ME/CFS Research at INIM: A Progress Report

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INIM

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Clinical Systems Biology
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TESTING NEW INTERVENTIONS IN ME/CFS
TARGETING MEDIATORS OF ILLNESS PERSISTENCE:

1. Gender Differences in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. (NIH RO1)
2. Genomic Approach to Find Novel Biomarkers and Mechanisms of CFS/ME. (NIH R21)
3. Male-specific genomic mechanisms of transcriptional regulation of ME/CFS/SEID (Solve CFS)
4. Effect of ME/CFS on Epigenetic Regulation in Specific Immune Cell Types (NIH R15)
5. Metabolic Abnormalities, Antioxidant Capacity and Toxic Exposures in ME/CFS. (NSU)
6. Clinical Nutrition Profile for ME/CFS (NSU)
7. Clinical Assessment of Patients with CFS and Biorepository Development. (CDC multicenter study)_.
8. Application of next-generation sequencing in identifying pathogenesis of ME /CFS.
9. **Resetting homeostasis in Women with ME/CFS , a phase 1 study foundation**
10. **Resetting homeostasis in Men with ME/CFS a phase 1 study , private donations**
11. The gene study interventions pilot – MTHFR pathway treatments in subgroup with defect (NSU HPD award)
12. An integrative medicine approach (NSU Presidents award)
13. **Realigning the Microbiome in ME/CFS (Kaneka)**
14. **Immune – GI Microbiome – Brain regulation in ME/CFS and GWI (Chaterjeee)**

Recruiting Now

	Study title	Who?	Where?	When
Pathogenesis-Chaterjee	Immune/Inflammatory Priming In Exacerbating Responses To GWI Stressors	**ME/CFS,** IBS	Miami VA	Recruiting now!
BBRAIN	Boston Biorepository, Recruitment and Integrative Network (BBrain) for GWI	**Healthy Controls**	Miami VA / INIM Kendall Location	Recruiting now!
Women V Men	Women Vs. Men With Gulf War Illness: Differences In Computational Models And Therapeutic Target	Healthy Women	Miami VA / INIM Kendall Location	Recruiting now!

	Study title	Who?	Where?	When
Kaneka Probiotic Study	"The Use of Directed Probiotics in ME/CFS Myalgic Encephalomyelitis/Chronic Fatigue Syndrome."	**ME/CFS**	INIM Davie/ Kendall	Recruiting Now!

The INIM Team

INIM Administration

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Kristy Pinkham
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VA clinical research

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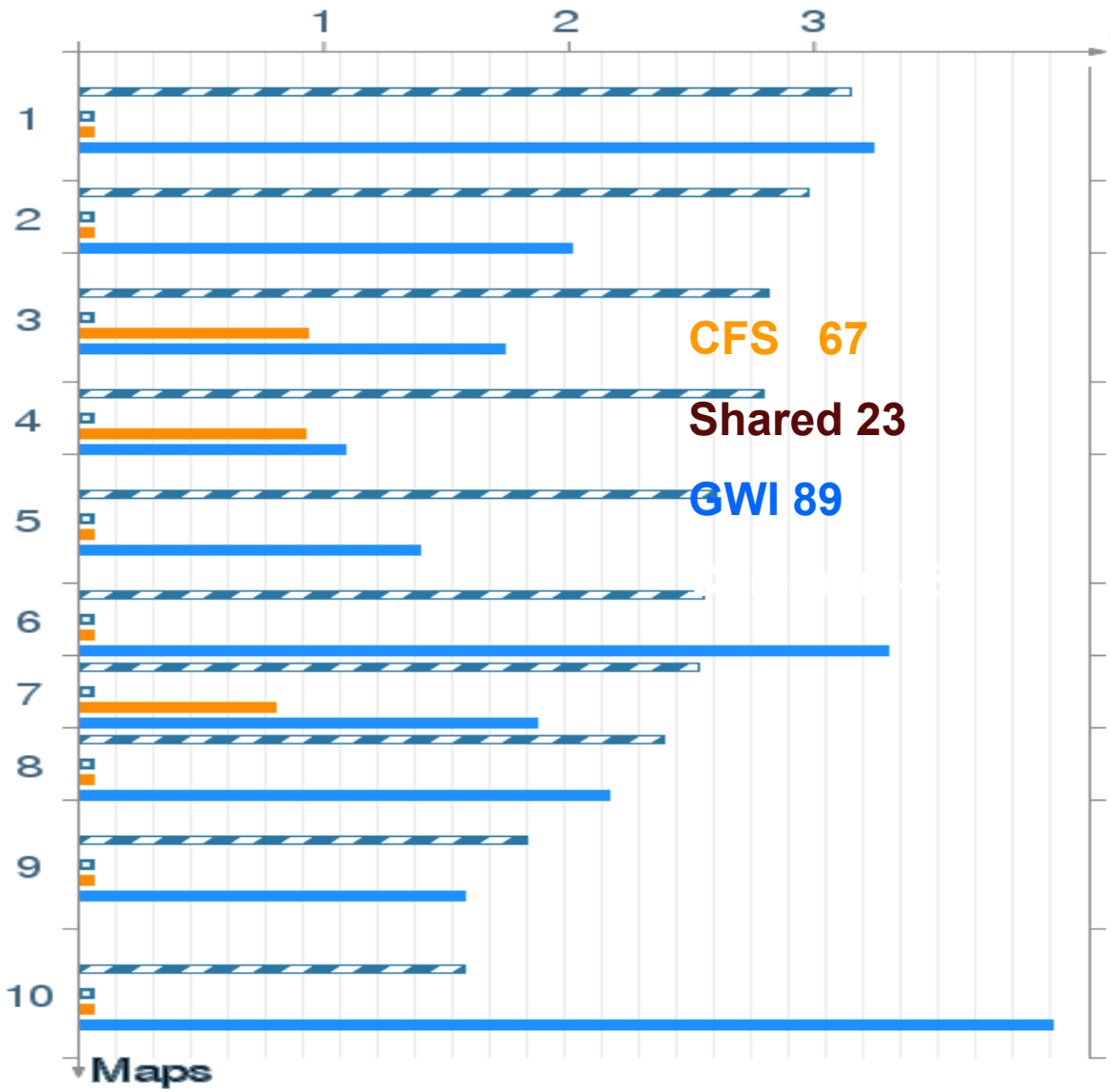
Clinical Systems Biology

- Create a modeling and simulation environment of neuro-endocrine immune regulation
- Use simulation to identify treatments which guide the biological system towards health

Peak of Exercise

From 650 potential pathways



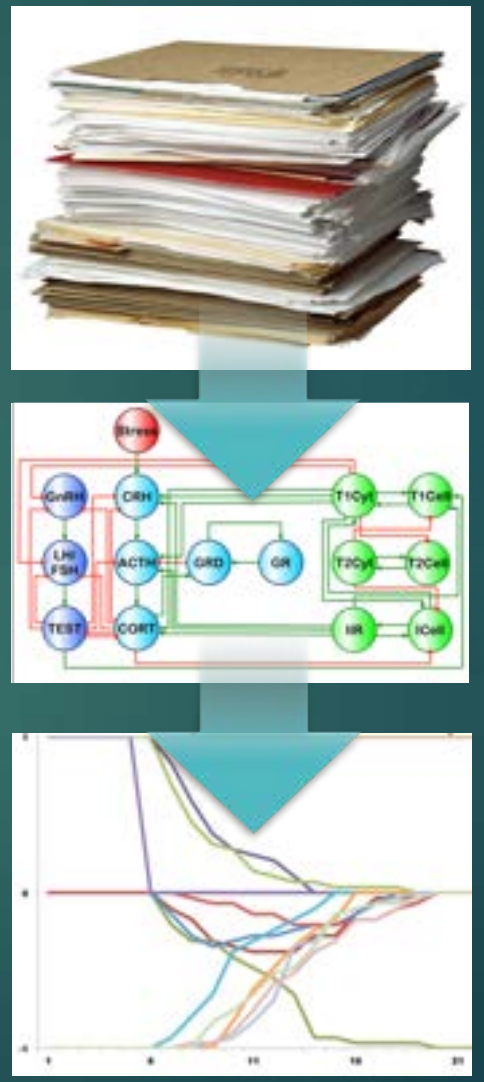
1. Immune response_IL-3 activation and signaling pathway
2. Development_ERBB-family signaling
3. Immune response_NF-AT signaling and leukocyte interactions
4. Development_HGF signaling pathway
5. Immune response _Immunological synapse formation
6. Development_EGFR signaling pathway
7. Immune response_CD40 signaling
8. Chemotaxis_Leukocyte chemotaxis
9. Immune response_Antigen presentation by MHC class II
10. Immune response _MIF-mediated glucocorticoid regulation

Top GeneGo Processes T0 to T2

4 hours post exercise	pvalue
regulation of multicellular organismal process	5.082e-11
negative regulation of blood pressure	3.656e-10
regulation of sensory perception of pain	3.640e-09
regulation of sensory perception	3.640e-09
positive regulation of nitric oxide biosynthetic process	3.115e-08
positive regulation of nitrogen compound metabolic process	4.041e-08
response to stress	6.203e-08
regulation of developmental process	6.445e-08
regulation of nitric oxide biosynthetic process	8.186e-08
regulation of blood pressure	9.707e-08

Approach

- Construct models from literature of known regulatory physiology and biochemistry for simulation
- Simulate evolution of the model to determine stable behaviors and response to external factors
- Identify and optimize the sequence and delivery of treatments

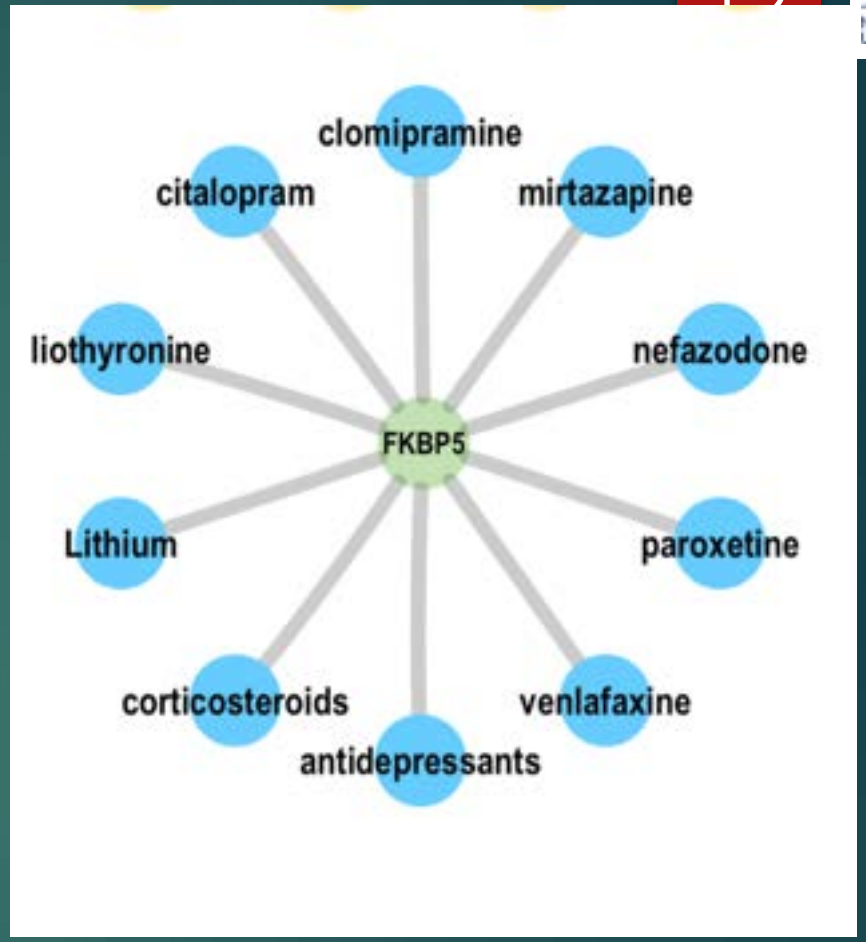


In other words

- Take what we know from our dynamic challenge data
- Take what we know about systems and homeostatic networks from the literature
- Merge the knowledge
- Create models of illness and wellness
- Use virtual clinical trials to try to move from “sick” homeostatic states to “well” homeostatic states.
- Take that back to the lab, to animal models, and to human translational clinical trials. (the end game!)

Putative Targets

- Cross referencing with PharmGKB database
  - 242 gene-drug interactions
  - 92 FDA-approved drugs affecting
  - 39 targetable gene products
- Treatable targets in 37 of the 50 gene modules
  - 23 identified to have a significant association with symptoms
  - Including Adaptive Immune System, B-cell receptors, TNFa
- 11 targetable gene products show significant change from HC in ME/CFS
  - NCOA1, UBE21, TRAF1, FKBP5, AHR, FYN, IKBKG, CASP9, CA9, DDIT3, CTNNB1



Chronic pain after trauma may depend on your stress gene

Linnstaedt, et al. (2018). A functional riboSNitch in the 3′ untranslated region of FKBP5 alters microRNA-320a binding efficiency and mediates vulnerability to chronic post-traumatic pain. *Journal of neuroscience*, *38*(39), 8407-8420.

Jeffrey et al. "Treatment Avenues in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Split-gender Pharmacogenomic Study of Gene-expression Modules. *Clinical Therapeutics*. (in press)

Virtual Clinical Trials

2-Pronged Approach:

1. Short term interim: focus on optimal design of treatment schedule using known and FDA-approved drugs alone or in combination.

   Advantage: rapid roll-out of treatment protocol that provides some relief of symptom severity

1. Longer term: identify maximal efficacy treatment targets and develop drug if none exists

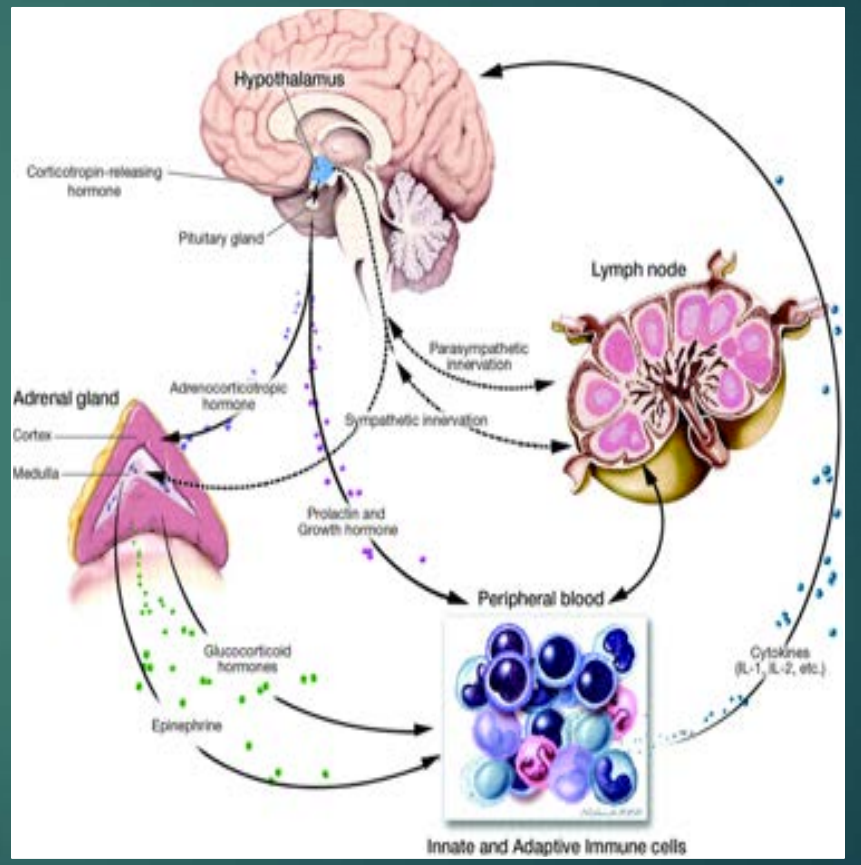
   Advantage: possible long-term cure

CSB Specific Goals

- Use computational modeling efforts to identify effective treatment courses for ME/CFS clinical trials
  - Step 1: Identify putative targets treatable with FDA approved drugs
  - Step 2: Optimize treatment course to reset system homeostasis
  - Step 3: Minimize adverse drug effects and off-target interactions

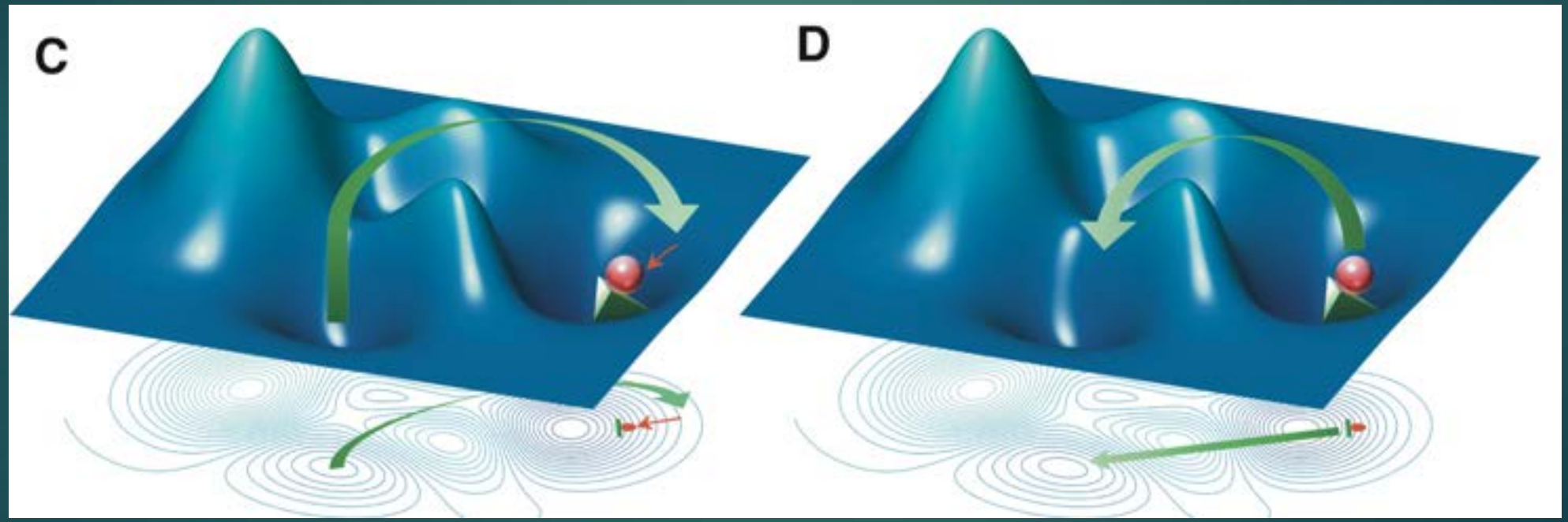
Going for the cure: Optimizing treatment course to reset system homeostasis

