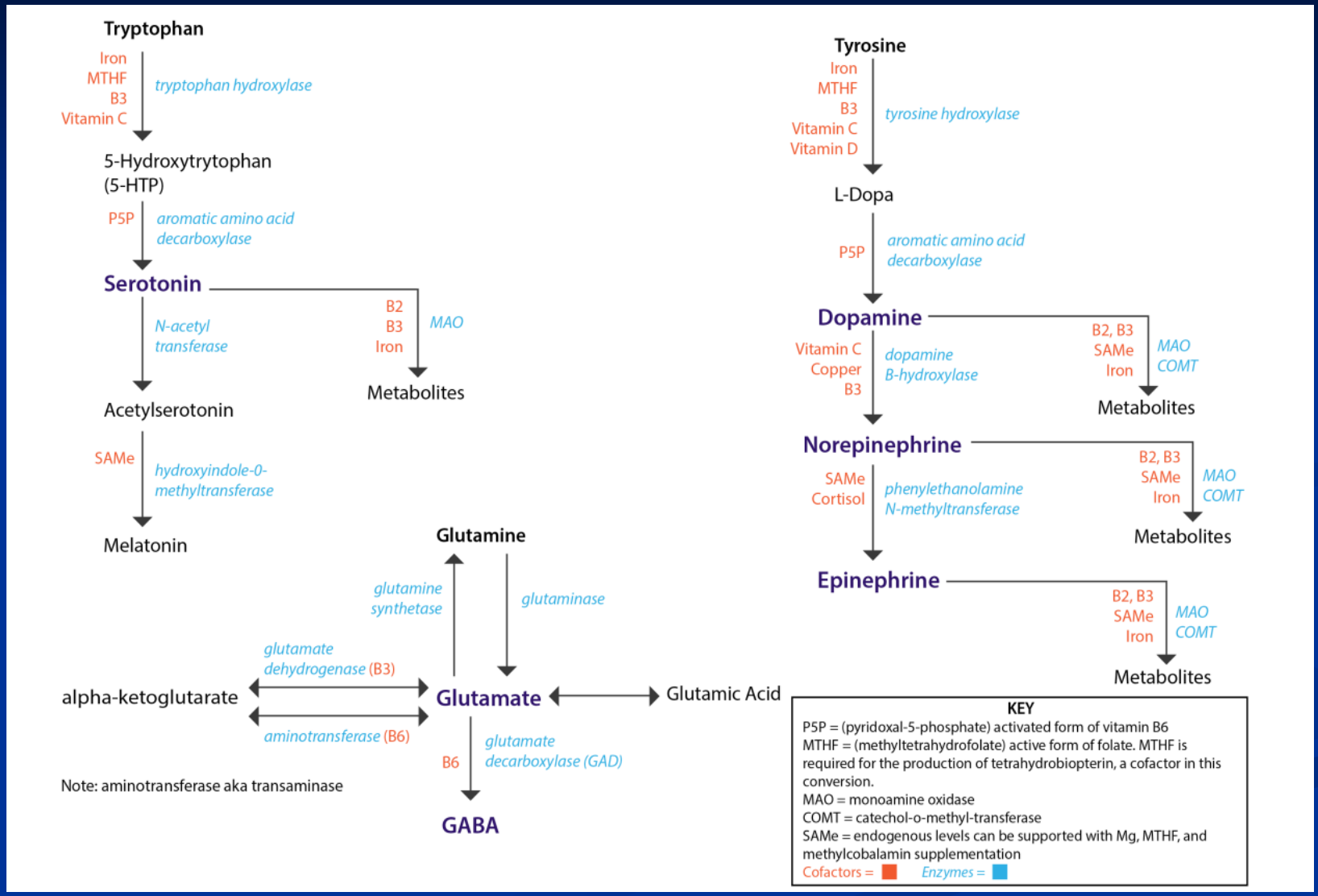
Endocrine/Hormone Support protocols

- Steroidogenic support (as before)
- Adrenal support
  - to avoid cortisol steal.
- Pregnenolone – 20-30 mg
  - Avoid cortisol steal
- DIM/I3C/Ca-d-glucarate
  - If needed for estrogenic detoxification
- Progesterone, BiEst (E2/E1), Estriol
- DHEA
- Exercise and lower carb diet (blood sugar)

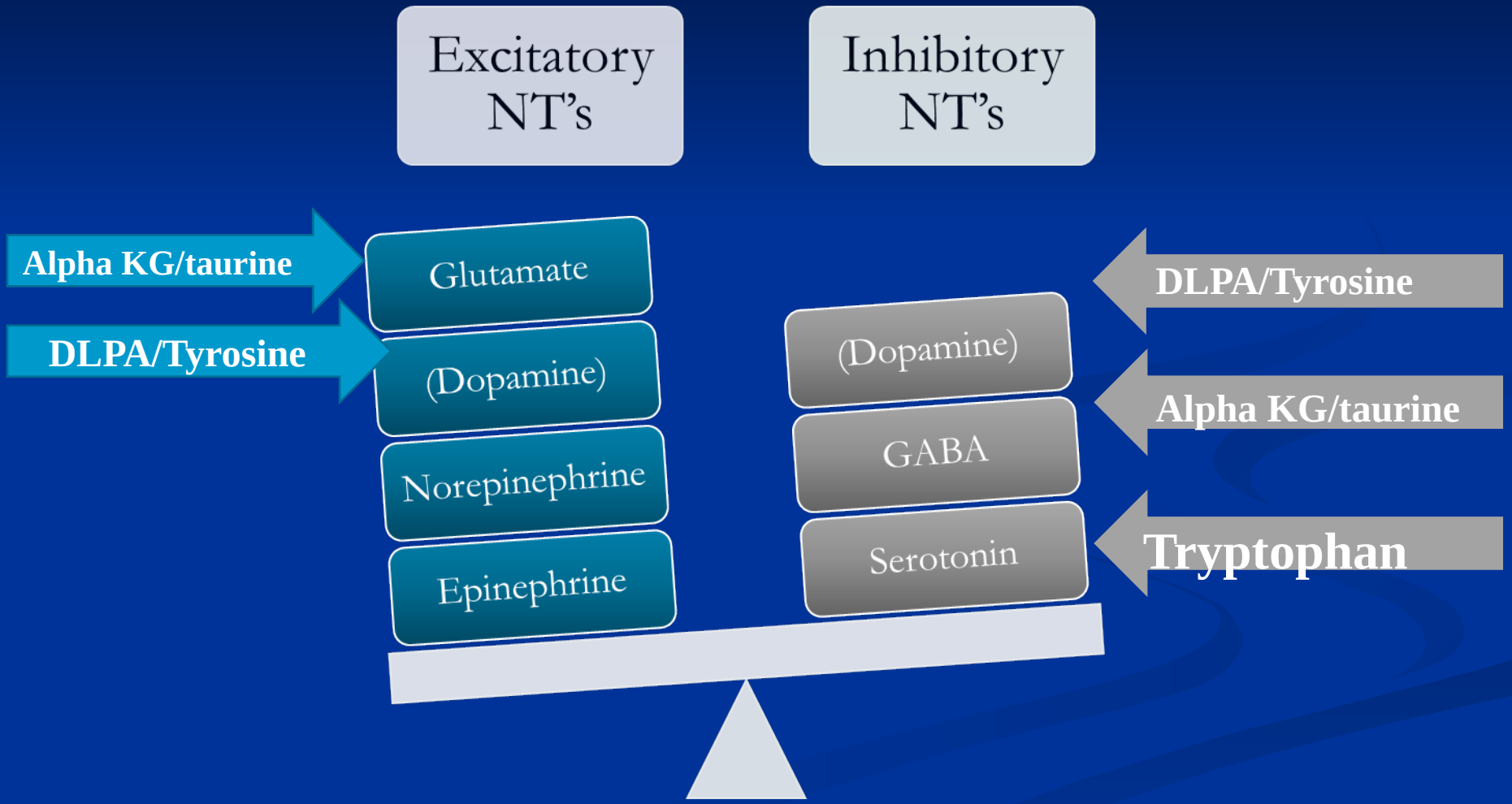
Neurotransmitters



Nutritional components of NT generation



A review of basic neurotransmitters



NT Nutritional Cheat Sheet *(give in case of...)*	High	Low
Serotonin	Mg, glycine, B2, B3, SAMe	5-HTP (50–100 mg), B6/P5P, St. John's wort (600 mg), SAMe, Estrogens
GABA	Progesterone, time	Glycine, L-theanine, Taurine, GABA, Magnesium
Glutamate	L-theanine, Glycine, molybdenum, yucca	Glutamine, alpha-ketoglutarate
Dopamine	L-theanine,Vitamin B2, B3, Iron, SAMe	Tyrosine, DL Phenylalanine, Mucuna cochinchinensis, Mucuna pruriens (velvet bean), Testosterone
NorEpinepherine	L-theanine,Vitamin B2, B3, Iron, Cu, SAMe	Rhodiola, Tyrosine, DL Phenylalanine, Mucuna cochinchinensis, Mucuna pruriens (velvet bean)
Epinepherine	L-theanine,Vitamin B2, B3, Iron, SAMe	Rhodiola, Tyrosine, DL Phenylalanine, Mucuna cochinchinensis, Mucuna pruriens (velvet bean), SAMe
Histamine	NAC, stinging nettles, Quercetin, Colostrum, SBI	Vit C, Colostrum, Cordyceps
Acetylcholine	Progesterone	Phosphatidyl choline, Acetyl-l-carnitine

Toxic factors

Polypharma and Interactions

Don’t forget the “toxins” of unintentional pharma side effects

The Average American over 60 takes 8 medications.

Determining the precise interactions and nutrient driven depletions is almost impossible.

Statins – side effects

- Numerous side effects noted in the literature:
- Muscle pain
- **Cognitive issues**
- Fatigue
- Sexual issues
- Kidney and liver damage

- *Zhang H, Skentzos S et. Al, Discontinuation of statins in routine care settings: a cohort study, Ann Intern Med 2013, 158:526-534*

The Truth of Lipitor

- Watch for depletions of CoQ10
- Rhabomyolysis, Alzheimer's, Fibromyalgia, etc.
- Watch for Vit D and hormone depletions if total cholesterol drops below 140.