- Key systems:
  - Immune system
  - Endocrine System
  - Nervous System
- All 3 systems intercommunicate.
- All systems must be considered.
- Multisymptom illness indicates multiple system involvement.
- **<u>One</u> intervention is not enough**



Hypothesis: External Insults and Treatments

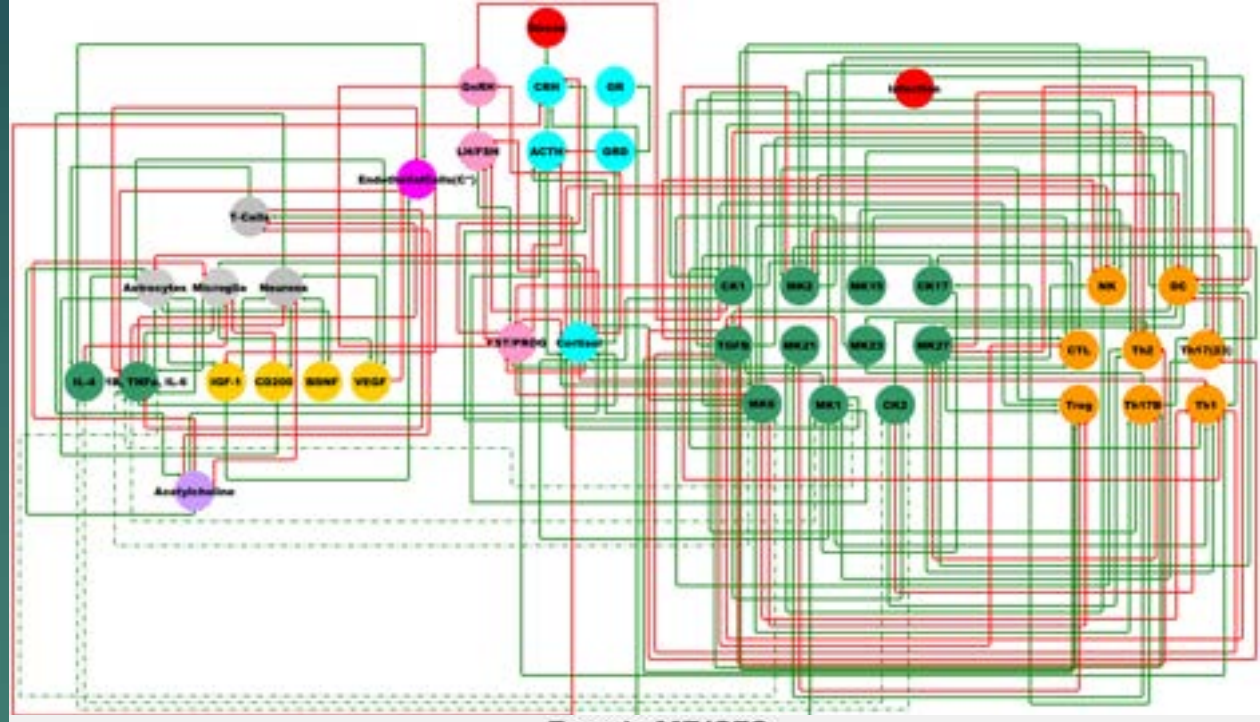
- Severe external factors can force the system into a new mode of behavior
- Optimized treatment can move the system towards healthy behavior

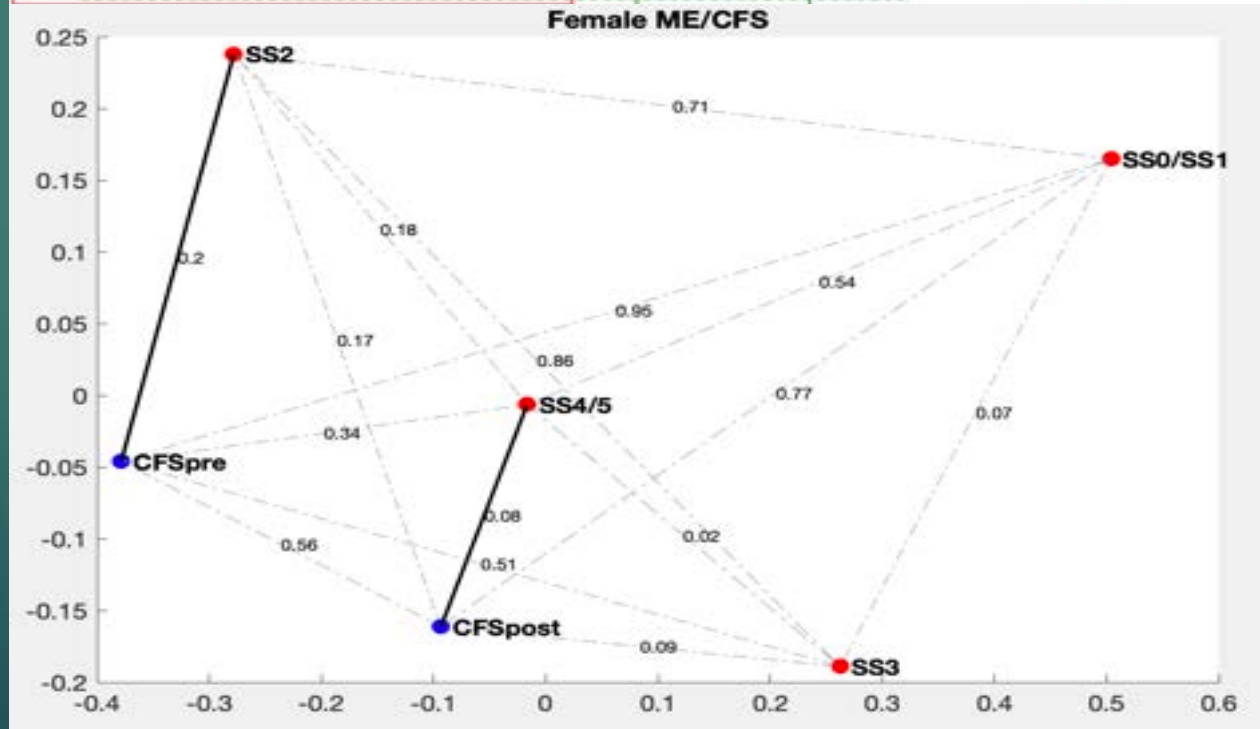


Fritsch et al.(2013). Exploring the sometimes pathogenic versatility of discrete immune logic. *Systems Biomedicine*, *1*(3), 179-194.

Prelim Female ME/CFS

- Compared to 14 healthy control women
- All ME/CFS
  - elevated HPA activity, depressed HPG activity, depressed NK activity increase in IL-10, IL-22, elevated T-regulatory cells
- 15 premenopausal ME/CFS women
  - elevated Th2 (IL-4, IL-5, IL-13), Th17 and proinflammatory cytokines (IL-1a, IL-6), depressed dendritic cells
  - Inhibit proinflammatory cytokines followed by glucocorticoids
- 6 postmenopausal ME/CFS women
  - elevated Th1 (IL-2, IFNγ, TNFa, TNFβ), cytotoxic lymphocytes
  - Replace hormones, suppress Th1 followed by glucocorticoids





VA Based Research

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INIM Based Research

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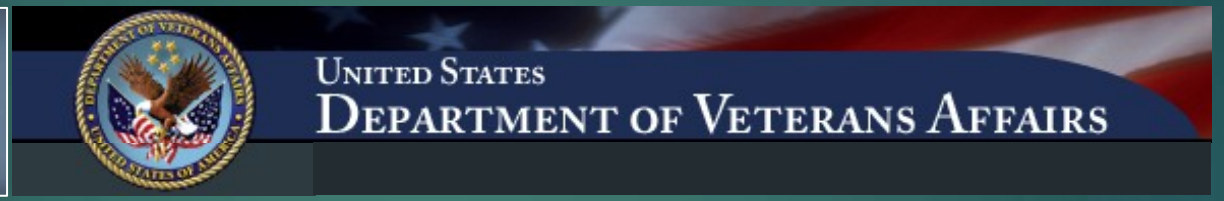
Thank You!

Funding Provided By



Computational Platform By

Awards to: Klimas
Broderick
Fletcher
Nathanson
Craddock

How to reduce vaccine risk when your immune system is in hyperdrive

Nancy Klimas MD

HOW DO THE VACCINES WORK?

- There are three main types of COVID-19 vaccines: messenger RNA (mRNA), protein subunit and vector.
- All three vaccine types either deliver, or cause our bodies to make, harmless proteins like the ones found on the surface of the COVID-19 virus.
- The vaccine teaches our immune system to recognize the virus. After we are vaccinated, if we are exposed to the virus, our immune system recognizes, attacks and blocks the virus.

From Hopkinsmedicine.org

THREE MAIN TYPES OF VACCINES

mRNA

mRNA is a molecule that tells our bodies to make proteins. mRNA in the COVID-19 vaccine tells our cells to make harmless proteins just like those on the virus. The Pfizer and Moderna vaccines work this way.

Protein Subunit

Protein subunit vaccines, such as the Novavax vaccine, contain harmless pieces of proteins unique to the COVID-19 virus.

Vector

Vector vaccines, like the J&J vaccine, use another virus that has been made safe to deliver material that tells our cells to make harmless proteins unique to the COVID-19 virus.

What is the difference between a booster and an additional dose?

A COVID-19 **booster** is given when a person has completed their vaccine series, and protection against the virus has decreased over time. Depending on the original series you had, some details will vary. Please review the booster eligibility information above and talk to your health care provider if you are not sure if you meet these guidelines. Please note, if you receive the Moderna booster, you will receive half of the original Moderna dose.

An **additional dose** is administered to people with moderately to severely compromised immune systems. This additional dose is intended to improve immunocompromised people's response to their initial vaccine series. Depending on the original series given, some details will vary. Please review the additional dose eligibility information and talk to your health care provider if you are not sure if you meet these guidelines. **These are very immunocompromised people, most MAST cell and ME/CFS patients DO NOT meet this criteria**

The Mast Cell Disease Society

- **COVID vaccine boosters are indicated for all patients** who received the initial vaccination with 2 doses (mRNA vaccines, for example, Moderna or Pfizer) or one dose (DNA vaccines, for example, Johnson and Johnson).
- In patients who received the initial vaccine with pre-medications, the same pre-medications are indicated. If a patient presented with a reaction to the initial vaccination, an evaluation by a board-certified allergist/immunologist is mandatory; receiving the booster with a different vaccine has been approved by the FDA and CDC with or without pre-medications.
- The interval time varies between 6 to 8 months after the second shot for the booster for mRNA vaccines and 2 months after the initial shot for DNA vaccines. For children with allergies and mast cell disorders there is no contraindication for vaccination and pre-medication is indicated based on their previous reactions to other drugs or their mast cell activation disorder.
- Flu vaccination has the same recommendations. One week between receiving the flu and COVID vaccines is recommended.
- Please see CDC link for latest booster recommendations: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/booster-shot.html

From:

- https://tmsforacure.org/

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

- Vaccination with mRNA vaccines recommended over J and J
- Response in patients on immunomodulators may be blunted
- For patients who previously completed the 2-dose mRNA series, an additional COVID-19 vaccine dose is recommended ≥28 days after the completion of the vaccine series for AIIRD patients receiving any immunosuppressive or immunomodulatory therapy other than hydroxychloroquine monotherapy.
- For patients who previously completed the mRNA COVID-19 vaccine series or 1-dose J&J COVID-19 vaccine, and who are receiving a booster dose, an mRNA vaccine supplemental dose of either type (Pfizer or Moderna) is preferred.
- If possible vaccinate before starting immunosuppressive /modulatory therapy
- Household should be vaccinated (“Cocooning”)
- Vaccines have roughly a 10% risk of flaring autoimmune condition, pre-medications may lessen that risk

How to reduce the risk of a serious vaccine reaction or ME/CFS flare.

- Stabilize your MAST cells and mop up after them

Stabilize: Quercetin, luteolin. Ketotifen , aspirin (used with care) Vitamin C

Mop up histamine:

H1 plus H2 (eg Famotidine(Pepcid)

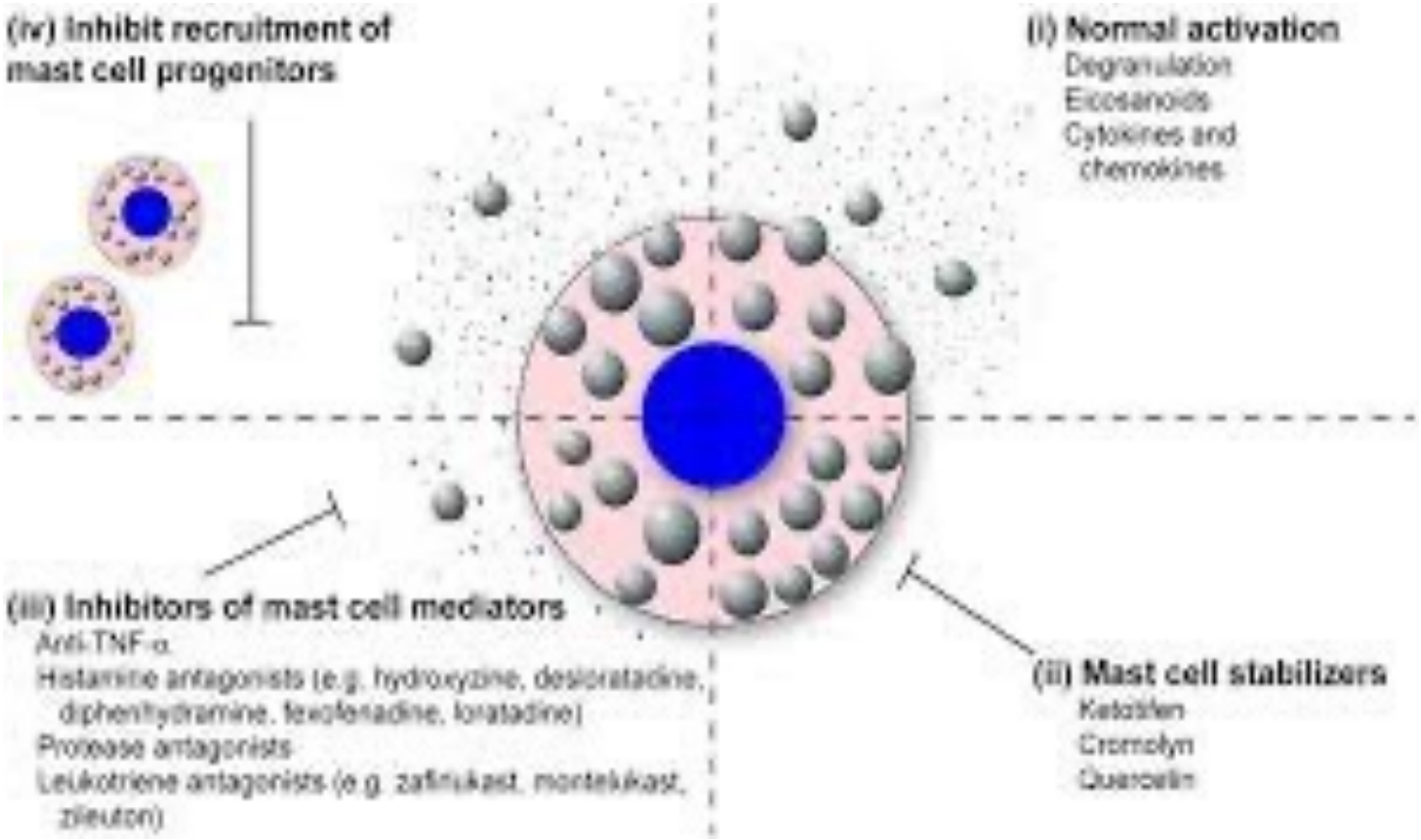
Plus a tolerable antihistamine – Diphenhydramine(Benadryl) Certizine (Zyrtec)

Ketotifen

Mop up Leukotrienes:

Montelukast (Singulair)

Zafirlukast, Zileuton



Joining the INIM team! Dr Theoharis Theoharides and Dr Kempuraj Duraisamy
Creating a Center of Excellence for Neuroinflammation

https://www.mastcellmaster.com/

Management of Long-COVID Symptoms
A Summary of Functional Medicine Protocols

Annette Fornos, MD, IFMCP, ABAARM, FAAMM
Institute for Neuro-Immune Medicine
Nova Southeastern University
Dr. Kiran C. Patel College of Osteopathic Medicine

Disclosures

Adapted from

Dr. Pamela W., Smith, MD, MPH, MS., COVID and Post COVID Syndrome. The American Academy of Anti-Aging Medicine Spring Congress. April 2022

Certification Program Online Review Course, Institute for Functional Medicine. Nov. 2020

Immune Advanced Practice Module, Institute for Functional Medicine. July 2020 review course Nov 2020

Resistance, Resilience, and Recovery, Patient Care in a Pandemic. Institute for Functional Medicine, Nov. 2020

Disclaimers

The following information is intended for educational purposes only

It is not meant to provide specific medical recommendations

Consult your physician before taking any new nutraceuticals or medications

Nutraceuticals and medications can sometimes have significant side effects or contraindications

Post-COVID Syndrome

The COVID-19 pandemic has given rise to a second pandemic of COVID long-haulers

Long-COVID symptoms should appear after the diagnosis of SARS-CoV-2 infection, but this is difficult to determine: not all patients with SARS-CoV-2 are diagnosed, and some patients had pre-existing conditions with overlapping symptoms

Post COVID symptoms may be relapsing-remitting

Post-COVID Syndrome

Proposed integrative classification of post-COVID symptoms:

Potentially infection-related symptoms: up to 4-5 weeks

Acute Post-COVID symptoms: From week 5-12

Long Post COVID symptoms: From week 12-24

Persistent Long COVID symptoms: From week 24 on

Post COVID Syndrome - Symptoms

Fatigue

SOB

Cough

Wheezing

Rhinorrhea

Pulmonary Fibrotic Changes

Joint pain

Intermittent fever

Myalgias

Palpitations

Myocarditis

CP

Cardiac Arrhythmias

Acute Kidney Injury

Rashes

Hair loss

Headaches

Thrombosis

Anosmia

Dysgeusia

Dysbiosis

Syncope

POTS

Autonomic Dysfunction

Post-COVID Syndrome

Long-Term Tissue Damage:

Cardiovascular: CP, Palpitations, Orthostatic intolerance

Pulmonary: SOB, cough

Neuro-Cognitive/Psychiatric: Headaches, Depression, Anxiety, Insomnia, Smell and Taste disturbance

Persistent Inflammation:

Inflammation: Myalgia, fatigue, joint pain

Gut Dysbiosis: Gastrointestinal and Neurological Symptoms

Autoimmunity: Fatigue, joint pain, Headache, Cognitive Impairment, Orthostatic intolerance

Nutraceuticals and Vitamins used in Post COVID Syndrome

The following slides show a number of nutraceutical and vitamin supplements that have been successfully used for managing post-COVID syndrome, supported by scientific research

Melatonin

Antiviral action- Decreases ACE 2 Surface expression, decreasing viral entry, and decreases viral protein replication by inhibiting chymotrypsin-like protease

Antioxidant and free radical scavenger: increases SOD, catalase, and glutathione

Anti-inflammatory- through various mechanisms: decreases inflammatory cascade (NF-kB, TLR4 activation, TNFa, IL-6, angiotensin II), increases SIRT-1 activity, and decreases macrophages

Decreases cytokine storm- (by inhibiting NF-kB signaling and IL-1B, IL-6, IL-17, CRP, TNF-a)

Melatonin

Insufficient melatonin may pose an increased susceptibility to SARS-CoV-2 infection and complications

This is a possible theory as to why small children get mild infections

Cautions with melatonin

Use with caution in patients who are on psychiatric medications, have mental illness, are pregnant, breastfeeding. It is an immune modulator.

Long-term high doses of melatonin may reduce serotonin levels

May affect metabolism of multiple drugs (through cytochrome p-450 inhibition)

Vitamin D

Studies have shown that vitamin D exerts immunomodulatory effects in the innate and the adaptive immune systems, on the renin-angiotensin-aldosterone system in the kidneys and lungs, and protective, anti-thrombotic effects on the endothelium

Conditions known to increase susceptibility to SARS-CoV-2 include advanced age, cancer, immunocompromised states, chronic respiratory illnesses, cardiac conditions, chronic kidney disease, and smoking, (nursing home residents are at a particularly higher risk). These populations tend to be low on Vit D. Therefore, Vit D deficiency has been found to contribute to morbidity and mortality in these populations.

*Ibid., Charoenngam

Low Dose Naltrexone (LDN)

Naltrexone, at higher doses, is a non-selective antagonist of opioid receptors used in the treatment of opioid intoxication and addiction

The off-label use of naltrexone at very low doses (LDN) has shown significant benefit in treating:

-autoimmune diseases

-Inflammatory processes

-Chronic pain

- Obesity

- Cytokine storm

Potential Side Effects of LDN

Insomnia

Vivid dreams

Fatigue

Appetite loss

Nausea

Hair thinning

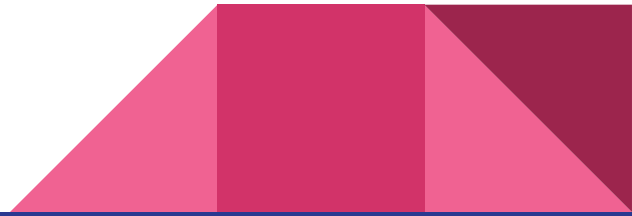
Mood swings

Mild disorientation

Potential Long Term Side Effects

Possible liver and kidney toxicity

Possible tolerance



LDN- Absolute Contraindications

LDN is absolutely contraindicated in patients who

Take opioid substances or medications

Have liver failure

Have acute hepatitis

Have alcohol and substance abuse issues

The Issue with Mitochondrial Dysfunction

Mitochondria are the energy-producing intracellular organelles

Four major major components of mitochondrial dysfunction:

-Reduced ATP Production

-Oxidative damage from excess free radical production

-Free radical damage leads to alterations in glucose metabolism, pain sensitization, neuroinflammation, faulty immune defense

-Altered metabolite utilization increasing risk for cancer

*Vasquez, A., et al., “Mitochondrial medicine arrives to primetime in clinical care: nutritionalbiochemistry, and mitochondrial hyperpermeability (“leaky mitochondria”) meet disease pathogenesis and clinical interventions, “Integrat Med 2014; 13(4):44-9

Key Nutrients for Mitochondrial Energy Production

Carbs/Fats/Proteins: B1, B2, B3, B5, Lipoate, L-Carnitine

Acetyl-CoA: Pantothenic acid (B5)

Citric Acid Cycle: Glutathione, Fe, Mag, Mn, B1, B2, B3, B5, Lipoate, CoQ-10

Energy Transporters: Niacin (B3), Riboflavin (B2)

Electron Transport Chain: CoQ-10, Vit C, Vit K, Alpha Lipoic Acid, Mag, Phosphatidyl Choline

Improving Mitochondrial Health

Magnesium Glycinate or Threonate

Coenzyme Q-10 – When combined with Selenium, decreases oxidative stress and inflammation

ALA – Antioxidant, anti-inflammatory (decreases CRP, IL-6, TNF-B), protects endothelial function by restoring nitric oxide, enhances glutathione. Must monitor thyroid function

D-Ribose - monosaccharide essential for mitochondrial function

NADH – Replenishes ATP, strong antioxidant, free radical scavenger

L-Carnitine – antioxidant, anti-inflammatory, transport fatty acids to mitochondrial matrix to be utilized in the Krebs Cycle, affects the development and maturation of T-lymphocytes, inhibits ROS production, modulates cytokines. Must monitor TMAO levels

- Must be done under medical supervision

B-Vitamins

Participate in proper activation of both the innate and adaptive immune responses, reduce pro-inflammatory cytokines, improve respiratory function, endothelial integrity, reduce risk of hypercoagulability, may reduce hospital stay

*Michelle, C., et al., “Vitamin supplements in the era of SARS-CoV-2 pandemic,” GCS Biol Pharm Sci 2020; 11(2):7-19

*Zhang, L., et al., “Potential interventions for novel coronavirus in China: a systematic review,” Jour Med Virol 2020; 92(5):7-19

In patients with COVID and Post COVID Syndrome, consider supplementing with B-Complex twice per day

Zinc

Clinical data suggest that higher Zn levels are associated with better clinical outcome and reduced risk of infection

Boosts acquired immunity

Anti-inflammatory action

The elderly are particularly susceptible to Zn deficiency

*Arentz, S., et al., “Zinc for the prevention and treatment of SARS-CoV-2 and other acute viral respiratory infections: a rapid review, “Adv Integr Med 2020; 7:252-60

*Mossink, J., “Zinc as nutritional interventions and prevention measure for COVID-19 disease,” BMJ Nutr Prev Health 2020; 3:111-17

Quercetin

Anti-inflammatory, antioxidant, analgesic properties, anti-thrombotic properties

Directly inhibits inflammasome NLRP-3

(Inflammasomes are nuclear complexes that activate inflammatory cytokine pathways in response to pathogen-associated molecular patterns or products of cell damage associated molecular patterns)

Co-administration of Quercetin and Vitamin C has synergistic effects, increasing efficacy of Quercetin

*Derosa, G.< et, al., “A role for quercetin in coronavirus disease 2019 (COVID-19),” PhytotherRes 2021; 3593:1230-36

*Saeedi-Boroujeni, A., et, al., “Antii-inflammatory potential of Quercetin in COVID-19 treatment,’ Jour Inflamm (Lond.) 2021; 18(1):3

Glutathione

Strongest antioxidant produced by the body

Antiviral, anti-inflammatory, anticoagulant properties

Endogenous glutathione deficiency appears to be a crucial risk factor for complications from SARS-CoV-2 such as ARDS, multiorgan failure, and death

It has been suggested that the clinical severity of SARS CoV-2 infection may be attributed to degree of impairment of balanced oxidation-reduction reactions, attributable to glutathione deficiency and increased ROS production

*Polonikov, A., et, al., “Endogenous deficiency of glutathione as the most likely cause of serious manifestations and death in COVID-19 patients,” ACS Infect Dis 2020; 6(7):1558-62

*Silvagno, F., et, al., “The role of glutathione in protecting against severe inflammatory response triggered by COVID-19,’ Antioxidants (Basel) 2020; 9(7):624

Probiotics

COVID -19 leads to inflammation of the gastrointestinal tract mucosa and occasional diarrhea, which may exacerbate inflammation and immune response

People with COVID-19 have changes in their gut microbiota

*Zhang, H., “Digestive system is a potential route for COVID-19: An analysis of single-cell coexpression pattern of key proteins in viral entry process,” Gut 2020; 69:1010-18

*Xiao, F., “Evidence for gastrointestinal infection of SARS-CoV-2,” Gastroenterology 2020; 158:1831-e3

*Ceccarelli, G., et, al., “Probiotics and COVID-19, “ Lancet Gastroenterol Hepatol 2020; 5:721-22

*Mark, J., et, al., “Probiotics and COVID-19: One size does not fit all,” Lancet Gastroenterol Hepatol 2020; 5:644-45

Proposed Functional Medicine Interventions in Post COVID-Syndrome.

Vit D

LDN

Glutathione

B-complex

Quercetin

Probiotics

Mitochondrial Support:

Magnesium

CoQ-10

ALA

D-Ribose

NADH

L-Carnitine (if normal TMAO)

- Pamela W. Smith, M.D., MPH, MS. American Academy of Anti-Aging Medicine. COVID and Post COVID Syndrome

Proposed Functional Medicine Interventions in Post COVID-Syndrome

Resveratrol 100-150 mg QD

Probiotics (S. boulardii blocks NFK-B (IL-8, TNF-a, TNF-G)

Green Tea

Diet: Rich in Phytonutrients and Healthy Fats

Others: The above were proposed based on evidence, multiple effects, easy of use, safety, cost

*Certification Program Online Review Course, Institute for Functional Medicine. Nov. 2020

Proposed Functional Medicine Interventions in Post COVID-Syndrome

Quercetin 1G PO Bid

Curcumin 500-1000 mg PO Bid

Vit D3 5000 iu daily (in the absence of serum levels or adjusted based on serum levels)

Melatonin 5-20 mg QD

Vit C 1-3 G PO QD

NAC 600-900 mg PO Bid and/or Liposomal Glutathione (cost may be issue)

Ubiquinol 200 mg daily

Multivitamins and Minerals: B1, B2, B3, B5, B6, Methyl Folate, Methyl or Hydroxy B12. Zn, Cu, Mg

Omega-3 (DHA/EPA)

Not the only ones

*Certification Program Online Review Course, Institute for Functional Medicine. Nov. 2020

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LONG COVID STUDIES

- Underway: COVID UPP (CDC Phenotyping study)
- Under NIH Review: INSPIRITOL in PASC and ME/CFS
- The Role of Viral Reactivation in Long COVID
- In Negotiation: MSC Stem Cells in PASC and ME/CFS
- COVID 19 specific antiviral therapies in Long COVID

DESPITE 30 YEARS OF STUDY, THIS BETTER UNDERSTANDING OF MEDIATORS HAS YET TO DRIVE SUCCESSFUL CLINICAL TRIALS – FEW TRIALS AND LUMPING HETEROGENEOUS GROUPS

- Biological subgroups with mediator focused interventions seem the most promising.
- Studies have failed when "lumping" vs "splitting"
- A lack of consensus on primary outcome variable(s), biomarker surrogates
- Funding issues have plagued the field, until PASC funding for the entire field has been modest.

PASC provide an opportunity to advance understanding of ME/CFS and potentially support clinical trials.

COVID-19: UNDERSTANDING THE POST-VIRAL PHASE (COVID UPP)

Nancy Klimas, MD** (CoPI) ; Ana Palacio, MD+**; Patrick Hardigan, PhD, Kristina Aenlle, PhD, Devra Cohen, MPH, Shahnaz Fatteh, MD, Irina Rozenfeld, DNP, Violetta Renesca, DNP, Alison Bested, MD, Julio Llanga, Matt Razavian, MD, Jay Caine. Institute for Neuro-Immune Medicine, Nova Southeastern University, University of Miami+, and Miami VAMC GRECC**

- Lily Chu, MD, Stanford ME/CFS Initiative, Stanford, California, U.S.A.;
- And the CDC COVID-UPP team

- Funding source: Centers for Disease Control Contract no. 75D30120C09554

COVID-19: UNDERSTANDING THE POST-VIRAL PHASE (COVID UPP)

Studying the Post COVID ill population, longitudinally and with phenotyping, and comparing the group to the MCAM ME/CFS study population.

Among a large, racially/ethnically diverse population who tested positive for SARS-CoV-2 infection and who report Post-acute COVID-19 symptoms:

- Describe the function, quality of life, and symptom complex (frequency and severity).
- Assess the rate of self-reported symptom persistence and extent to which the symptom profile matches that of ME/CFS.
- Describe the trajectory of Post-acute COVID symptoms and associated risk factors of population who continue to report being unrecovered from the infection over time.
- Perform in-depth clinical and biologic phenotyping to describe the clinical presentation and laboratory findings of unrecovered individuals compared with individuals who have fully recovered.

MULTI-SITE CLINICAL ASSESSMENT OF ME/CFS (MCAM)

- Work with clinical experts in ME/CFS - 7 expert clinical sites
  - Phenotyping study with longitudinal design measuring trajectory, biomarkers, domains of illness, illness severity and impact on function
- Collect standardized information on illness domains
  - Data used to inform dialogue on case definition and to identify biologically meaningful subgroups

MCAM STUDY DESIGN AND SUBSTUDIES

- Unger ER, Lin JS, Tian H, Natelson BH, Lange G, Vu D, Blate M, Klimas NG, Balbin EG, Bateman L, Allen A, Lapp CW, Springs W, Kogelnik AM, Phan CC, Danver J, Podell RN, Fitzpatrick T, Peterson DL, Gottschalk CG, Rajeevan MS; MCAM Study Group. Multi-Site Clinical Assessment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (MCAM): Design and Implementation of a Prospective/Retrospective Rolling Cohort Study. Am J Epidemiol. 2017 Apr 15;185(8):617-626. doi: 10.1093/aje/kwx029. Erratum in: Am J Epidemiol. 2017 Jul 1;186(1):129. PMID: 28338983; PMCID: PMC5565838.
- Dane Cook et al: Cardiopulmonary, metabolic, and perceptual responses during exercise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): A Multi-site Clinical Assessment of ME/CFS (MCAM) sub-study; PLoS One. 2022; 17(3): e0265315. Published online 2022 Mar 15. doi: 10.1371/journal.pone.0265315

LONG COVID AND ME CFS

- We need comparator studies to advance both fields!
- Recover COVID - no ME CFS comparator groups
- COVID – UPP - designed to compare PASC to ME/CFS
- Clinical trials supported by industry and foundations

Introduction to an Environmental Approach to CFS/ME

IRMA REY M.D.
FAAEM,DABEM,DABIM

PAST CME CHAIR AMERICAN BOARD OF ENVIRONMENTAL MEDICINE

PAST PRESIDENT AMERICAN ACADEMY OF ENVIRONMENTAL MEDICINE

BOARD MEMBER AMERICAN BOARD OF ENVIRONMENTAL MEDICINE

Irma Rey, M.D. FAAEM,DABEM

has no relevant financial relationships to disclose

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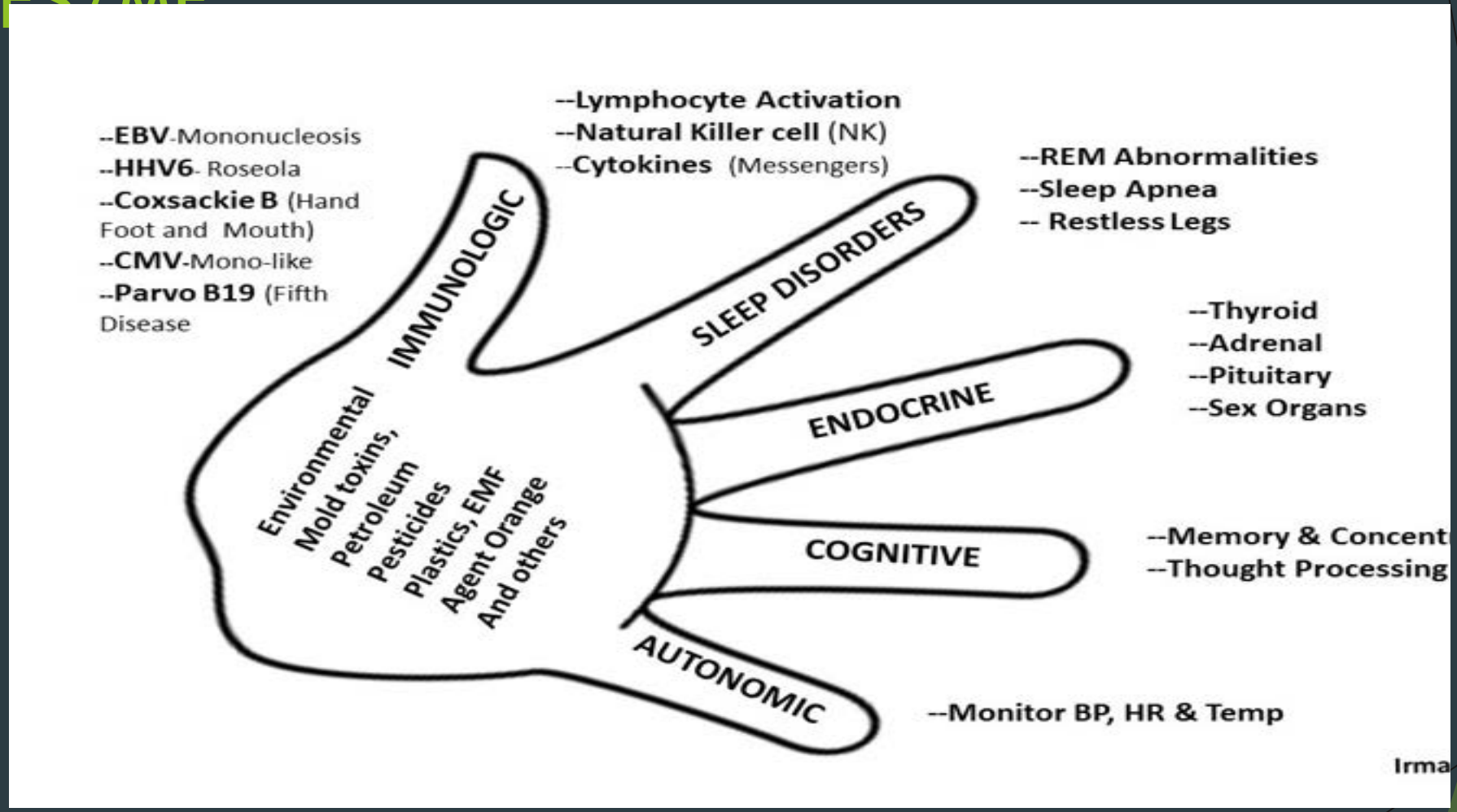
LEVEL OF EVIDENCE 2,3 and 4