Medications	Proven Nutrient Depletions	Selected Side Effects
Antacids – (H-22 Blockers, Proton Pump Inhibitors - Nexium®, Prevacid®, Protonix®, Maalox®, Mylanta®, Tagamet®, TUMS®, Pepcid®, Zantac®, Prevacid, Prilosec	Vit B12, folic acid, Vit D, calcium, Iron, Zinc, Vit B1, Phosphorus	Anemia, fatigue, cardiovascular risk, birth defects, muscle weakness, hair loss, lowered immunity, osteoporosis
Antibiotics – Amoxicillin, Ampicillin, Pennicillin, Tetracycline, Cephalosporin, Ciprofloxacin	Bifidobacteria species, Lactobacillus species, Vit B1, B2, B3, B6, B12 Inositol, Biotin, Vit K, Vit C, Vit E, Magnesium, Zinc	Weak immune system due to alterations in gut flora, digestion and absorption issues. Candida, possible supra infections
Anti-Convulsants – Clonazepam, diazepam, phenobarbitol, valproic acid, phenytoin	Vits B1, B12, Biotin, Folic acid, Vit D, Vit K, calcium, magnesium and carnitine.	Depression, irritability, anemia, cardiovascular disease, osteoporosis, muscle cramps, fatigue and heart or blood pressure irregularities
Anti-Depressants and Anti-Psychotics-Amitriptyline, Thorazine, haloperidol, Prolixin	Melatonin, CoQ10, B12, B-2	Heart disease, fatigue, headache, insomnia, nerve pain, muscle aches, numbness, confusion, memory loss, Candida

Beta Blockers - Propanolol, Atenolol, Metoprolol, Toprol	CoQ10	High blood pressure, congestive heart failure, fatigue
B2 Adrenergic Agonists – Albuterol, terbutaline	Potassium	Heartbeat irregularities, fatigue, weakness, edema
Calcium channel blockers – Verapamil	Potassium	Heartbeat irregularities, fatigue, congestive heart failure
Corticosteroids – Cortisone, Dexamethosone, Prednisone	Calcium, Vit D, Potassium, Zinc, Vit C, Magnesium, Folic acid, Selenium, Vit B12, Chromium	Osteoporosis, blood pressure irregularities, lowered immunity, anemia, fatigue, weight gain

Depakote (Valproic Acid)	Folic Acid, Carnitine	Anemia, Cardiovascular disease, muscle weakness, cramps, fatigue
Dilantin	Biotin, Vit D, Calcium, Folic acid, Vit K, Vit B12, Vit B1	Hair loss, depression, muscle weakness, cardiovascular disease, memory loss, edema
Diuretics – Lasix, Vasotec, Aldomet	Calcium, Magnesium, Vit B1, Vit B6, Vit C, Potassium, Zinc, CoQ10	Osteoporosis, cardiovascular disease, cramps, PMS, depression, lowered immunity
HRT Therapies	Vit B6, Magnesium, Melatonin	Depression, sleep disturbances, cardiovascular disease risk

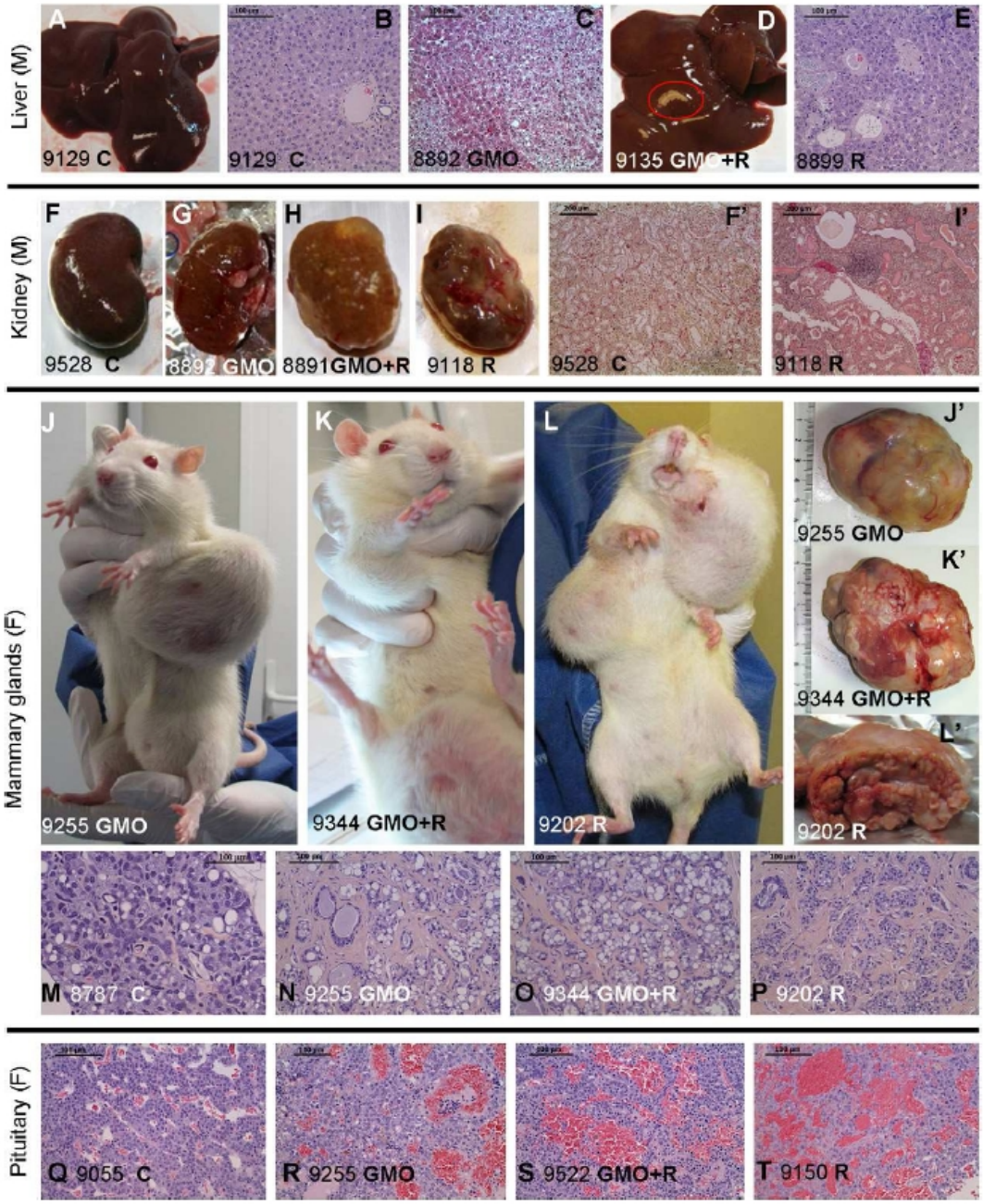
Metformin (Glucophage)	Vit B12, CoQ10, folic acid	Anemia, fatigue, cardiovascular disease, hypertension, weight gain
Oral Contraceptives	Folic acid, Vit B6, Vit B12, Vit B2, Vit C, Magnesium, Zinc, Vit B3, Melatonin	Birth defects, cervical dysplasia, anemia, cardiovascular disease, fatigue, osteoporosis, cramps, insomnia, lowered immunity
Statins – Zocor, Simvastatin, Lipitor, Mevacor	Vit A, Vit B6, B12, Vit D, Vit E, Vit K, Iron, Calcium, Magnesium, Zinc and CoQ10	Immune response, fatgue, weakness, muscle cramps, memory loss, shortness of breath, liver damage and heart disease.

Endocrine disruptors

- Other disruptors include:
  - Alkylphenols
  - Bisphenol A (BPA)
  - DDT
  - Polychlorinated biphenyls
  - Phthalates
  - Polybrominated diphenyl esters
- Lower dosages far worse sometimes than elevated dosages. (LD 50 not as important).

- BPA present in most recycled paper, flyers, magazines, bus and train tickets, envelopes, newspapers, food wrappers and cartons, airplane boarding passes, printing paper, business cards, napkins, paper towels, and toilet paper(!?). Also lines food cans and functions as epoxy resin in everything from medical equipment to receipt paper
- In nearly 5000 adult Americans, greater urinary BPA levels associated with a much higher body fat percentage and greater risk of obesity
- Study points to lowering BPA exposure as primary treatment for obesity in the U.S.
- BPA increases body fat because it alters insulin sensitivity, slows metabolism, causes inflammation, and decreases levels of hormone adiponectin that regulates fat burning
- In addition, BPA mimics estrogen in the body, contributing to fat gain as well as altered behavior and cognitive function

- Trasande, L., Association between Urinary BisphenolA Concentration and Obesity Prevalence in Children and Adolescents. Journal of the American Medical Association. 2012. 308(11), p.1113-20
- Shankar, A., TeppalaS., et al. Urinary BPA Levels and Measures of Obesity: Results from the NHANES 2003-2008. International Scholarly Research Network-Endocrinology2012. Article ID 965243



. 3. Anatomopathological observations in rats fed GMO treated or not by Roundup, and effects of Roundup alone. Macroscopic and microscopic photographs show male ers (A–E) and left kidneys (F–I'), female mammary glands (J–P) and pituitaries (Q–T), according to Table 2. The number of each animal and its treatment is specified. acroscopic pale spots (D) and microscopic necrotic foci in liver (C clear-cell focus, E basophilic focus with atypia), and marked or severe chronic progressive nephropathies, illustrated. In females, mammary tumors (J,J',N adenocarcinoma and K,K',L,L',O,P fibroadenomas) and pituitary adenomas (R–T) are shown and compared to controls (C er the rat number).

The Grim Reality Of GMO'd foods

Seralini, G.E. Et al,

Long term toxicity of a Roundup Herbacide and a Roundup-tlerant genetically modified maize. Food Chem Toxicol (2012) http://dx.doi.org/10.10101 6/j.fct.2012.08.005

There has been considerable pressure to retract and discredit this study despite new studies confirming these results.