CFS / ME



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Total Body Toxic Load

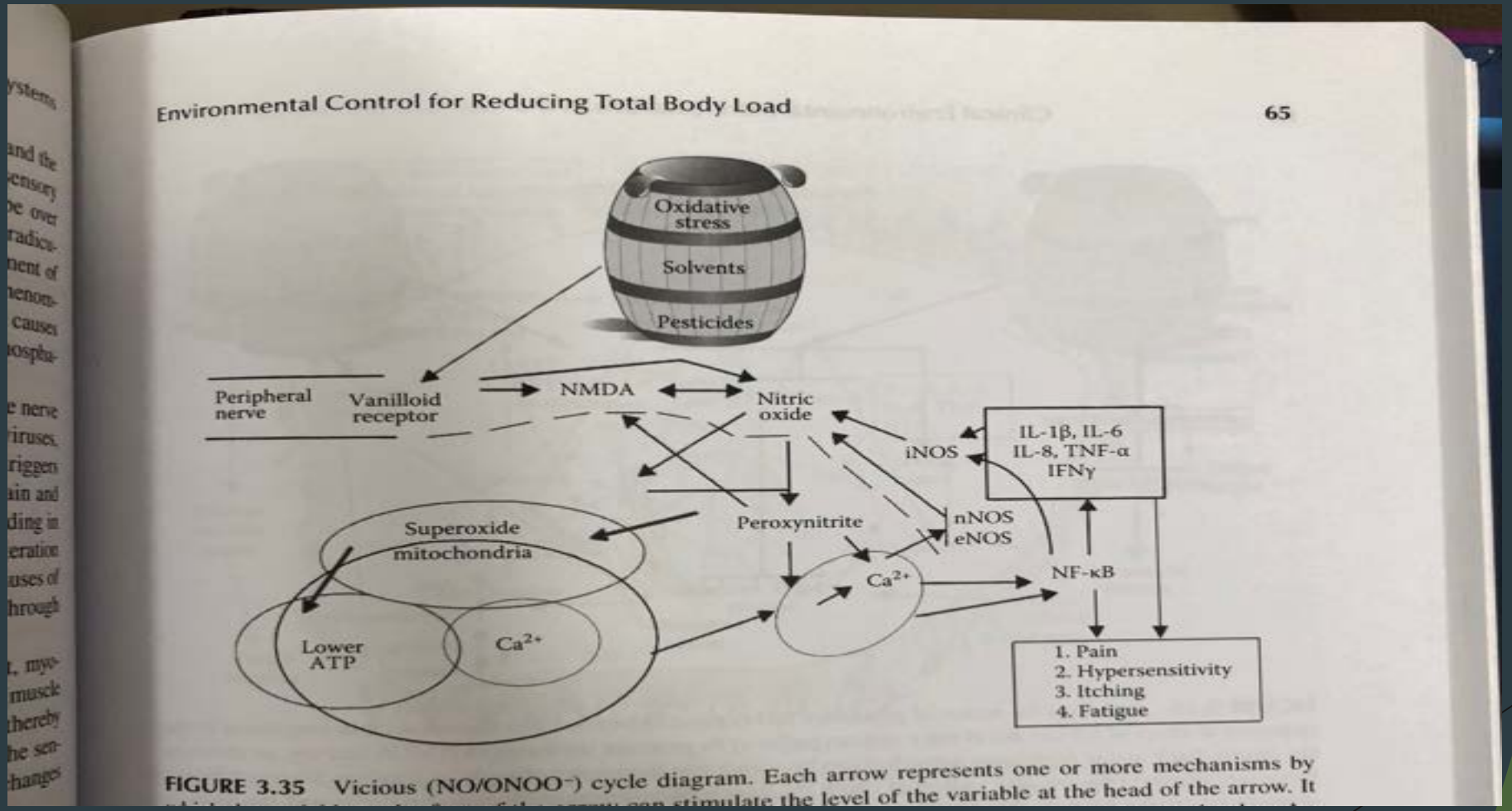

FIGURE 3.35 Vicious (NO/ONOO⁻) cycle diagram. Each arrow represents one or more mechanisms by

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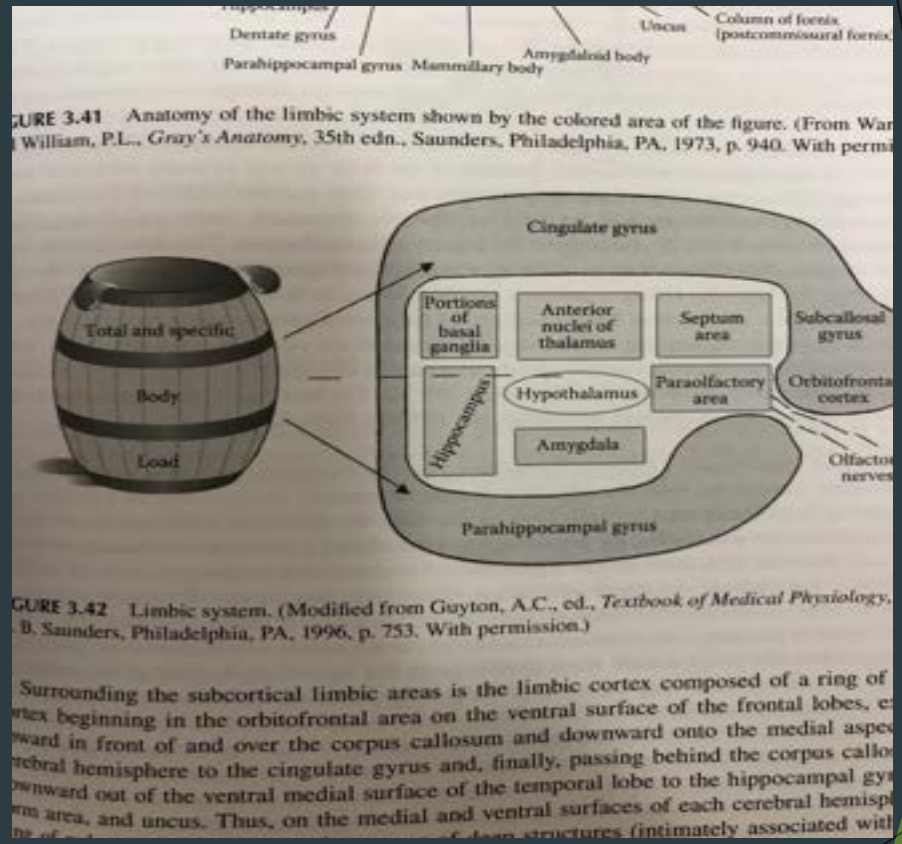
Neurologic effects of total body toxic load



GURE 3.41 Anatomy of the limbic system shown by the colored area of the figure. (From War
William, P.L., *Gray's Anatomy*, 35th edn., Saunders, Philadelphia, PA, 1973, p. 940. With permi

GURE 3.42 Limbic system. (Modified from Guyton, A.C., ed., *Textbook of Medical Physiology*,
B. Saunders, Philadelphia, PA, 1996, p. 753. With permission.)

Surrounding the subcortical limbic areas is the limbic cortex composed of a ring of
rtex beginning in the orbitofrontal area on the ventral surface of the frontal lobes, e
ward in front of and over the corpus callosum and downward onto the medial aspe
rebral hemisphere to the cingulate gyrus and, finally, passing behind the corpus callo
ownward out of the ventral medial surface of the temporal lobe to the hippocampal gy
rm area, and uncus. Thus, on the medial and ventral surfaces of each cerebral hemisp
ne of deep structures (intimately associated wit

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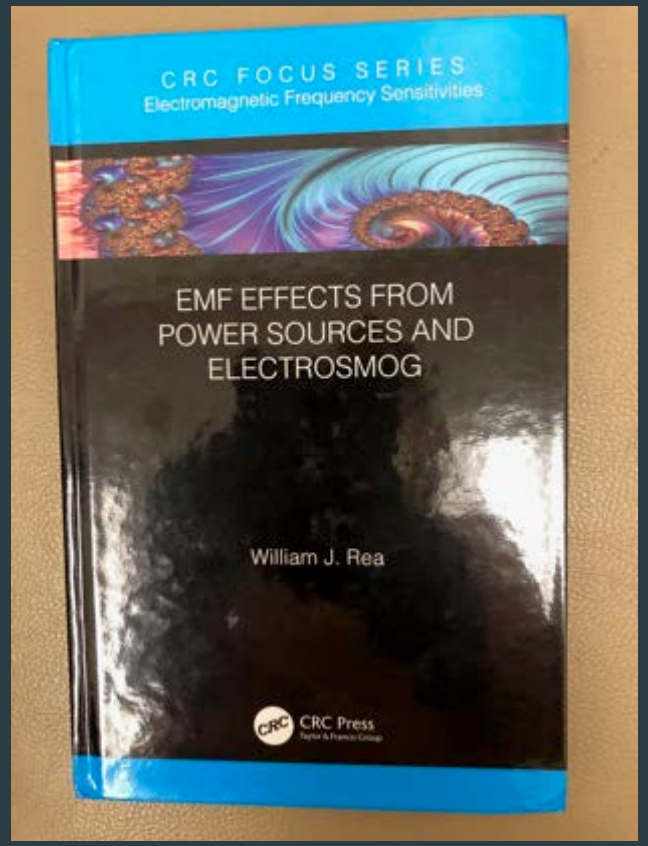
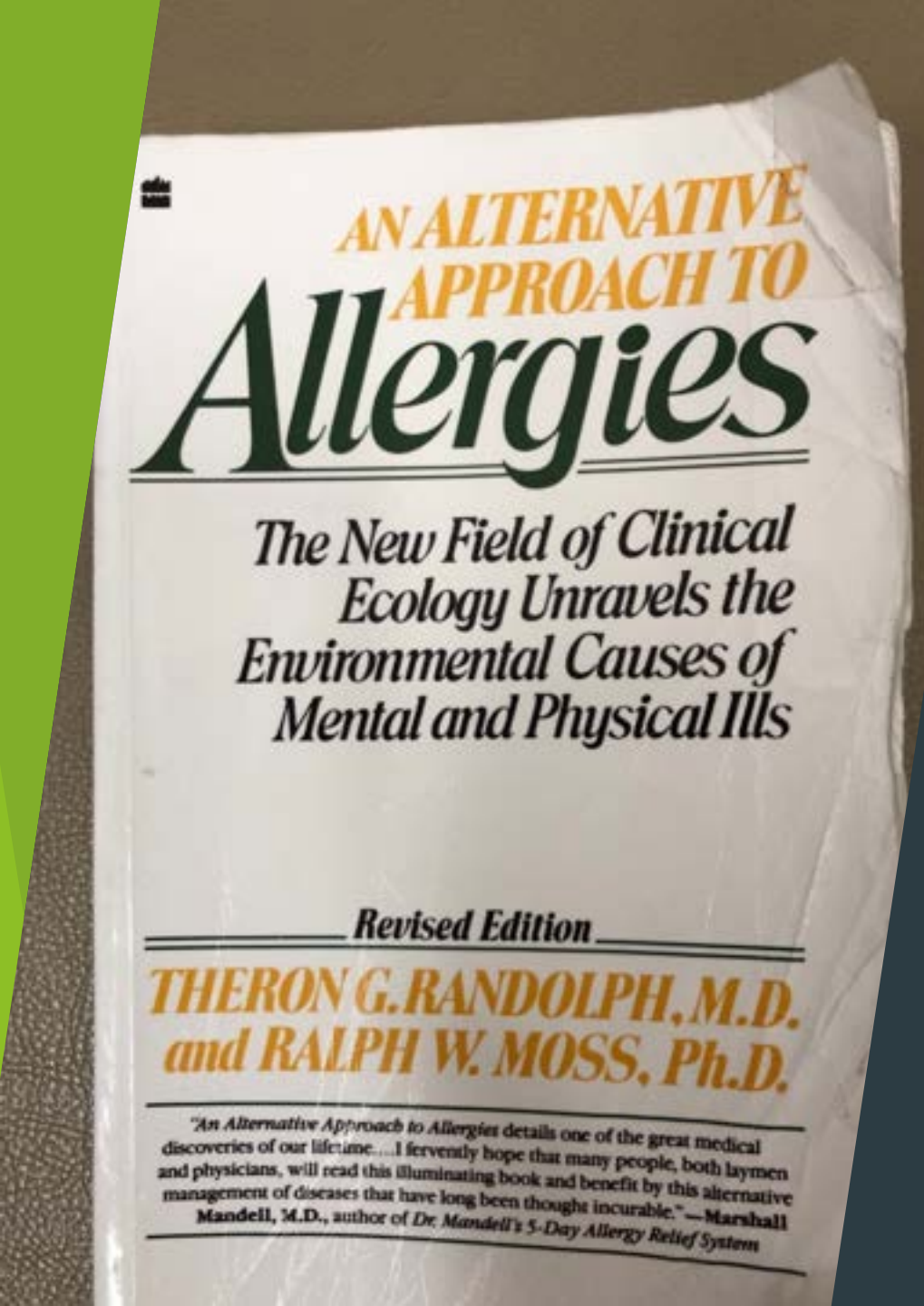
EMF effects


CRC FOCUS SERIES
Electromagnetic Frequency Sensitivities
EMF EFFECTS FROM POWER SOURCES AND ELECTROSMOG
William J. Rea
CRC Press



Environmental approach to Allergies

Environmental approach to chronic fatigue

- Exposure to environmental toxins noted in 20% of patients taking a detailed survey concerning initial and subsequent stages of CFS illness
- Taking a thorough environmental history including an exposure history
- Total body toxic load
- Determining risk for heavy metals, petroleum exposures, pesticide exposures, electromagnetic force exposure, plastics exposures, water damaged building exposure, dietary habits, drug exposures , antibiotic exposures, cigarettes/tobacco exposure including secondhand smoke.
- Travel history including immunization exposure
- Occupational and hobbies exposures
- Chemical sensitivity history

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Environmental testing for toxic exposures- a partial list

- There are multiple available tests for determining toxic exposures in patients with CFS ME.
- Among these are :
- Real-time Labs urine testing for mycotoxin- covered by Medicare
- Great Plains labs urine testing for mycotoxin – may be covered by some insurances
- Great Plains lab urine testing for nonmetal environmental toxins- includes metabolite testing for petroleum , plastic , Styrofoam, pesticide including pyrethrins, benzene, Agent orange (found even in patients who never served in Vietnam and sometimes not related to Vietnam service members) ,rubber and also includes Tiglylglycine measurements which serve as a marker of mitochondrial toxicity.
- Great Plains testing for glyphosate

Environmental testing for toxic products continued

- Great Plains metals- fecal, hair, RBC, urine , and whole blood test.
- Great Plains Organic Acid Test which reveals microbial influences on organic acids (e.g. Candida and Clostridium)
- Genova stool and G.I. effects now with functional scores–tests digestion, inflammation/immune response and gut microbiome and includes tests for dysbiosis imbalance of commensal bacteria , pathogenic bacteria with sensitivity, secretory Ig A , tests for pancreatic elastase, tests for n butyrate, and products of protein digestion ,and fecal fats ,ova and parasite testing including PCR testing. Methanogen dysbiosis biomarkers may be associated with lowering of the immune response. High methane production may affect peristalsis and barrier production.
- Microgen labs- tests various body fluids for bacteria using PCR testing and is more sensitive in IC patients to detect pathogenic bacteria.

Environmental testing (cont)

- Quest labs testing for urine and blood heavy metals
- Labcorp testing for urine and blood heavy metals
- Doctors Data testing for heavy metals, nutritional status, environmental exposure, gastrointestinal health, and toxic elements
- Microbiology DX- testing for biofilm,mold and MARCONs which may be found in mold toxin patients

Treatment of other environmental toxins

- There are multiple resources available on whole food treatment of heavy metal toxicity. Amongst these natural chelators are cilantro, celery, blueberries, garlic, lemon water, chlorella, barley grass, green tea, curry, tomatoes, and probiotics.
- Some heavy metals require chelation and therefore I refer the patients to Nephrologists or other practitioners familiar with heavy metal chelation such as Dr. Gervasio Lamas – NIH funded TACT1 and TACT 2 trials.
- Genova stool testing results include both natural agent sensitivity and antibiotic sensitivity for pathogenic bacteria and yeast. Some patients may have evidence of Inflammatory bowel disease and are therefore referred to Gastroenterology.
- Biofilm/MARCONs/MRSA or other pathogens found in nasal swab are treated with BEG spray (Bactroban, EDTA, Gentamicin) or just Bactroban (mupirocin) as indicated.

Methods

- In a prospective cohort study, a total of **236 CFS patients** were recruited for urine analysis of OTA(Ochratoxin), AF(Aflatoxin) and Gli(Gliotoxin) exposure at INIM. Many of these patients had a history of living in water-damaged buildings, which may be associated with chronic exposure to mold.
- Inclusion criteria: Patients being evaluated for CFS at INIM. Testing was dependent on medical insurance coverage.
- Results above normal ranges were designated “positive” (P) and those below “negative” (N).

  OTA normal range: 1.8-2.00 ppb
  AF normal range: 0.8-1.0 ppb
  Gliotoxin normal range: 0.5-1.0 ppb

- Data was compiled in Microsoft Excel 2018 and stratified by gender, age, mycotoxin type.

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Results

- The average prevalence of at least 1 exposure in females was **0.91** (OTA= 0.80, AF = 0.34, Gli = 0.39), and the average prevalence in males was **0.93** (OTA = 0.76, AF = 0.30, Gli= 0.48).

RTL		Total Pt	91
OTA prevalence	0.5604	OTA Total	51
AF prevalence	0.5165	AF Total	47
GT prevalence	0.7692	GT Total	70
Mycotoxin prevalence	0.8462	Total Exposure to at least 1 toxin	77
GPL		Total Pt	118
OTA prevalence	0.9661	OTA Total	114
AF prevalence	0.1949	AF Total	23
GT prevalence	0.1356	GL Total	16
Mycotoxin prevalence	0.9746	Total Exposure to at least 1 toxin	115
OVERALL prevalence	0.9187	TOTAL Patients	209

	Total	At least 1 exposure	Prevalence	OTA	AF	GT
Female	163	149	0.9141	130	56	64
Male	46	43	0.9348	35	14	22
			F	0.7975	0.3436	0.3926
			M	0.7609	0.3043	0.4783

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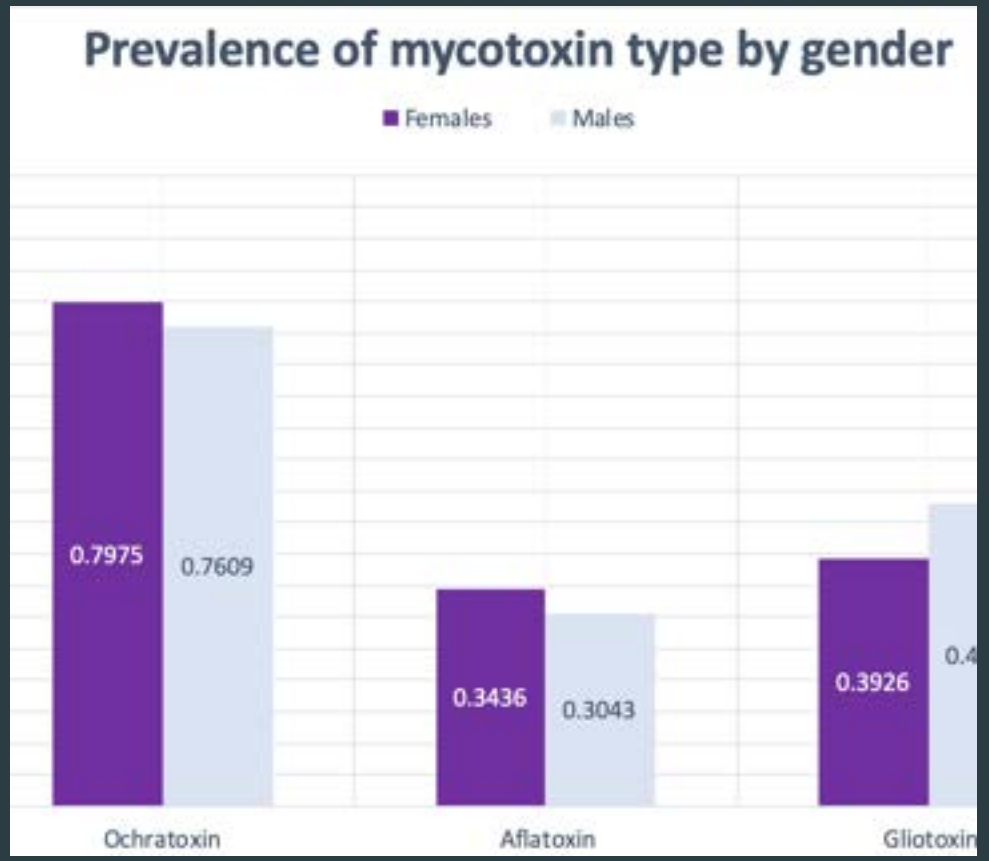
Results

- The prevalence for females to have more than one exposure was slightly lower than in males, but this is likely due to large differences in sampling size for gender. The most prevalent toxin in both female and male sampling populations was **Ochratoxin**. The least prevalent in both was **Aflatoxin**



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Published results

- Int J Environ Res Public Health. 2022 Feb; 19(4): 2052.
- Published online 2022 Feb 12. doi: 10.3390/ijerph19042052
  - PMCID: PMC8872248
    - PMID: 35206241

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Published results

- Prevalence of Aspergillus-Derived Mycotoxins (Ochratoxin, Aflatoxin, and Gliotoxin) and Their Distribution in the Urinalysis of ME/CFS Patients
- Ting Yu Wu,[1] Taura Khorramshahi,[1] Lindsey A. Taylor,[1] Nikita S. Bansal,[1] Betsy Rodriguez,[1] and Irma R. Rey[2,*]
- Zhaomin Dong, Academic Editor, Ying Wang, Academic Editor, and Xiaomin Li, Academic Editor
- Author information Article notes Copyright and License information Disclaimer

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Published results

- Abstract

- Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a known complex, multi-organ system disorder with a sudden or subacute onset. ME/CFS occurs most commonly among women between 30 and 50 years of age. The current diagnostic criteria of ME/CFS, as defined by the Centers for Disease Control and Prevention, includes: profound fatigue and post-exertional malaise (>6 mo) unrelieved by rest, persistent cognitive impairment or orthostatic intolerance, and chronic unrefreshing sleep. Despite reported associations between ME/CFS onset and exposure to infectious agents (viral, bacterial, or fungal), the pathophysiology of ME/CFS remains unknown. In this prevalence study, we investigated the rates of Aspergillus-derived toxin levels, Aflatoxin (AF), Ochratoxin A (OTA), and Gliotoxin (GT), in the urinalysis of 236 ME/CFS patients with a history of chronic exposure to mold (i.e., from water-damaged buildings). Among ME/CFS patients reporting chronic exposure to mold, we found evidence of exposure in 92.4 percent of patients, with OTA being the most prevalent mycotoxin. Mold distributions (OTA, AF, and GT) in the urinalysis all demonstrated right skewness, while the distribution of age of ME/CFS patients diagnosed showed no deviation from normality. This study aims to provide preliminary, epidemiological evidence among ME/CFS patients who were diagnosed in South Florida with a history of exposure to mycotoxins. Based on these findings, we proposed how future control studies should approach investigating the association between chronic mold exposure and the diagnosis of ME/CFS.

- **Keywords:** ochratoxin A, aflatoxin, gliotoxin, Myalgic encephalomyelitis, Chronic Fatigue Syndrome, urinalysis

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  International Journal Environmental Research Public Health 2002 Feb: 19 (4): 2052

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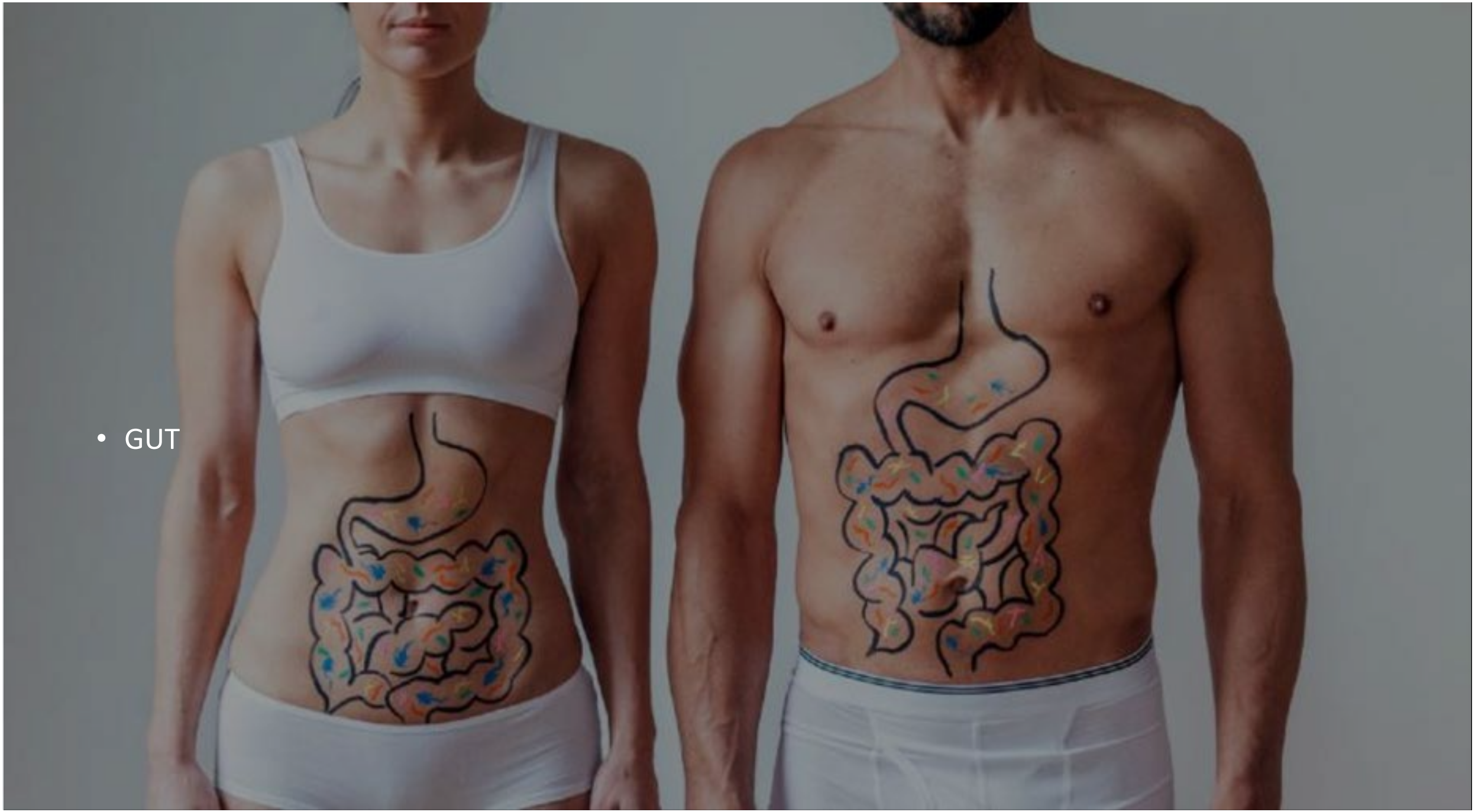
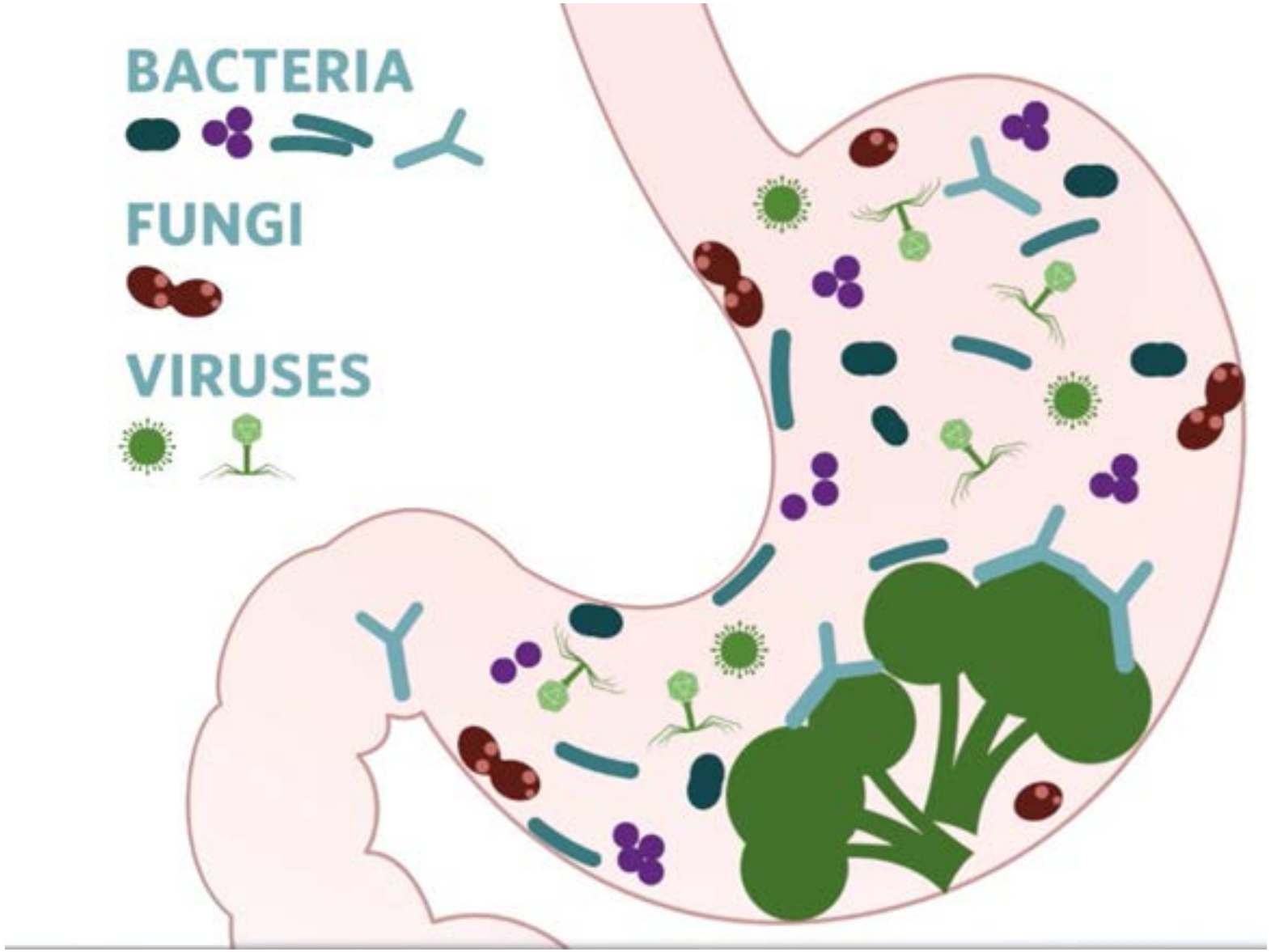
Three Organ Systems & ME/CFS

GUT & BRAIN& IMMUNE SYSTEM

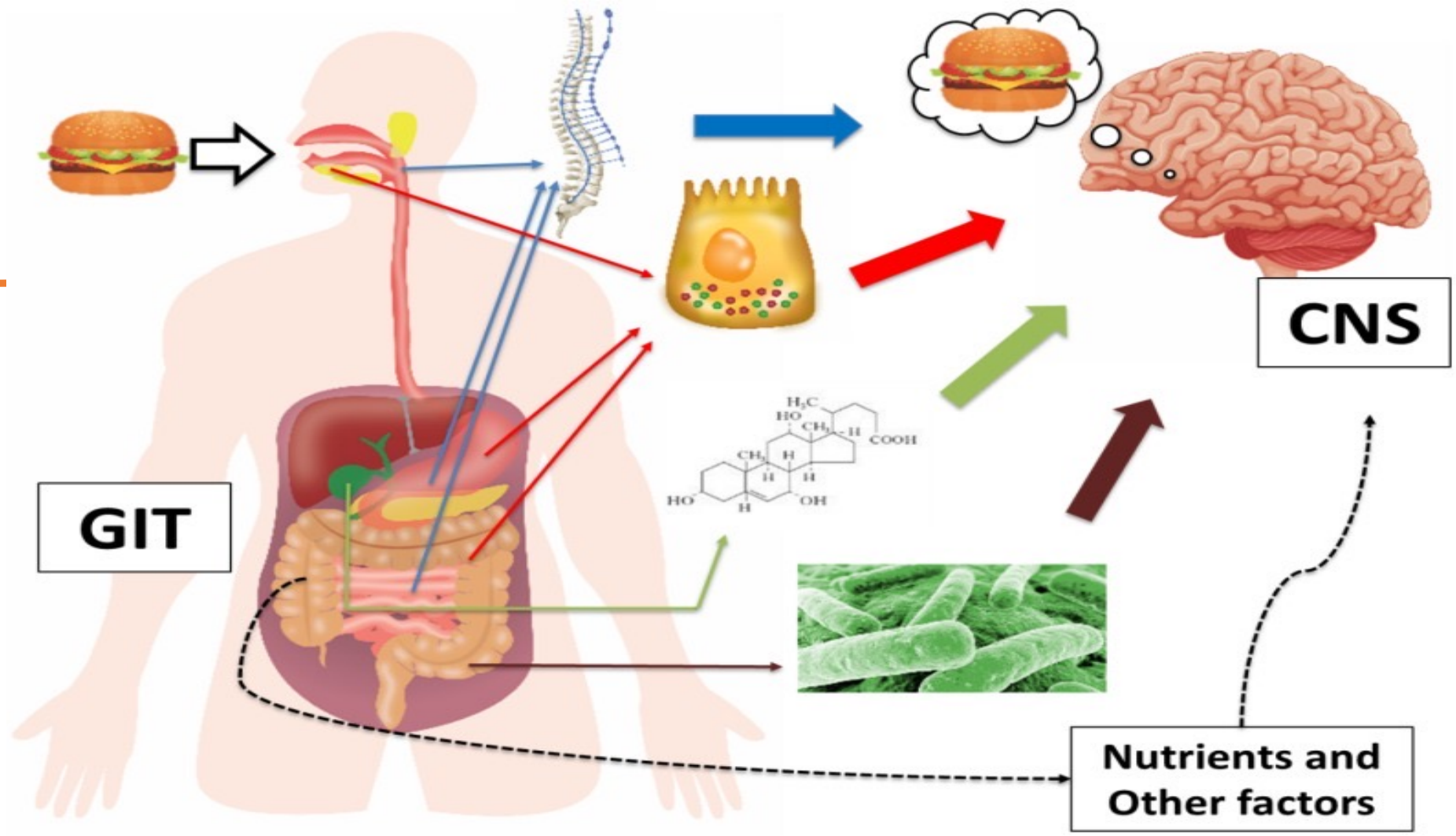
Irina Rozenfeld, DNP, MSc, MSN, APN-BC, APRN