Roundup

- Shikimic Acid - makes DLPA, tryptophan and tyrosine
  - Inhibited by glyphosate (Monsanto's Roundup)
- Glyphosate – first used on crops as a mineral chelator
  - Creates antigenic proteins.
  - Strong antibiotic
  - Attacks lactobacilli
  - Clostridia are resistant to it.
  - Gene silencing mechanism
    - AT least12 carbohydrate storing genes in animals inhibited by glyphosate. (diabetes, metabolic syndrome)
  - Alter immune activity and cytokine
  - Downreulates DLPA production (NE, Epi, Dopaamine)
  - **Down regulates 5HTP – serotonin, melatonin**
  - Methionine, serine, glycine all downregulated in production by glyphosate
  - Increases ammonia in individual cells. (think CBS)

Aspartame

- 1996 paper suggested link between rise in brain cancers and aspartame.
  - Supported with rat models which showed the aspartame molecule has mutagenic potential
    - J Neuropathol Exp Neurol. 1996 Nov;55(11):1115-23.
- Paper in 2006 disputed this with a large n-value sample, but only looked at specific brain and blood cancers with aspartame use.
    - Cancer Epidemiol Biomarkers Prev 2006;15(9):1654 – 9
- Hypothesis is that only small amounts enter our blood stream because aspartame is broken down so quickly, except in those with phenylketonuria (PKU).

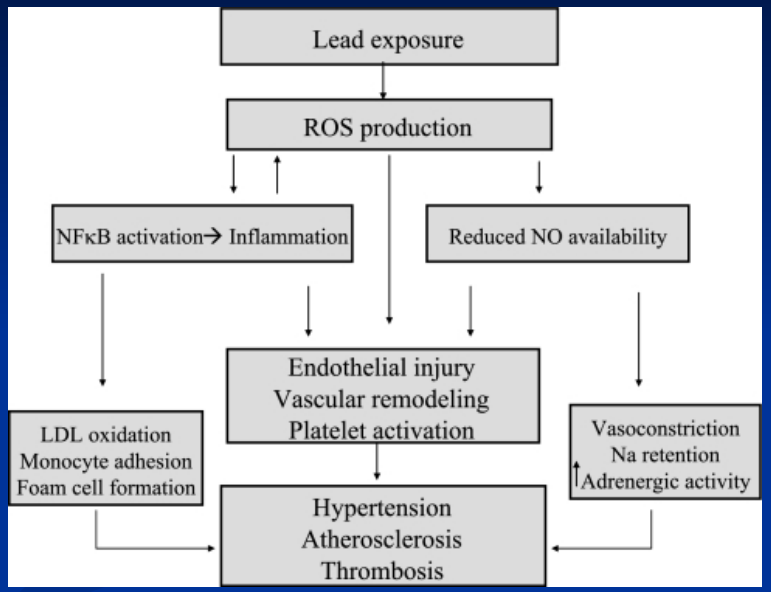
Aluminum and AD

- Some evidence peripheral pathology via a glycogen synthase kinase pathway resulting in hyperphosphorylation of the tau protein.
- Aluminum also found associated with the paired helical filaments (PHF's) in AD
  - Though this is not necessarily causal

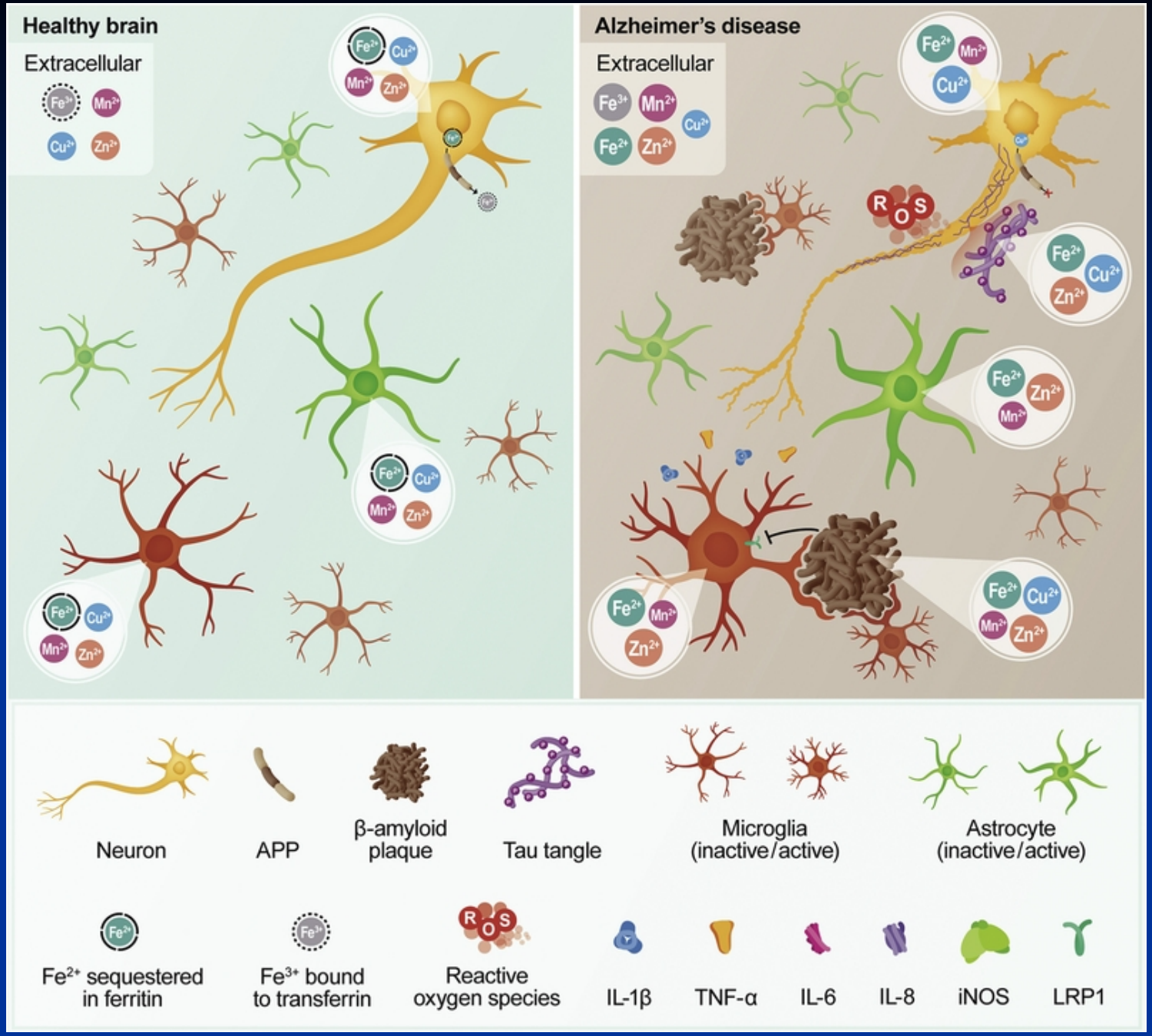
- *Sanajou S, Erkekoğlu P, Şahin G, Baydar T. Role of aluminum exposure on Alzheimer's disease and related glycogen synthase kinase pathway. Drug Chem Toxicol. 2023 May;46(3):510-522. doi: 10.1080/01480545.2022.2065291. Epub 2022 Apr 21. PMID: 35443844.*
- *Colomina MT, Peris-Sampedro F. Aluminum and Alzheimer's Disease. Adv Neurobiol. 2017;18:183-197. doi: 10.1007/978-3-319-60189-2_9. PMID: 28889268.*
- *Huat TJ, Camats-Perna J, Newcombe EA, Valmas N, Kitazawa M, Medeiros R. Metal Toxicity Links to Alzheimer's Disease and Neuroinflammation. J Mol Biol. 2019 Apr 19;431(9):1843-1868. doi: 10.1016/j.jmb.2019.01.018. Epub 2019 Jan 18. PMID: 30664867; PMCID: PMC6475603.*
- *McLachlan DR. Aluminum and Alzheimer's disease. Neurobiol Aging. 1986 Nov-Dec;7(6):525-32. doi: 10.1016/0197-4580(86)90102-8. PMID: 3550508.*
- *Shore D, Wyatt RJ. Aluminum and Alzheimer's disease. J Nerv Ment Dis. 1983 Sep;171(9):553-8. doi: 10.1097/00005053-198309000-00005. PMID: 6350535.*