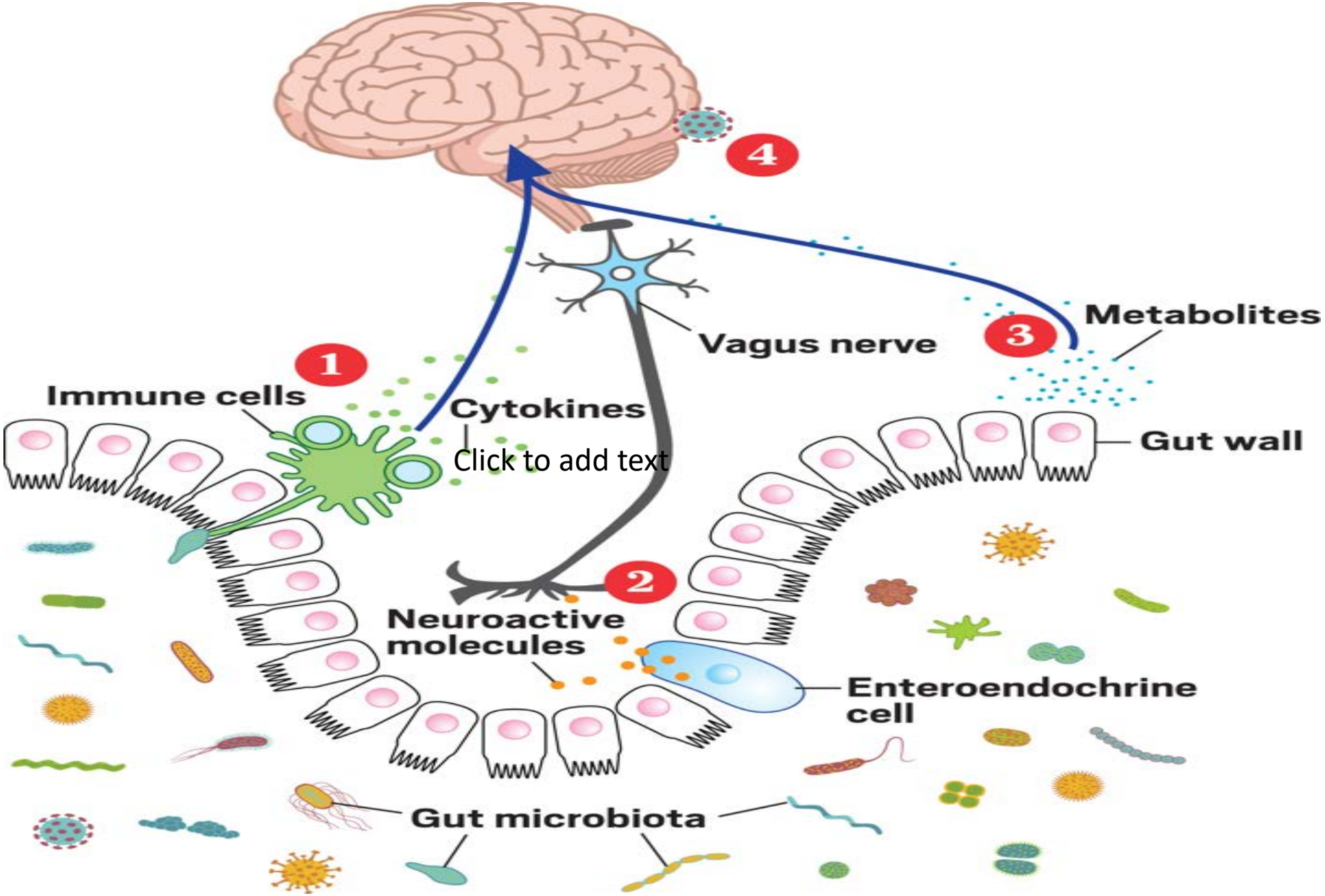
- GUT


BACTERIA
FUNGI
VIRUSES

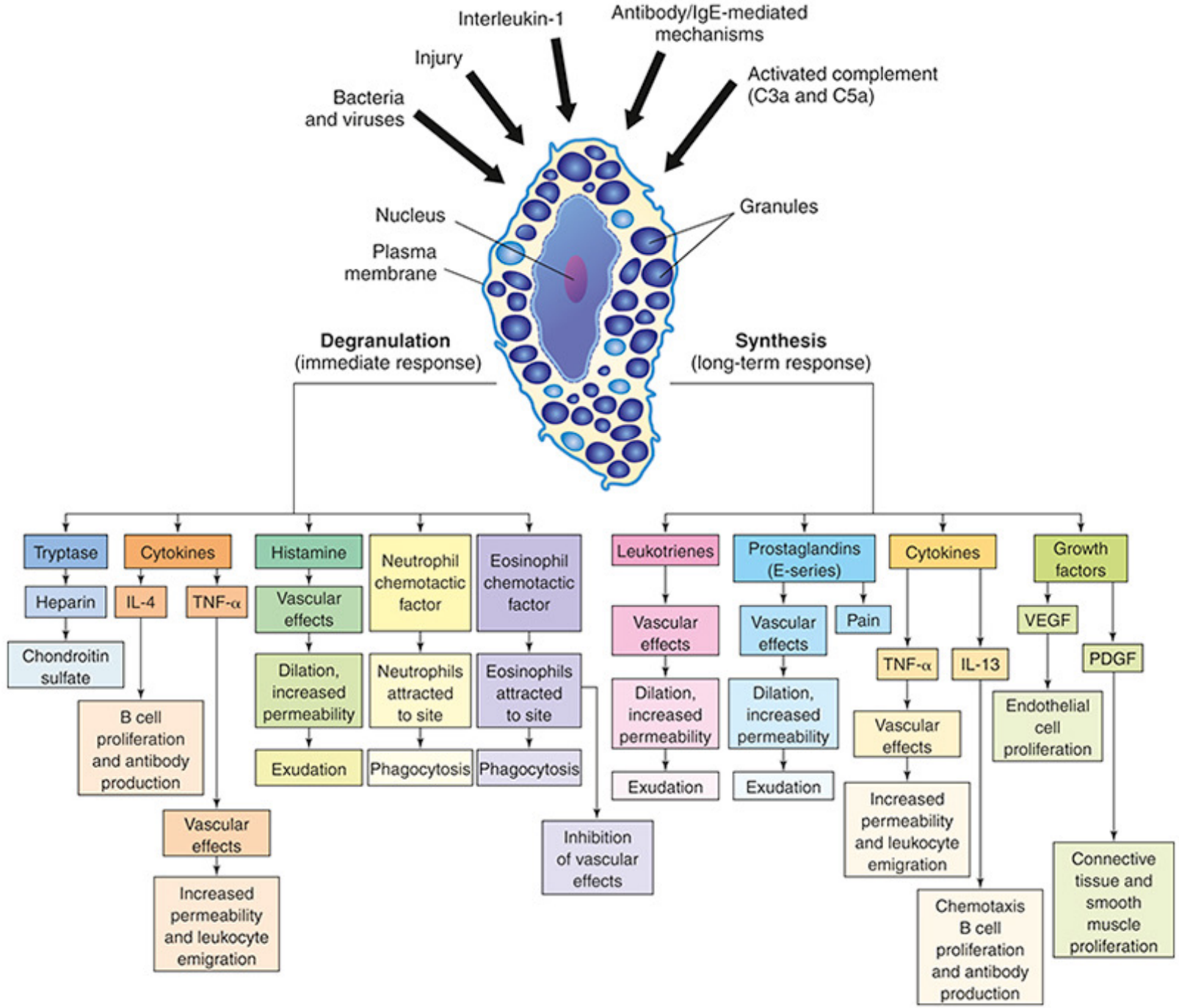
- BRAIN

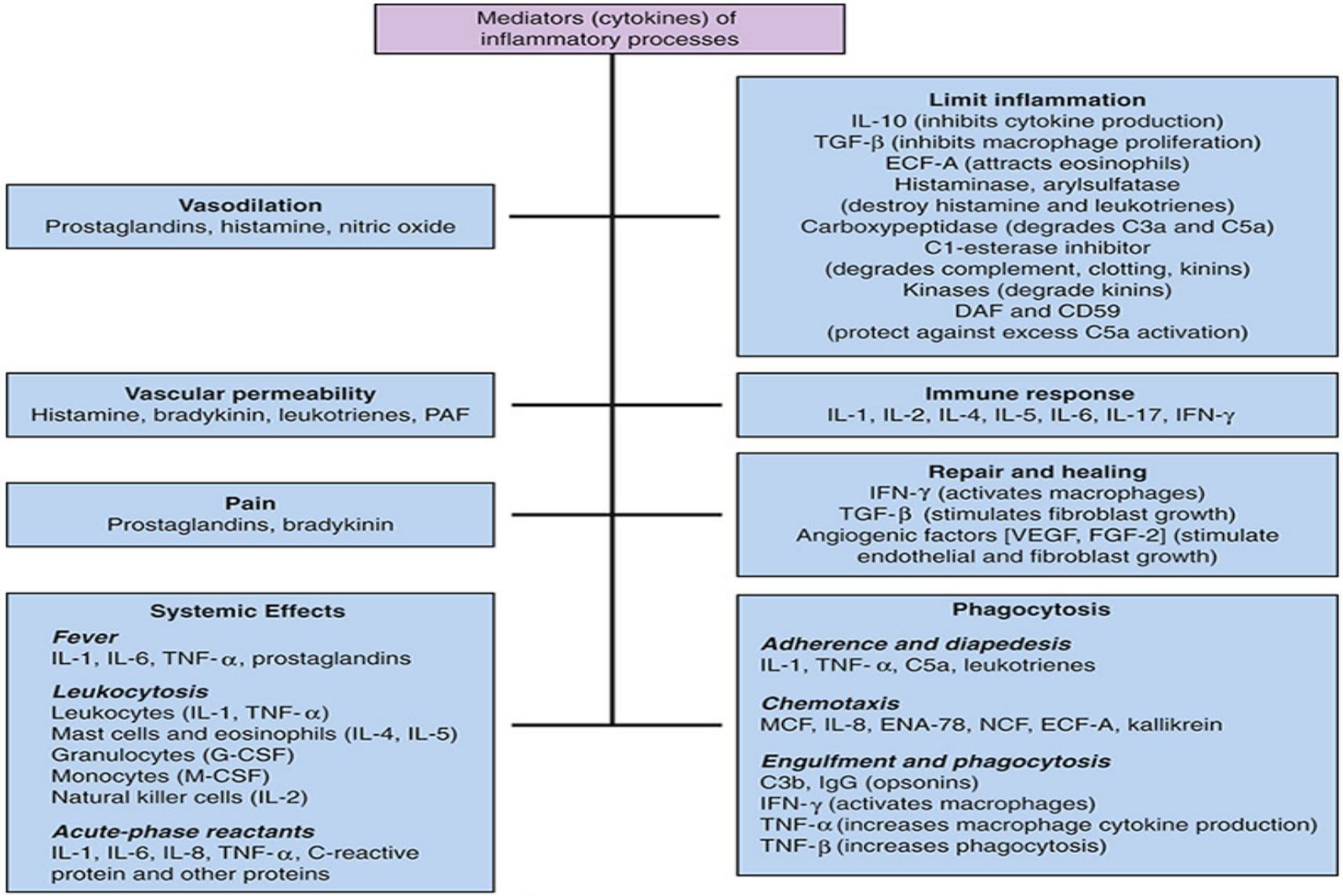


From: Endocrinology of the Gut and the Regulation of Body Weight and Metabolism



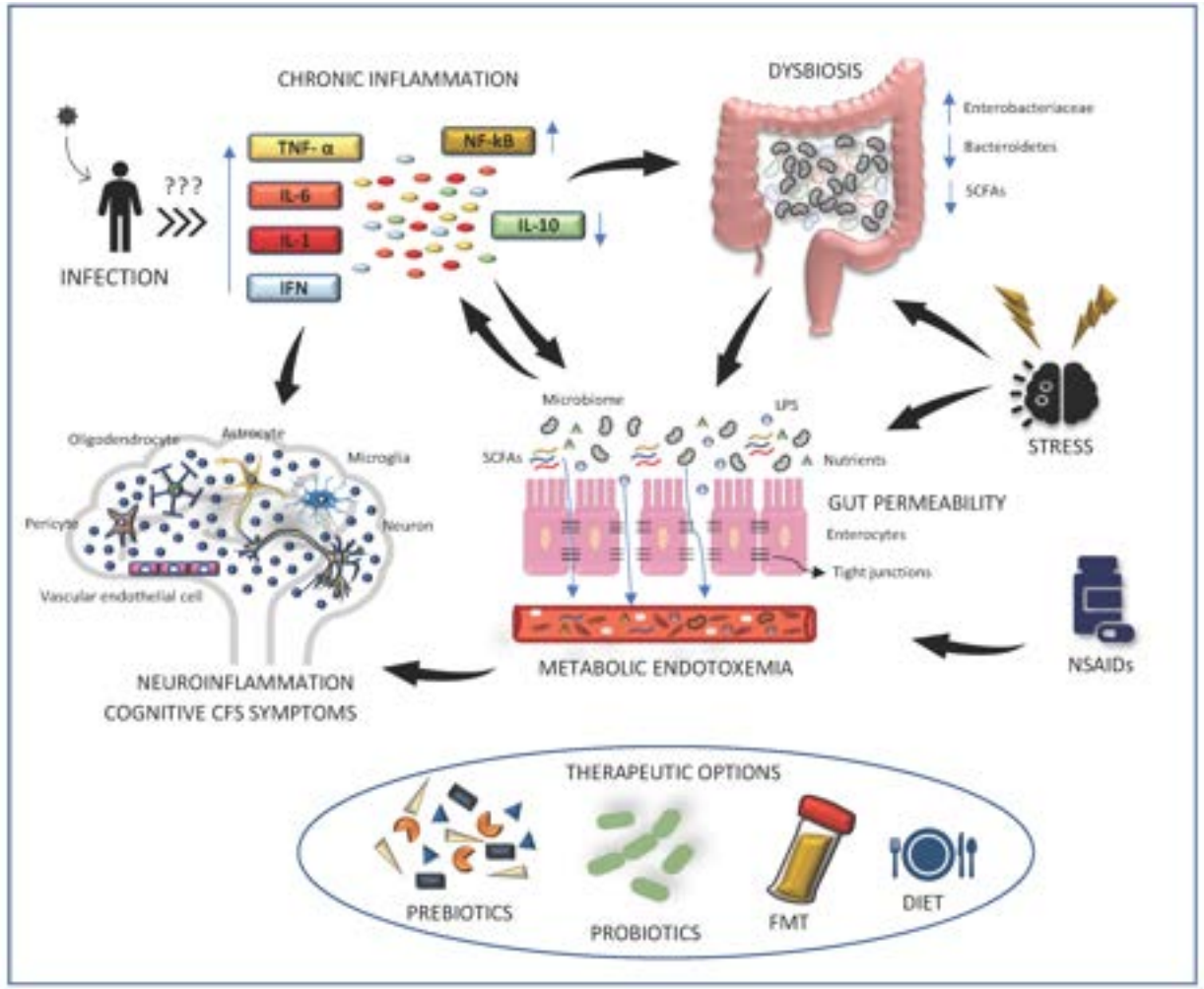
https://cen.acs.org/biological-chemistry/microbiome/gut-might-modify-mind/97/i14





Open Access Review

The Emerging Role of Gut Microbiota in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): Current Evidence and Potential Therapeutic Applications



Main findings:

- Alterations of Human Microbiome in ME/CFS
- Increased Gut Permeability in ME/CFS
- Oxidative Stress and Inflammation in
- Disease Pathogenesis

Therapies Aimed at Microbiota May Alleviate ME/CFS Symptoms

(Varesi, Deumer, Ananth S, & Ricevuti, 2021)

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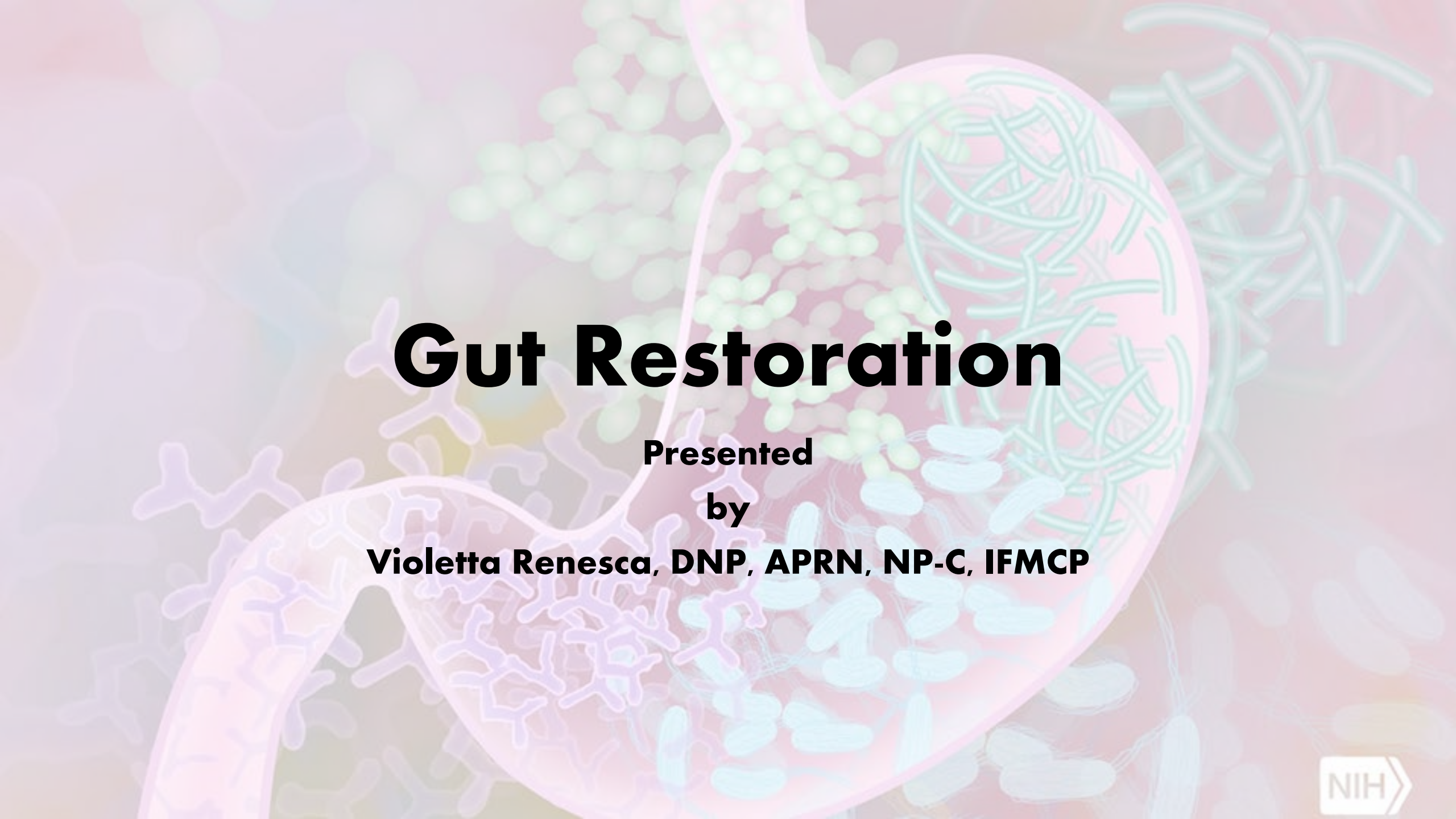
Sherman, M., Zaghouani, H. & Niklas, V. Gut microbiota, the immune system, and diet influence the neonatal gut–brain axis. Pediatr Res 77, 127–135 (2015). https://doi.org/10.1038/pr.2014.161

Varesi A, Deumer U-S, Ananth S, Ricevuti G. The Emerging Role of Gut Microbiota in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): Current Evidence and Potential Therapeutic Applications. Journal of Clinical Medicine. 2021; 10(21):5077. https://doi.org/10.3390/jcm10215077



Gut Restoration

Presented

by

Violetta Renesca, DNP, APRN, NP-C, IFMCP

Food Antigens

Stress

Infection

Inflammation

Dysbiosis

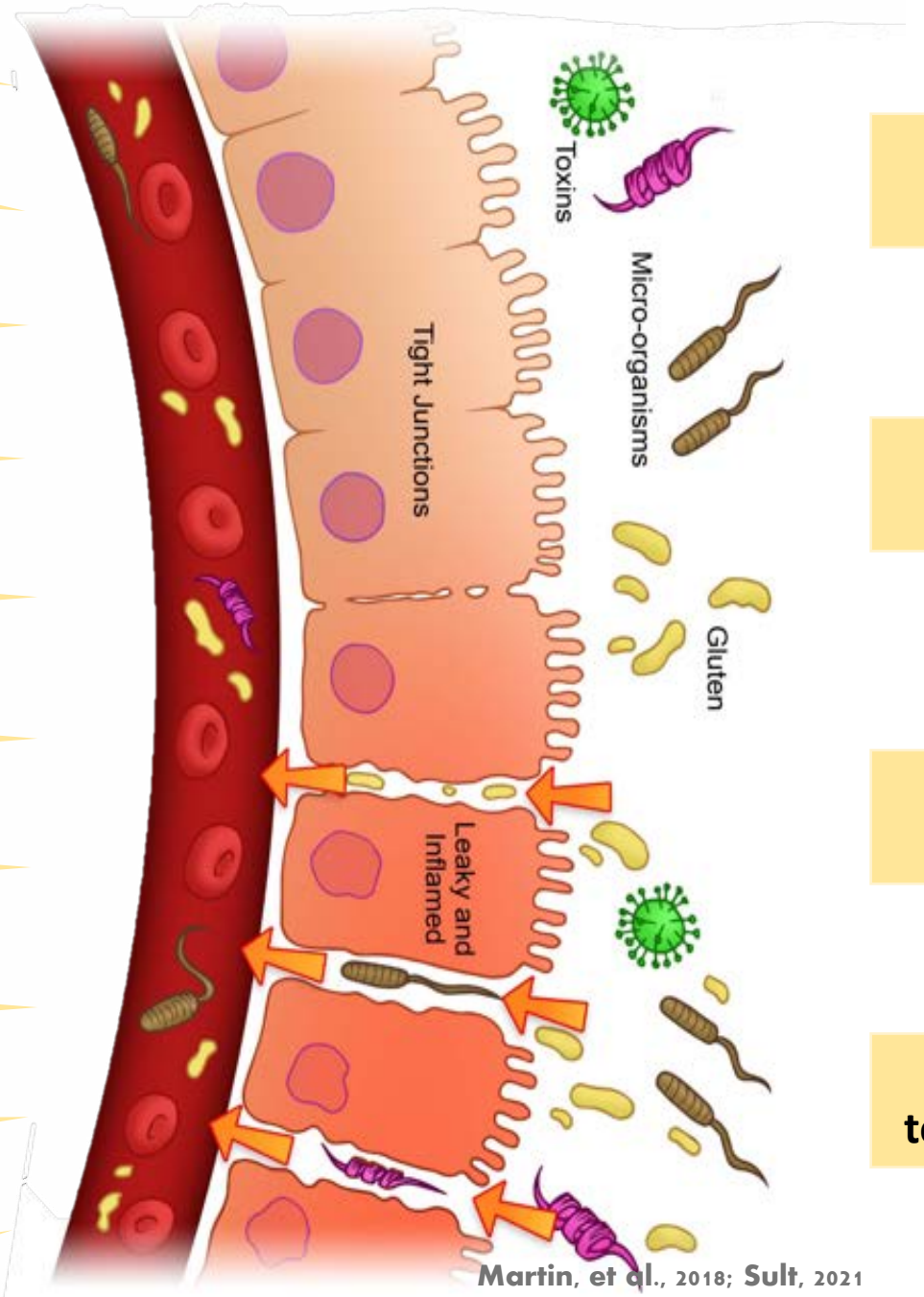
Diseases

Toxins

Impaired Digestion

Nutritional Insufficiencies

Medications



Increased uptake of food antigens

Malabsorption

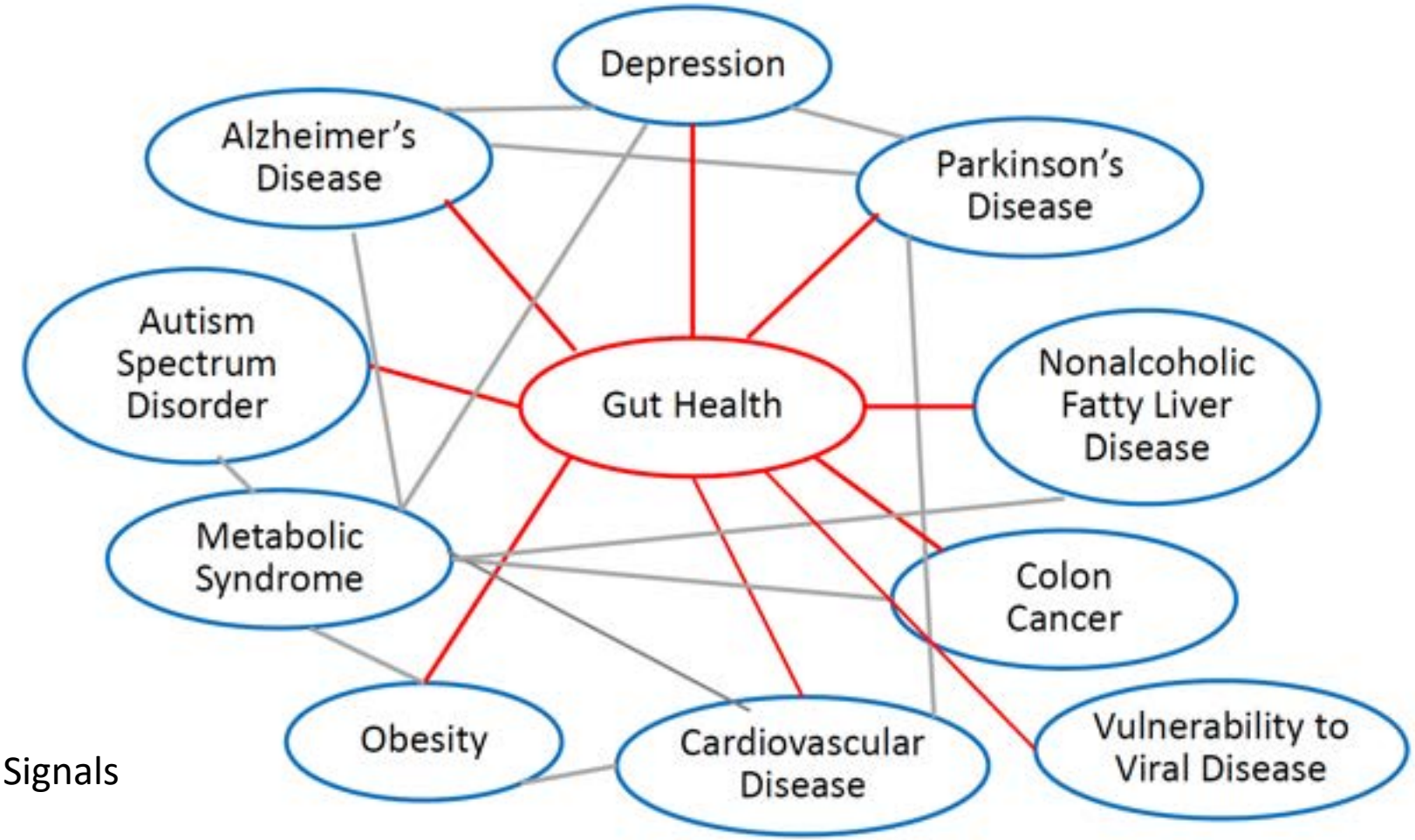
Immune Activation
Inflammation
Systemic Disease