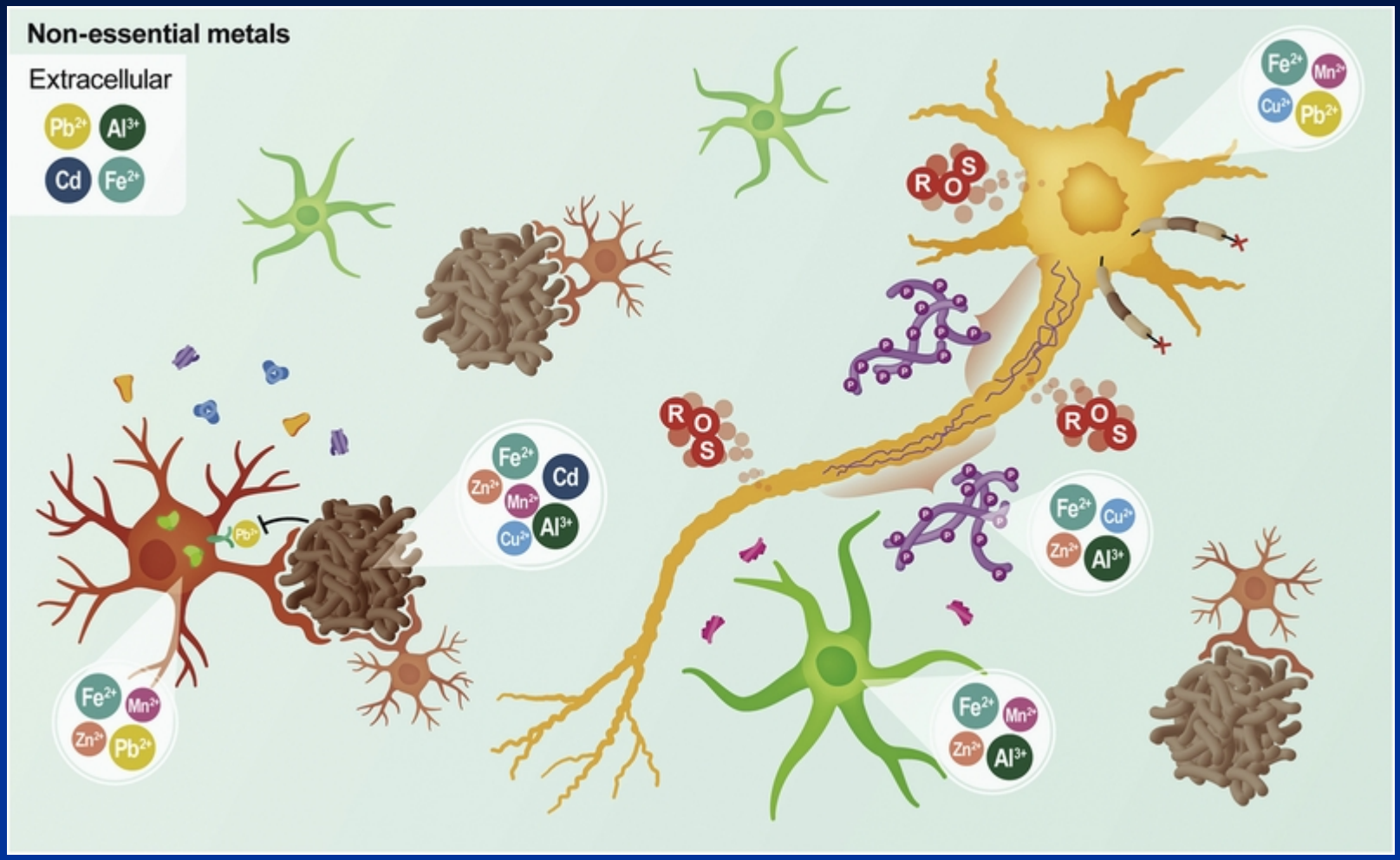
Lead

- Lead exposure associated with:
  - Hypertension (HTN)
  - Cardiovascular disease
  - Oxidative stress
  - Limiting nitric oxide availability and signaling
  - Augmenting adrenergic activity
  - Altering the renin-angiotensin system
  - Raising vasoconstrictor prostaglandins
  - Promoting inflammation
  - Disturbing vascular smooth muscle Ca(2+) signaling
  - Diminishing endothelium-dependent vasorelaxation
  - Endothelial injury and repair
  - Inhibit angiogenesis
  - Stimulate vascular smooth muscle cell proliferation
  - Reduce tissue plasminogen activator
  - Raise plasminogen activator inhibitor-1 (PAI-1)
  - Via these and other actions, lead exposure causes HTN and promotes arteriosclerosis, atherosclerosis, thrombosis,
  - **and vascular dementia**.



- *Am J Physiol Heart Circ Physiol. 2008 Aug;295(2):H454-65. doi: 10.1152/ajpheart.00158.2008. Epub 2008 Jun 20.* ***Mechanisms of lead-induced hypertension and cardiovascular disease.***
- *Environ Health Perspect. Jun 1988; 78: 91–99* ***Cardiovascular actions of lead and relationship to hypertension: a review. S J Kopp****, J T Barron, and J P Tow*
- *Vupputuri S, He J, Muntner P, Bazzano L, Whelton PK, Batuman V. Blood lead level is associated with elevated blood pressure in blacks. Hypertension.2003; 41: 463–468.*
- *Den Hond E, Nawrot T, Staessen JA. The relationship between blood pressure and blood lead in NHANES III. J Hum Hypertens. 2002; 16: 563–568.*
- *Nawrot TS, Thijs L, Den Hond EM, Roels HA, Staessen JA. An epidemiological re-appraisal of the association between blood pressure and blood lead: a meta-analysis. J Hum Hypertens. 2002; 16: 123–131.*





Treatments for Heavy Metals

Heavy Metals	Pharmaceutical	Natural
Mercury	DMSA, DMPS	IMD, DE, Chlorella, Cilantro, Garlic, OSR, Z naturals
Lead	DMSA, EDTA, DMPS	IMD, DE, Chlorella, Cilantro, Garlic, OSR, Z naturals
Cadmium	DMSA, EDTA, DMPS	IMD, DE, Chlorella, Cilantro, Garlic, OSR, Z naturals
Arsenic	DMSA, EDTA, DMPS	IMD, DE, Chlorella, Cilantro, Garlic, OSR Z naturals
Antimony	DMSA, EDTA, DMPS	IMD, DE, Chlorella, Cilantro, Garlic, OSR, Z naturals

Baseline Detox Protocol

- Gall bladder support:
  - Gentian, bile salts, beet concentrates, taurine
- N-Acetyl-Cysteine
- Liposomal Glutathione
- Fulvic/Humic Acid binder or
- Greens Drink
- High dose probiotics
- Milk Thistle based detox support
  - Milk Thistle, Vits B6/9/12,
  - Artichoke, green tea extract, MSM, Pomegranate
- Ca-d-glucarate/I3C/DIM if warranted

This will be covered in detail in the lecture immediately after me:

Tackling Toxins

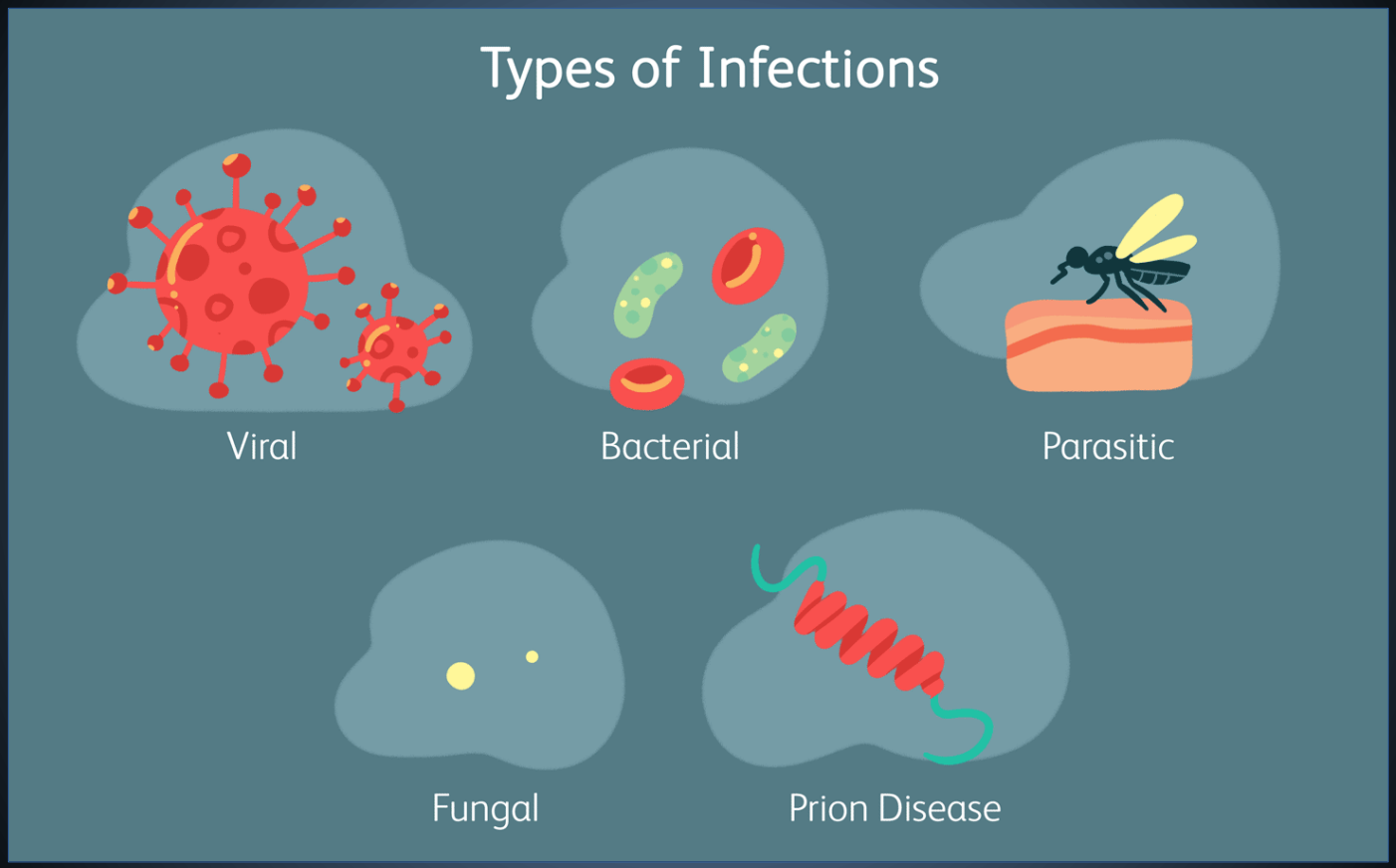
Step 1- Heavy Metals (low hanging fruit)

- Zeolites
- Silica (Fiji Water)
- Chlorophyll
- Chlorella
- Bentonite Clay
- Modified Citrus Pectin
- Activated Charcoal

The Gut Work Supplements (Build Up)

- Digestive Enzymes/ Proteolytic Enzymes
- Probiotics
- Anti-Inflammatories (Fish oils, DGL)
- Polyphenols
- Resistant Starches
- Antimicrobials
- Liver Support
- Vitamins
- Minerals

Infections and Dysbiosis



Alzheimer's Disease Associated Amyoid β–protein is an AntiMicrobial Peptide (AMP)

- Metabolic by product that induces an inflammatory response.
- Experimental evidence against at least 8 common and clinically relevant microorganisms.
- AD whole brain homogenates show significantly higher anti-microbial activity than aged matched controls.
- Suggests may have normally function in the innate immune system.
- Potent, broad spectrum antibiotic activity targeting gram neg and positive bacteria, mycobacteria, enveloped virii, fungi, protozoa, or tranformed cancerous host cells.
  - C. albicans, E coli, S. epidermidis S. pneumonia, HSV 1
- AMP's potent immunomodulators for cytokine release.

Soscia SJ, Ingelsson, M et al, (2010) Alzheimer's Disease Associated Amyoid β–protein is an AntiMicrobial Peptide, PloS ONE 5(3): e9505

HSV1

- Strong association of HSV1 IgG and IgM seropositivity to HSV1 with activation of AD.
  - 512 elderly Pts initially free of AD followed for 14 years.
  - 5 seropositive w/o AD vs 17 seropositive developed AD in the same time frame.
  - Hazard Ratios:
    - Anti HSV IgM status - 2.55
    - Female gender - 1.48
    - High educational level - 0.87
    - APOE-ε4 allele - 2.00
- Reactivation of seropositivity highly correlated with incident AD. HSV chronic infection may therefore be contributive to the progressive brain damage of AD.
- Recurrent reactivation of HSV might act as a potent microglia stimulation.
- During acute HSV1 infection, same brain regions affected as in AD.
- APOE-ε4 neither necessary nor sufficient for AD
    - APOE-ε4 interestingly increased risk for cold sores.

Letenneur L et al, (2008) Seropositivity to Herpes simplex Virus antibodies and Risk of Alzheimer's disease: a population-Based cohot Study. PLoS ONE, 1 November 2008, 3(11): e3637
Itzhaki RF, Woziak MA, Journal of Alzheimer's Disease 13 (2008)393-405

APOE-ε4 Allele and HSV1 in AD

- HSV 1 virions competed better against APOE-ε4 than APOE-ε3 enriched lipoprotein particles in in vitro experiments for receptor binding and intracellular internalization.
- Strong evidence that HSV1 is a major factor in AD, giving a target for prevention and treatment.
- HSV1 DNA found to be localized within the AD amyloid plaques.

Journal of Alzheimer's disease 13(2008) 421-435
Wozniak MA, et al, J Pathology 2009; 217: 131-138

C pneumoniae - AD and MS

Monoclonal Ab staining confirms presence of C pneumoniae in the astrocytes, microglia, and neurons of 20/27 AD patients, but only 3/27 controls.

Hervé C. Gérard, Ute Dreses-Werringloer, Kristin S. Wildt, Srilekha Deka, Cynthia Oszust, Brian J. Balin, William H. Frey, Elizabeth Z. Bordayo, Judith A. Whittum-Hudson, Alan P. Hudson, Chlamydophila (Chlamydia) pneumoniae in the Alzheimer's brain, FEMS Immunology & Medical Microbiology, Volume 48, Issue 3, December 2006, Pages 355–366

Of note:

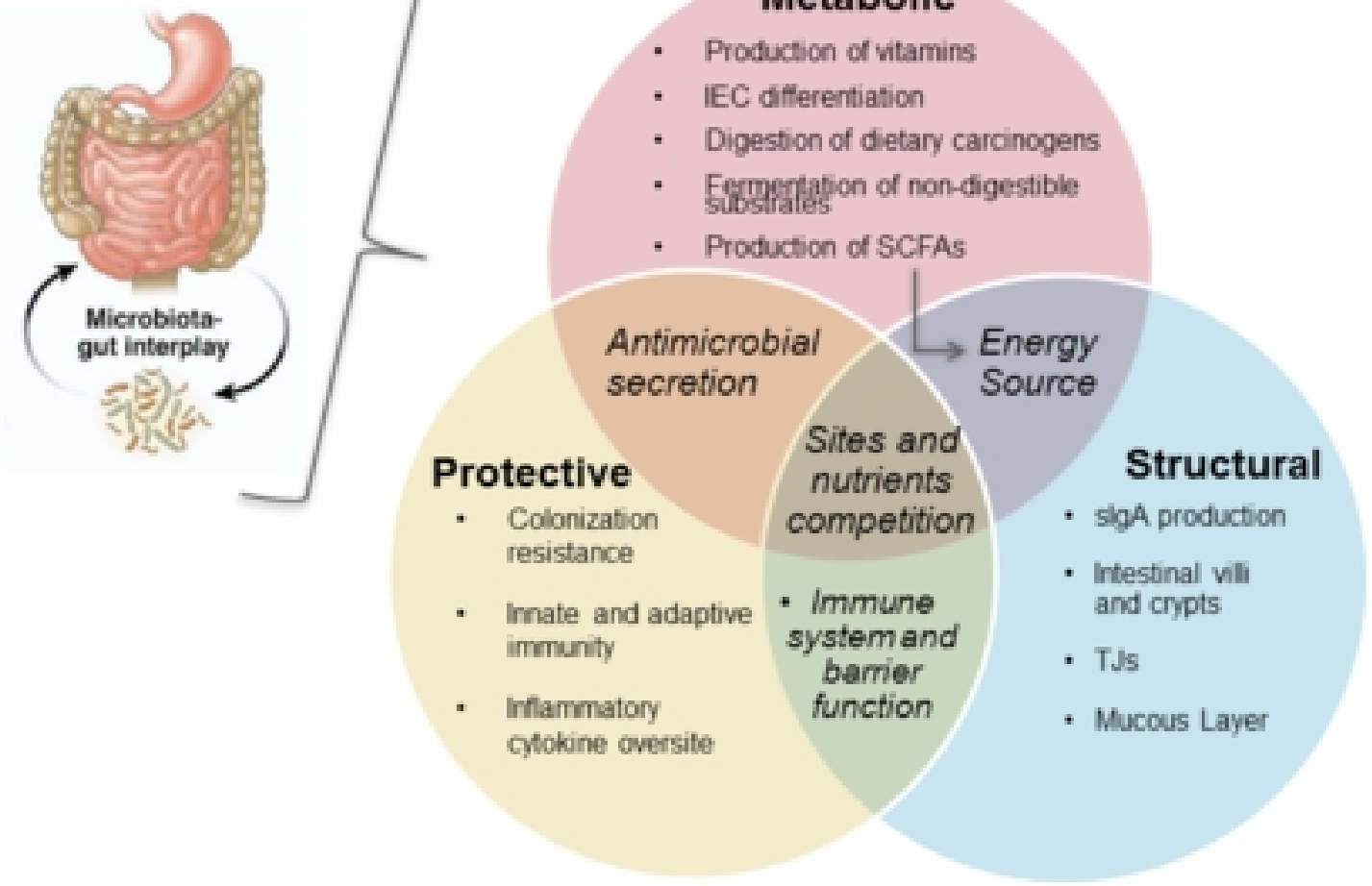
CSF oligoclonal bands in MS include antibodies aainst Chlamydophila antigens.

Lancet Neurology 2005; 4: 195-202

This strongly suggests subclinical and chronic “stealth” infections from a variety of pathogens as a primary stimulatory factor for microglial activation and subsequent neuronal damange in a variety of Neurocognitive disorders.

The larger question is, why the neurologic immune system is unable to address what is undoubtedly a normal exposure to pathogens historically, that is showing increased prevalence in recent years?

The Microbiota-gut Interplay Serves Many Functions

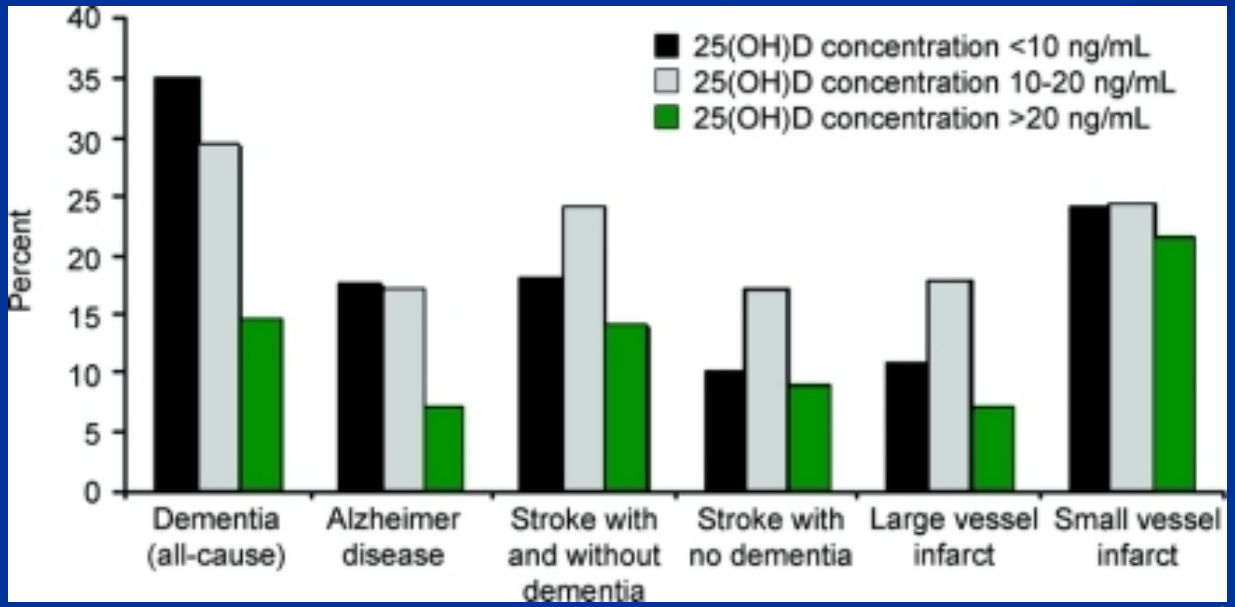


Grenham S, Clarke G, Cryan JF, Dinan TG. Brain-gut-microbe communication in health and disease. Front Physiol. 2011;2:94. Epub 2011 Dec 7. PubMed PMID: 22162969; PubMed Central PMCID: PMC3232439

Vit D

Vitamin D insufficiency and deficiency was associated with all-cause dementia, Alzheimer disease, stroke (with and without dementia symptoms), and MRI indicators of cerebrovascular disease. These findings suggest a potential vasculoprotective role of vitamin D

Buell JS, Dawson-Hughes B, Scott TM, Weiner DE, Dallal GE, Qui WQ, Bergethon P, Rosenberg IH, Folstein MF, Patz S, Bhadelia RA, Tucker KL. 25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services. Neurology. 2010 Jan 5;74(1):18-26. doi: 10.1212/WNL.0b013e3181beecb7. Epub 2009 Nov 25. PMID: 19940273; PMCID: PMC2809024.



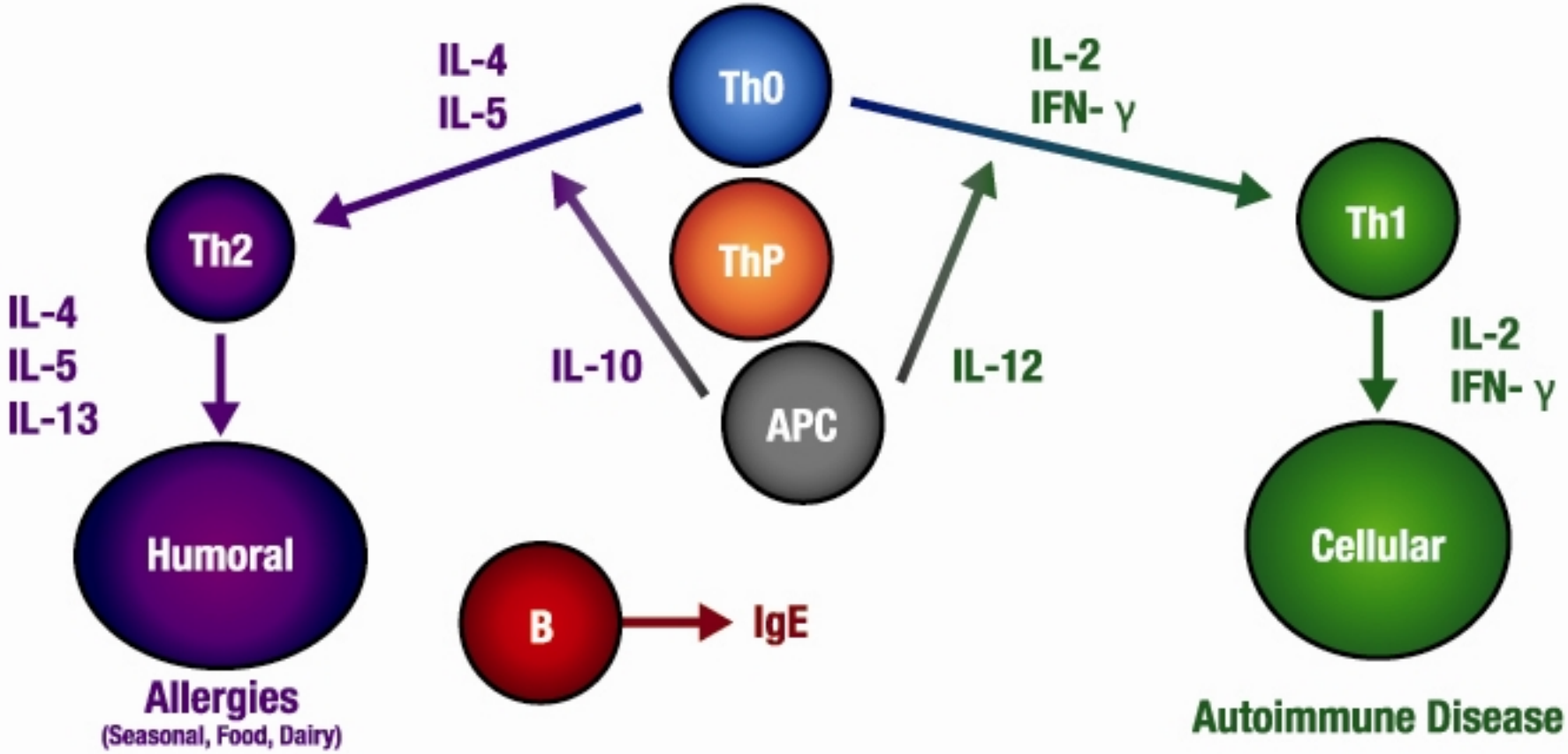
Vitamin D3, Cathelicidin

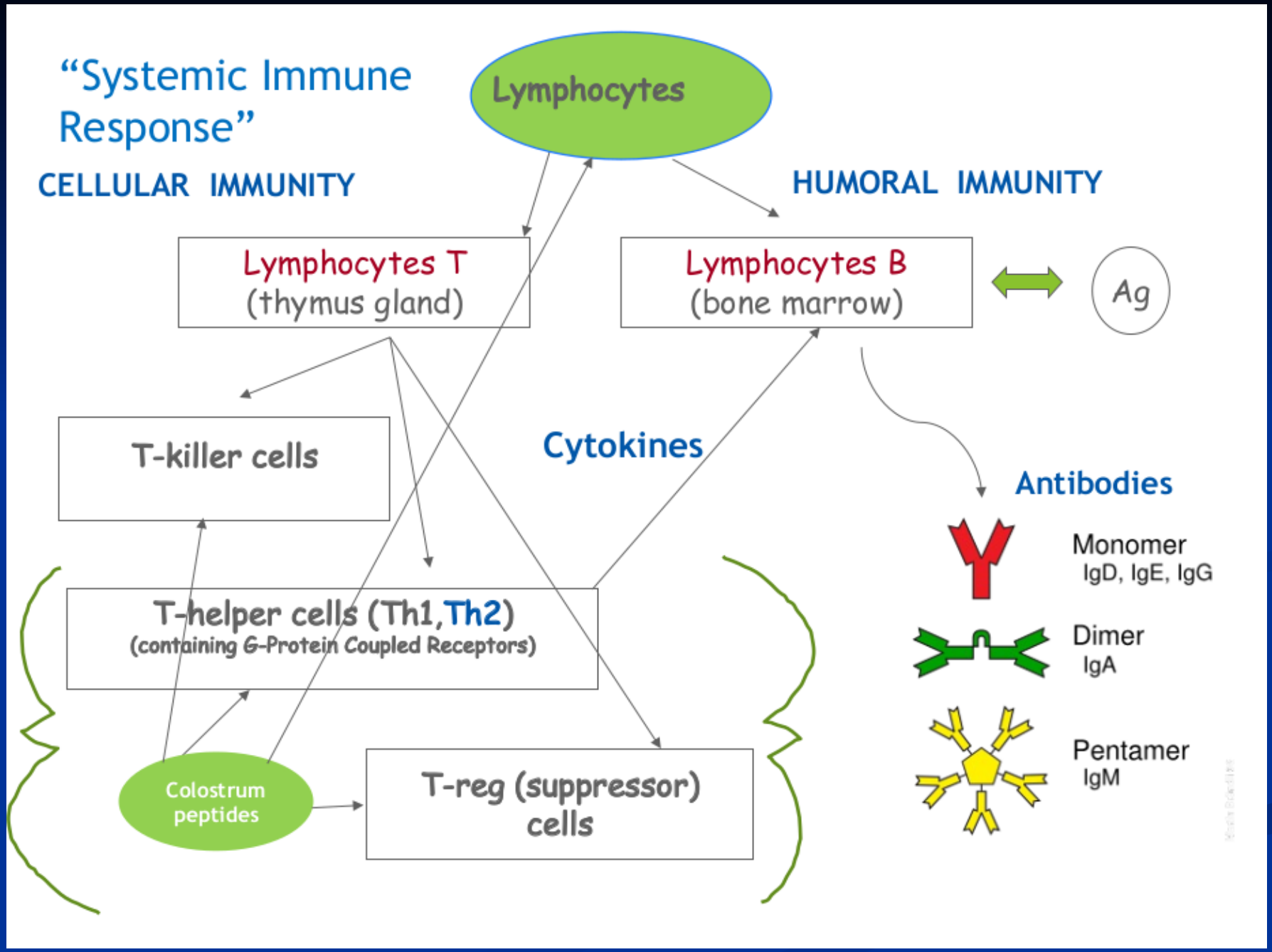
- Human Cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the Vitamin D receptor and is strongly upregulated in myeloid cells by 1,25 dihydroxyvitamin D3.
- Novel activity of 1,25 Vit D3 in regulation of primate innate immunity.
- Not conserved in other mammals
- May be responsible for the “antibiotic/antiviral” effects of Vitamin D
  - WBC maturation, membrane anti-oxidant, enhances neurotrophins, increases hippocampal density, suppresses expression of inflammatory cytokines.
- Dose dependent release of cathelicidin in animal models
- Amyloid protein therefore may be less of a causative agent itself, and is more likely part of a response mounted by the innate immune system.
- >600 iu qd intake of 25OH Vit D associated with statistically significant decrease in AD

Gombart et al, FASEB, Vol 19, July 2005; 1067-1077
Gombart AF, Future Microbiology. 2009; 4(9): 1151-1165
J Immunology, April 1, 2009: 182(7) 4289-85
Soscia SJ, Kirby JE, Washicosky KJ, Tucker SM, Ingelsson M, et al (2010)
Buell JS et al, Neurology, 2010: 74:18-26

Stealth Infection, Dysbiosis and Immunomodulation

- Anti-virals
  - Senolytics (fisetin), Vitamin D, Barberry, Goldenseal, monolaurin, Grapeseed extract
- Dysbiosis (parasites/fungi/bacteria)
  - Oregano oil, black walnut, wormwood, gentian, pumpkin
- Immunomodulators
  - Colostrum/PRP's, SBI, N-Acetyl-D-Glucosamine, Cordyceps (cordyceps militaris), Lion's Mane (Hericium Erinaceus), Turkey Tail (Trametes versicolor)





Neuronal and Mitochondrial Support Protocols

- Liposomal CoQ10 w PQQ
- D-ribose
- Alpha lipoic acid (MT replication)
- NAD/nicotinamide riboside
- L-ornithine
- Trans-resveretrol
- Acetyl-l-carnitine
- MCT oil
- Magnesium threonate/malate
- EXERCISE
- Stem cell support
- Fish oils
- Citrulline based nitric oxide support
- Sulforaphane w/ myrosinase

Example Protocol 1

- Low carb, higher fat diet - Keto, carnivore
- Exercise
- Sleep regulation

- ALA
- EPA/DHA
- Tumeric
- sulforaphane

- CoQ10 w/ PQQ
- MCT oil - 1 tblspn bid

- L-lysine - 1500 mg qd
- Vit D

- Methylated B's
- Greens drink (Anti-oxidants)

- Milk thistle based phase 1 and 2 mix
- Liposomal Glutathione
- NAC
- Fulvic Acid Binder

Example Protocol 2

- Carnivore - Gluten Free
- Exercise to Tolerance

- Citrulline based Nitric Oxide Suport
- Vitamin D3
- Black Cumin Seed Oil
- Monolaurin
- SBI with N-acetyl-glucosamine

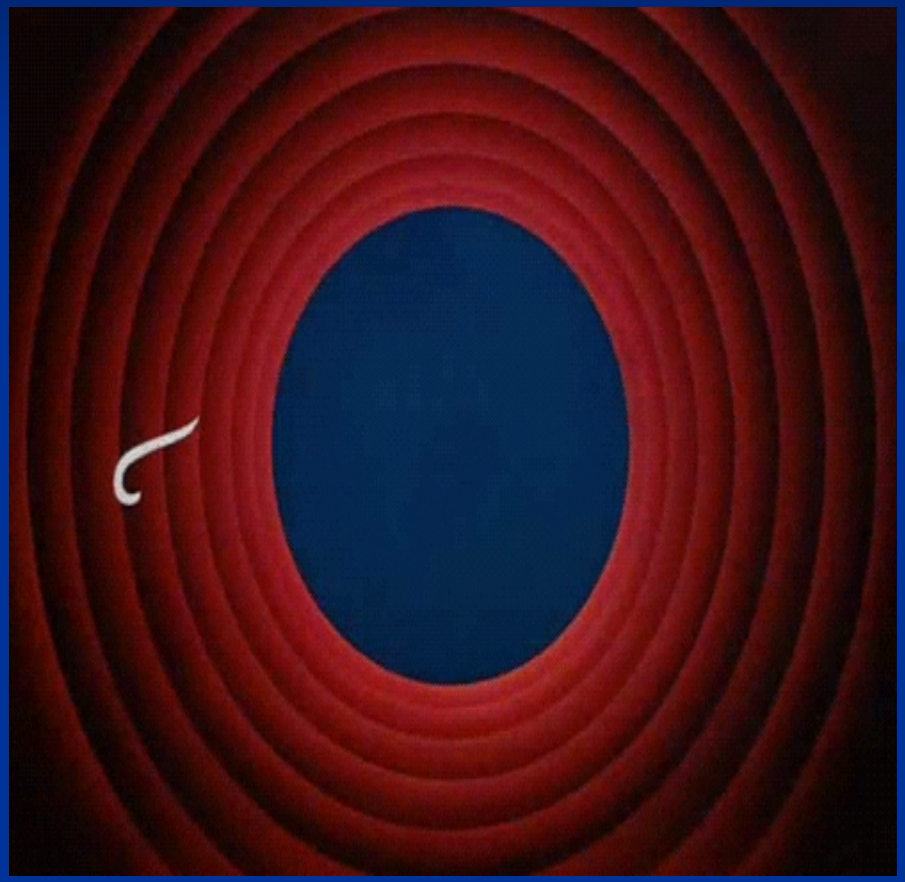
- Digestive Enzymes
- Probiotic >50 bil cfu

- D-ribose
- Liposomal CoQ10 w/ PQQ
- EPA/DHA

- Liposomal Glutathione
- Milk Thistle based detox mixture
- Fulvic Acid binder

- 5HTP w/ B6
- L-theanine

Thank you for your time and attention



RESERVES

CDID lecture to be added – 2 hours/60 slides

- Lyme (Holtorf)
  - Breakdown of Th1/TReg and overstimulation of Th2/Th17
  -

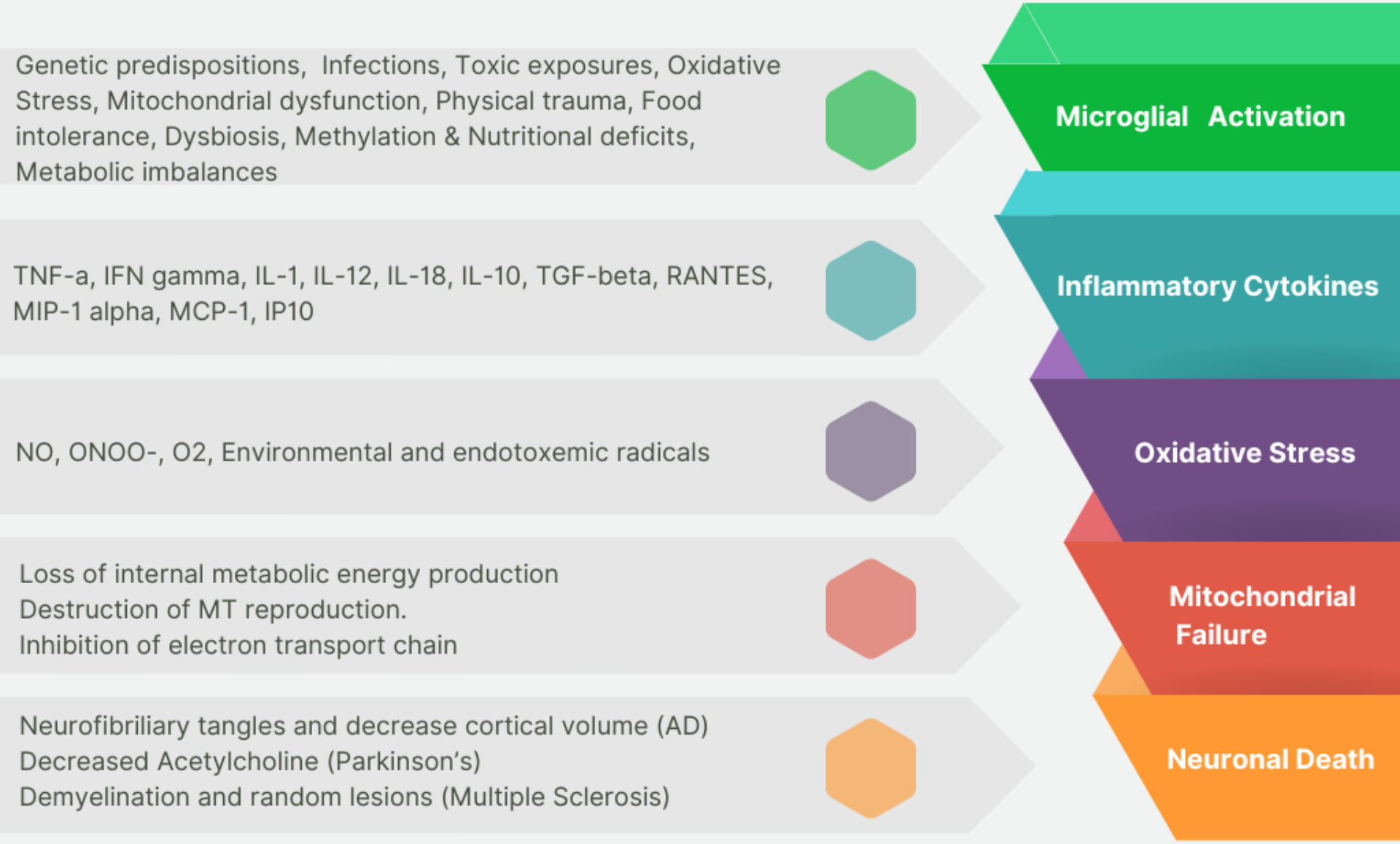
- Peptides for immunomodulation – Cerebrolysin (slide 120)
  - BPC 157 for ALZ/Parkinston's – immunomodulation (Holtorf) (slide 88) (slide 136)

Toxicity

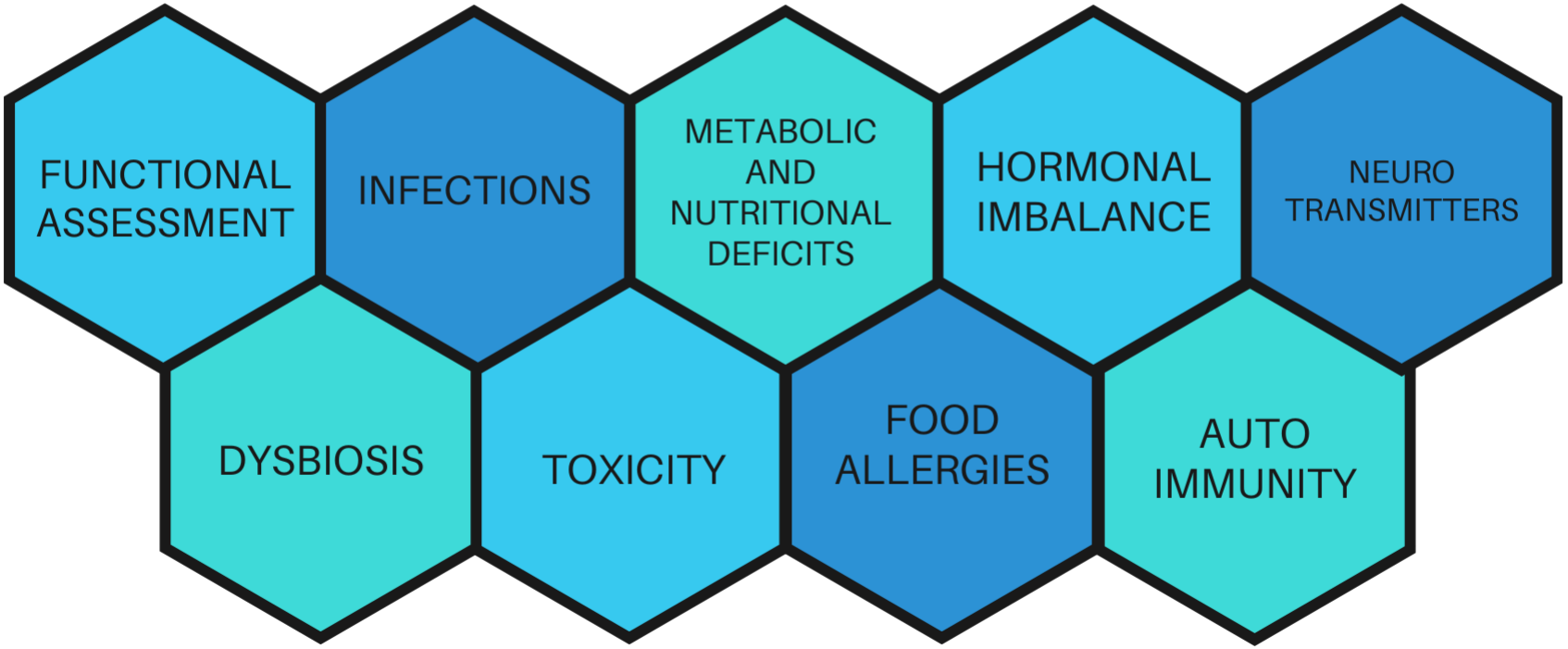
GSH for ALZ – Wallace Bridge PhD (A4M) and Perlmutter

Tie in with Greer next

A Functional Medicine Model of Neurocognitive Decline



Functional Medicine Assessment of Neurocognitive Disorders



Key Brain Health Factors

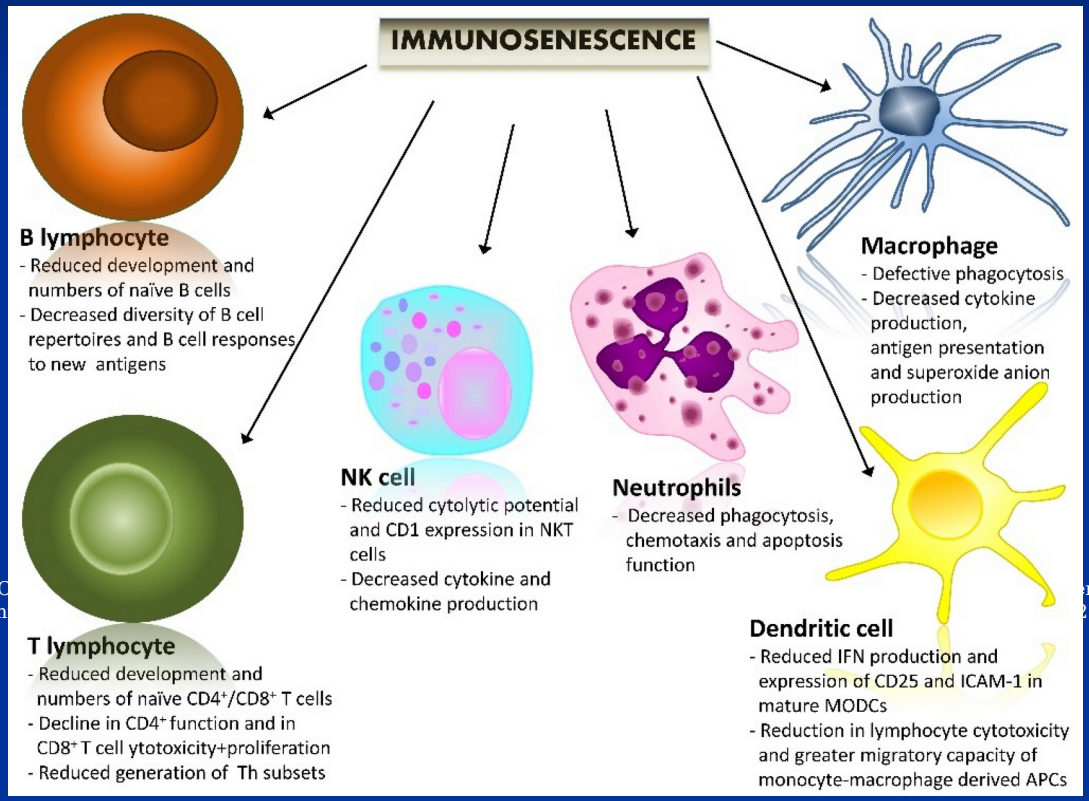
Increased Risk

Metabolic	Cardiovascular	Other
Diabetes	Hypertension	Poor Sleep
Insulin Resistance	Hyperlipidemia	Neurobehavioral
Obesity	Vascular	Hearing Difficulties
Inflammation	Smoking	Traumatic Brain Injury

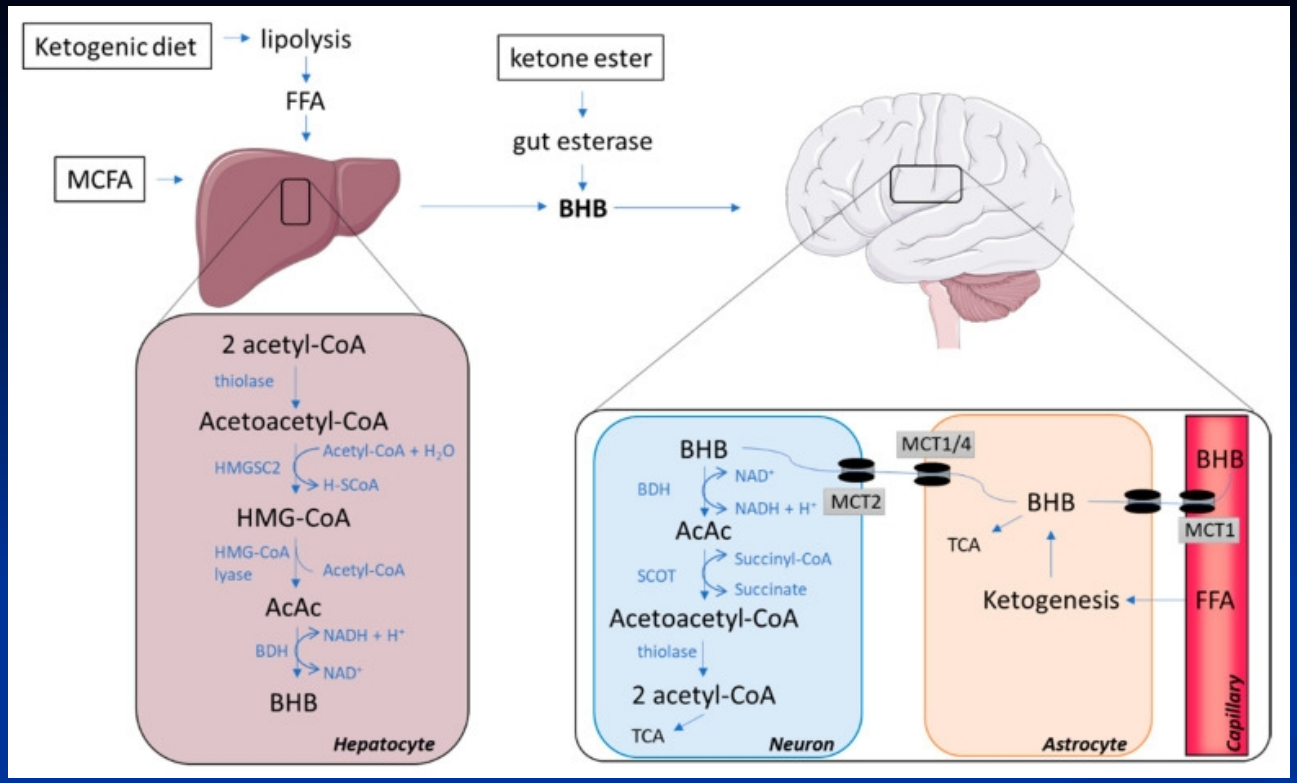
Diet	Exercise	Other
MIND Diet	Walking	Years of Education
Mediterranean	CORE Exercises	Mental Activities
Keto Diet	Aerobic	e.g., Cognitive Training
Other	Other	Social Engagement

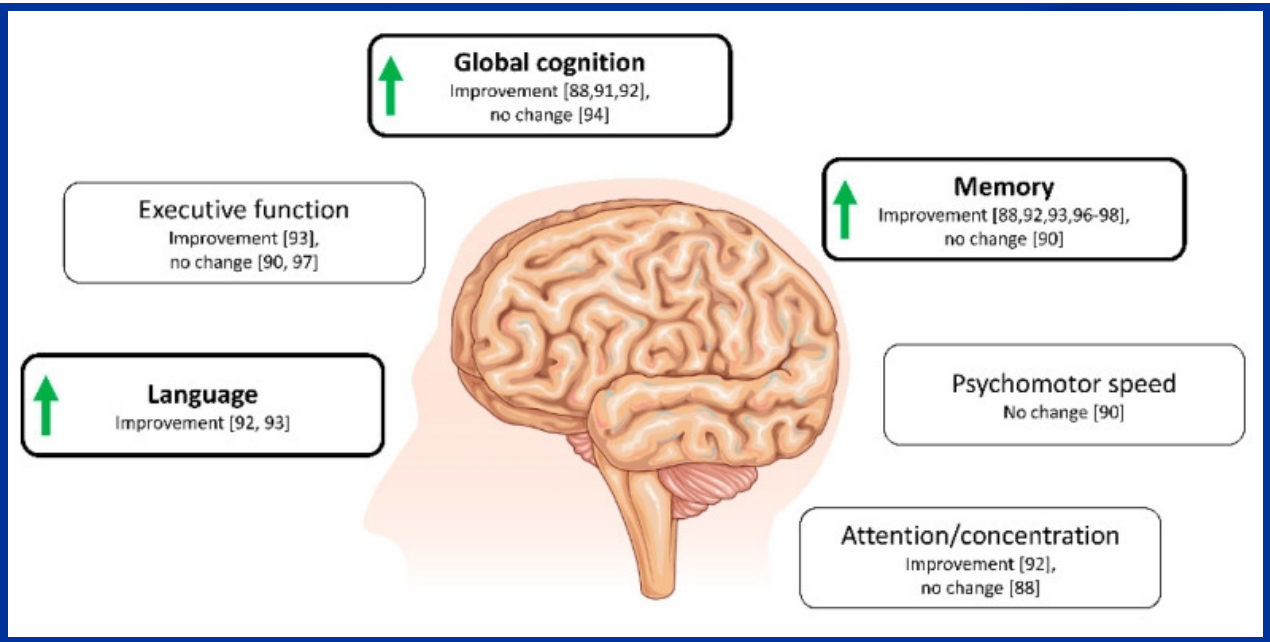
Decreased Risk

- **Immunosenescence:** The gradual deterioration of the immune system associated with aging that results in a reduced adaptive capacity towards infections and immune challenges.
- How do you fight time and aging itself?



- Isidori A, Loscocco F, C ence and Immunotherapy in Elderly Acute Myeloid Leukem 211


Ketogenic diet
lipolysis
FFA
MCFA
ketone ester
gut esterase
BHB
2 acetyl-CoA
thiolase
Acetoacetyl-CoA
HMGSC2
Acetyl-CoA + H2O
H-SCoA
HMG-CoA
HMG-CoA lyase
Acetyl-CoA
AcAc
BDH
NADH + H+
NAD+
BHB
Hepatocyte
BHB
BDH
NAD+
NADH + H+
MCT2
AcAc
SCOT
Succinyl-CoA
Succinate
Acetoacetyl-CoA
thiolase
2 acetyl-CoA
TCA
Neuron
MCT1/4
BHB
TCA
Ketogenesis
Astrocyte
BHB
MCT1
FFA
Capillary


Global cognition
Improvement [88,91,92],
no change [94]
Executive function
Improvement [93],
no change [90, 97]
Memory
Improvement [88,92,93,96-98],
no change [90]
Language
Improvement [92, 93]
Psychomotor speed
No change [90]
Attention/concentration
Improvement [92],
no change [88]

ALS and Keto

- Monotherapy: Time Restricted Ketogenic Diet for ALS
- TRKD - two meals per day, encouragement to eat to satiation and not restrict caloric intake.
- Roughly 60% fat, 30% protein, 5% fiber, and 5% net carbohydrate by weight.
- Blood glucose and ketones were measured daily at bedtime.
- Results:
  - Improvements in depression, fatigue, and quality of life.
  - Declines in physical function, maximal inspiratory pressure, and maximal expiratory pressure
  - But improvements in ALS-related function, forced expiratory volume, and forced vital capacity.
  - FVC predicted 2-3% decline per month in ALS patients - subject improved from a baseline of 3.3 L to 4.33 L.
  - Revised ALS Functional Rating Scale (ALSFRS-R) (0 to 48)
  - Subject predicted to decline from 42 at baseline to 24 over the 18-months study
  - Instead subject improved to 45.