Malnutrition

Increased uptake of toxins and endotoxins

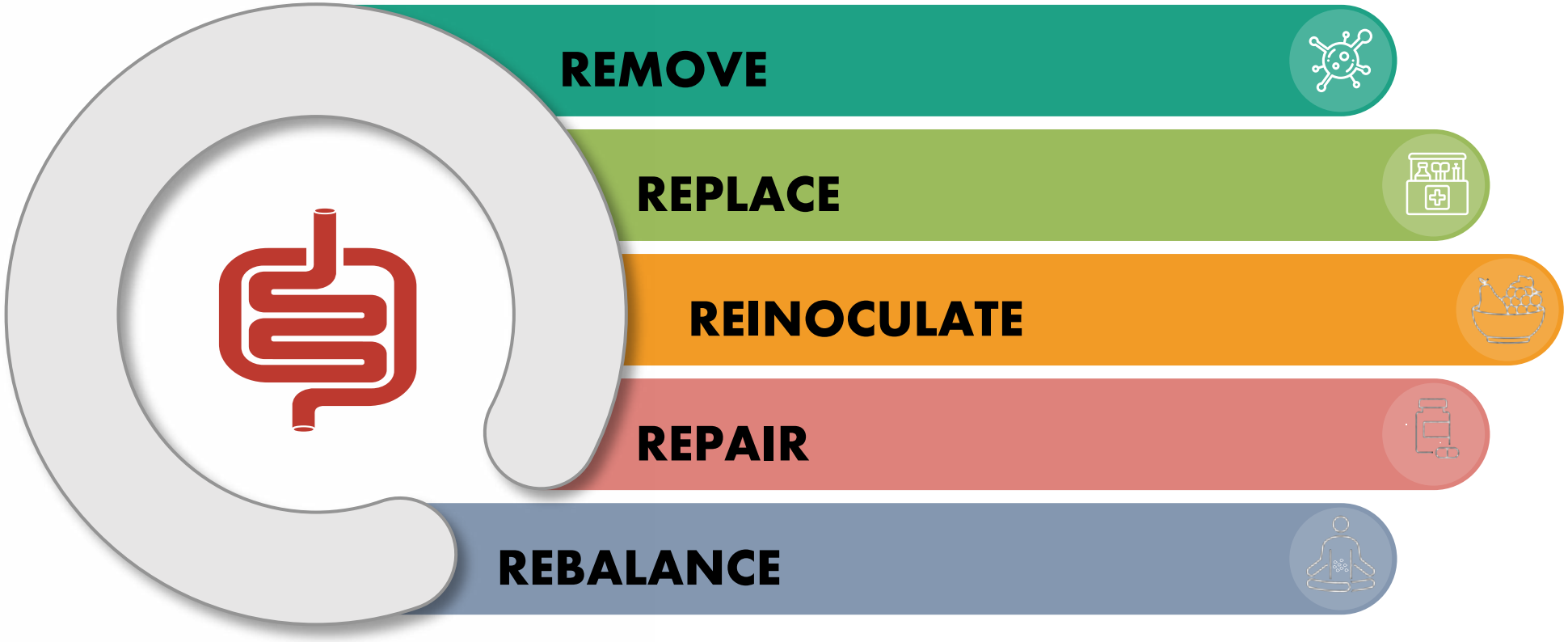
Martin, et al., 2018; Sult, 2021

Dysregulation of the GI system can have a profound impact on health



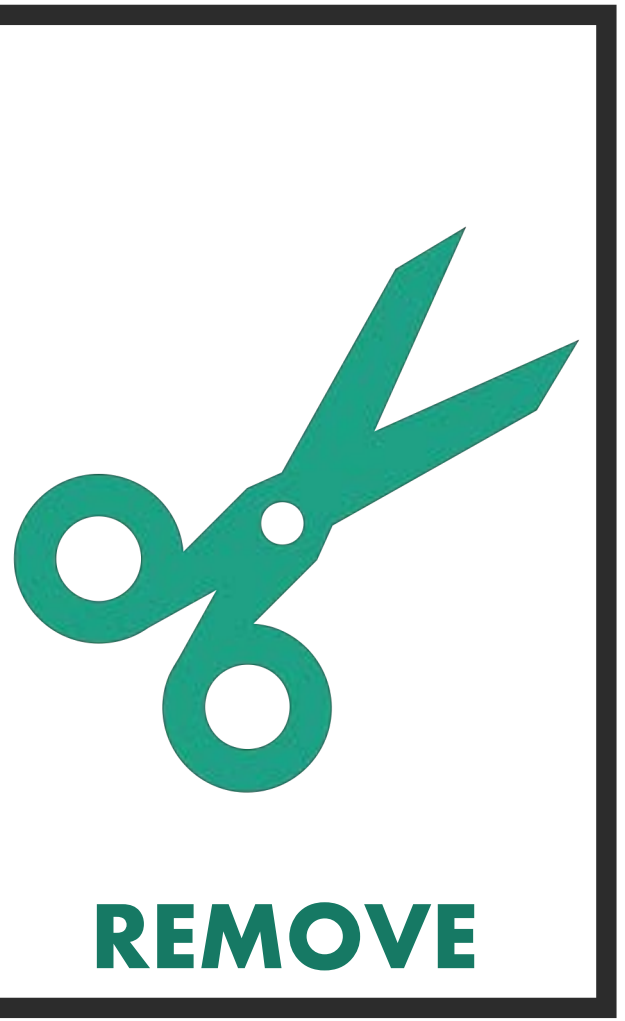
Mayer, 2021

5 R Framework for Gut Restoration



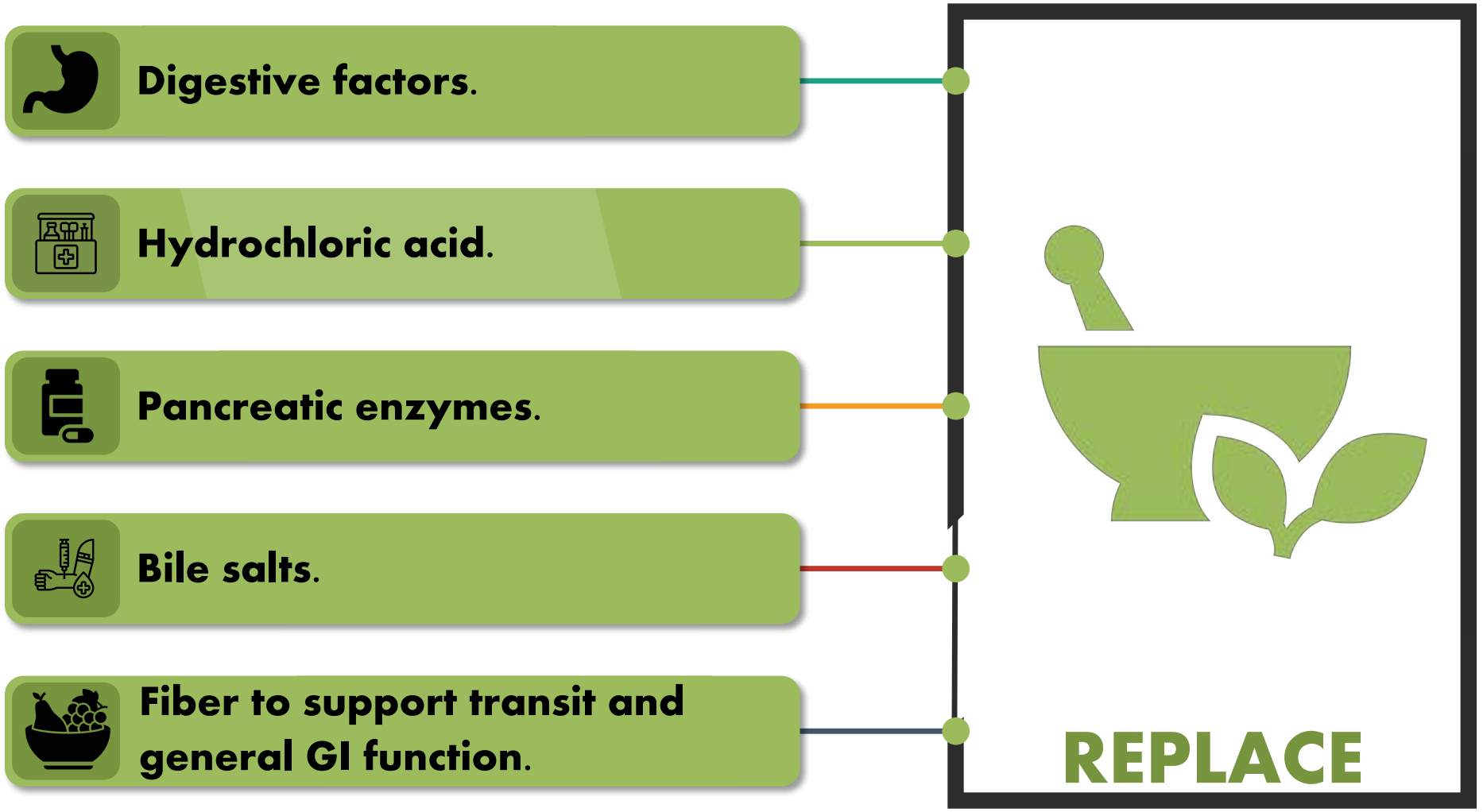
IFM, 2022

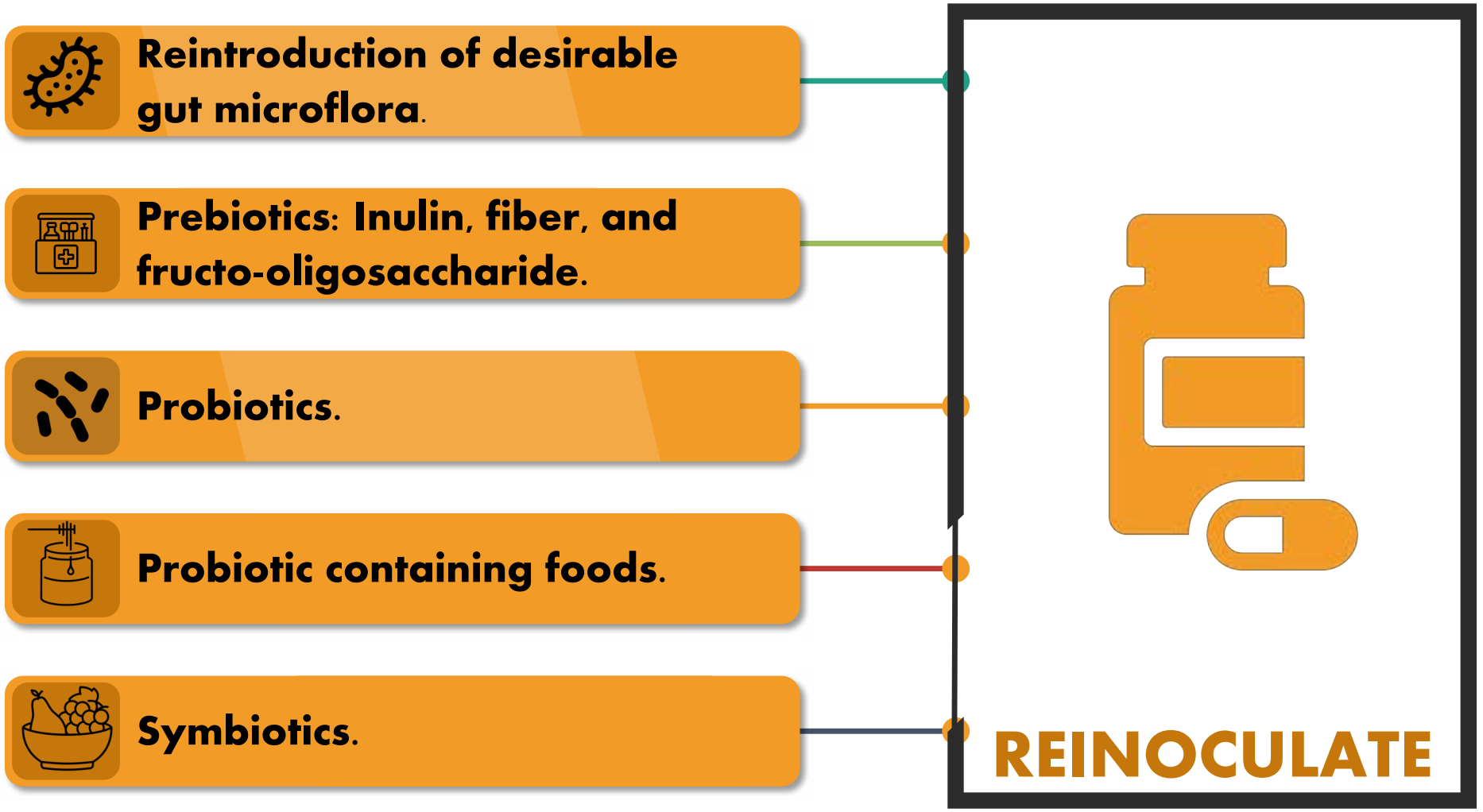
- Foods that you allergic, sensitive, or intolerant.
- Pathogens: bacteria, viruses, fungi, or parasites.
- Toxins and pollutants.
- Stress.
- Treatments: diet, medication, botanicals.



Reducing foods that can trigger systemic reactions in order to reduce inflammation, lower the allergenic load, and provide gut with dietary bases to allow restoration.

IFM, 2022


Digestive factors.
Hydrochloric acid.
Pancreatic enzymes.
Bile salts.
Fiber to support transit and general GI function.
REPLACE


Reintroduction of desirable gut microflora.
Prebiotics: Inulin, fiber, and fructo-oligosaccharide.
Probiotics.
Probiotic containing foods.
Symbiotics.
REINOCULATE

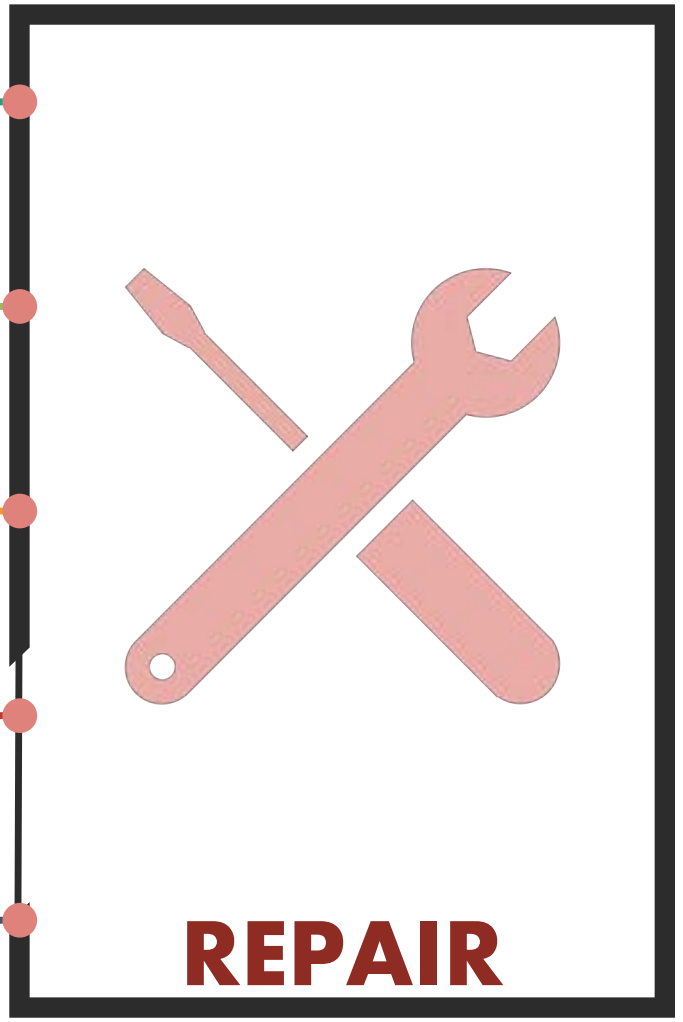
GI repair: glutamine, zinc, vitamin D, E, B_5 and A, carotenoids.

Mucosal lining support: PSC, slippery elm, marshmallow root.

Mucosal secretion protectants: plantain, polysaccharides.

GALT function: lactoferrin, immunoglobulins.

Antioxidants and anti-inflammatories: fish oil, curcumin, catechins (green tea).



- **Lifestyle approaches: sleep, exercise, stress.**
- **Mindful eating / better choices.**
- **Heart rate variability, biofeedback.**
- **Yoga, meditation, prayer, deep breathing.**
- **Psychotherapy.**

REBALANCE

The Use of Directed Probiotics in ME/CFS.

- Males and females between age 45-70 diagnosed with ME/CFS
- With or without diagnosis of IBS
- Study length 6 months- 8 weeks of probiotic intervention
- Interested- contact:

Anthony Park, DO
Study Coordinator, INIM
Phone 801 910 0491
Email: ap2139@nova.edu

References

Institute for Functional Medicine. (2022). *The 5R framework for gut restoration*. Retrieved from https://functionalmedicine.widencollective.com/portals/6ymhcnjh/Toolkit-SearchA-Z

Martin, C. R., Osadchiy, V., Kalani, A., & Mayer, E. A. (2018). The brain-gut-microbiome axis. *Cellular and molecular gastroenterology and hepatology*, *6*(2), 133–148. https://doi.org/10.1016/j.jcmgh.2018.04.003

Mayer, E. (2021). *The gut-immune connection*. Harper Wave

Sult, T. (2021). *Treatment of GI Dysfunction in the Context of the Functional Medicine Matrix* [Conference session]. Applying Functional Medicine in Clinical Practice, United States.

Addressing Brain Health Issues in ME / CFS

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1

Brain Fog in Fatiguing Illnesses

- Prominent Symptom
- Often poorly described and measured by clinicians; however, it can be measured and quantified with appropriate tools which we will discuss today
- A comprehensive approach to understanding root causes will often unsurface additional opportunities for successful clinical intervention
- Improvement in symptoms can either happen as a result of directly treating the underlying condition versus treatments that address brain issue directly

2

Using objective biomarkers to understand nature of problem & track improvement

- **Cognitive Performance**
  - CNS Vital Signs – validated metrics, easy to administer
  - Brain HQ - subscription, brain training
- **Self Assessment**
  - Validated surveys
- **Anatomical Imaging**
  - MRIs do not pick up inflammation well which is a problem
  - NeuroQuant as a cost-effective option
- **Functional Imaging to measure brain network function**
  - QEEG – highly cost-effective, can be used to track performance effectively
  - SPECT scans
  - Functional MRI

3

CNS Vitals Signs baseline

CNS Vital Signs Report — **Test Date: February 01, 20[redacted]50**

Patient: [redacted] — Administrator: administrator

Age: — Language: English (United States)

Total Test Time: 29:48 (min:secs) — CNSVS Duration: 29:47 (min:secs) — Version 4.0.87

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	Valid Score**	Above	Average	Low Average	Low	Very Low
Neurocognition Index (NCI)		88	21	Yes			x		
Composite Memory	105	113	81	Yes	x				
Verbal Memory	55	109	73	Yes		x			
Visual Memory	50	113	81	Yes	x				
Psychomotor Speed	148	80	9	Yes			x		
Reaction Time*	764	73	4	Yes				x	
Complex Attention*	8	91	27	Yes		x			
Cognitive Flexibility	37	82	12	Yes			x		
Processing Speed	48	83	13	Yes			x		
Executive Function	37	81	10	Yes			x		
Simple Attention	40	107	68	Yes		x			
Motor Speed	100	87	19	Yes			x		

Domain Dashboard: Above average domain scores indicate a standard score (SS) greater than 109 or a Percentile Rank (PR) greater than 74, indicating a high functioning test subject. Average is a SS 90-109 or PR 25-74, indicating normal function. Low Average is a SS 80-89 or PR 9-24 indicating a slight deficit or impairment. Below Average is a SS 70-79 or PR 2-8, indicating a moderate level of deficit or impairment. Very Low is a SS less than 70 or a PR less than 2, indicating a deficit and impairment. Reaction times are in milliseconds. An * denotes that "lower is better", otherwise higher scores are better. Subject Scores are raw scores calculations generated from data values of the individual subtests.

V** - Validity Indicator. Denotes a guideline for representing the possibility of an invalid test or domain score. "No" means a clinician should evaluate whether or not the test subject understood the test, put forth their best effort, or has a clinical condition requiring further evaluation.

Verbal Memory Test (VBMI)	Score	Standard	Percentile

4

4

22 weeks into treatment

CNS Vital Signs Report — **Test Date: July 19, 20[redacted]59**

Patient ID: — Administrator:

Age [redacted] — Language: English (United States)

Total Test Time: 24:07 (min:secs) — CNSVS Duration: 23:19 (min:secs) — Online Version 1.1.0

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	Valid Score[V]	Above	Average	Low Average	Low	Very Low
Neurocognitive Index (NCI)	NA	119	90	Yes	X				
Composite Memory	105	114	82	Yes	X				
Verbal Memory	56	112	79	Yes	X				
Visual Memory	49	110	75	Yes	X				
Psychomotor Speed	229	144	99	Yes	X				
Reaction Time*	573	112	79	Yes	X				
Complex Attention*	3	111	77	Yes	X				
Cognitive Flexibility	55	113	81	Yes	X				
Processing Speed	84	140	99	Yes	X				
Executive Function	56	113	81	Yes	X				
Simple Attention	40	106	66	Yes		X			
Motor Speed	145	129	97	Yes	X				

Domain Dashboard: Above average domain scores indicate a standard score (SS) greater than 109 or a Percentile Rank (PR) greater than 74, indicating a high functioning test subject. Average is a SS 90-109 or PR 25-74, indicating normal function. Low Average is a SS 80-89 or PR 9-24 indicating a slight deficit or impairment. Below Average is a SS 70-79 or PR 2-8, indicating a moderate level of deficit or impairment. Very Low is a SS less than 70 or a PR less than 2, indicating a deficit and impairment. Reaction times are in milliseconds. An * denotes that "lower is better", otherwise higher scores are better. Patient Scores are raw scores calculations generated from data values of the individual subtests.

V** - Validity Indicator: Denotes a guideline for representing the possibility of an invalid test or domain score. "No" means a clinician should evaluate whether or not the test subject understood the test, put forth their best effort, or has a clinical condition requiring further evaluation.

Verbal Memory Test (VBM)	Score	Standard	Percentile	
Correct Hits - Immediate	14	111	77	Verbal Memory test: Subjects have to remember 15 words and recognize them in a field of 15 distractors. This test is repeated at the end of the battery. The VBM test measures how well a subject can recognize, remember, and retrieve words e.g. exploit or attend literal
Correct Passes - Immediate	15	110	75	

5

Detailed assessment surveys

Brain Function Assessment Form

Notice word pronunciation and speaking fluency change at times — ○0 ○1 ○2 ●3

Parietal Somatosensory Area and Parietal Superior Lobule (Areas 3, 1, 2 and 7)

Difficulty in perception of position of limbs — ●0 ○1 ○2 ○3

Difficulty with spatial awareness when moving, laying back in a chair, or leaning against a wall — ●0 ○1 ○2 ○3

Frequently bumping body or limbs into the wall or objects accidently — ○0 ○1 ●2 ○3

Reoccuring injury in the same body part or side of the body — ●0 ○1 ○2 ○3

Hypersensitivities to touch or pain perception — ●0 ○1 ○2 ○3

Parietal Inferior Lobule (Area 39 and 40)

Right/left confusion — ○0 ○1 ●2 ○3

Difficulty with math calculations — ○0 ●1 ○2 ○3

Difficulty finding words — ○0 ○1 ●2 ○3

Difficulty with writing — ○0 ○1 ●2 ○3

Difficulty recognizing symbols or shapes — ●0 ○1 ○2 ○3

Difficulty with simple drawings — ○0 ○1 ●2 ○3

Difficulty interpreting maps — ●0 ○1 ○2 ○3

Temporal Lobe Auditory Cortex (Areas 41,42)

Reduced function in overall hearing — ○0 ○1 ○2 ●3

Difficulty interpreting speech with background or scatter noise — ○0 ○1 ●2 ○3

From Dr. Datis Kharazzian

6

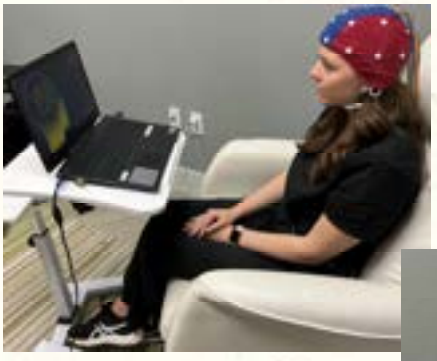
Volumetric MRI to assess atrophy and inflammation

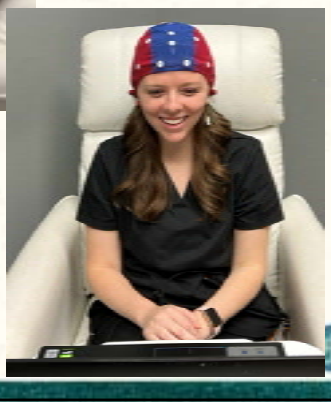

NeuroQuant®
Triage Brain Atrophy Report

7

Quantitative EEG

- Can measure functional performance and dysregulation
- Compared to database of patients with excellent cognitive and emotional health
- Can localize issues and correlate with symptoms
- Can do after initial history and assessment and get results that day if clinician knows how to read ; the hand-held ultrasound for the brain!
- Can track improvement in real-time





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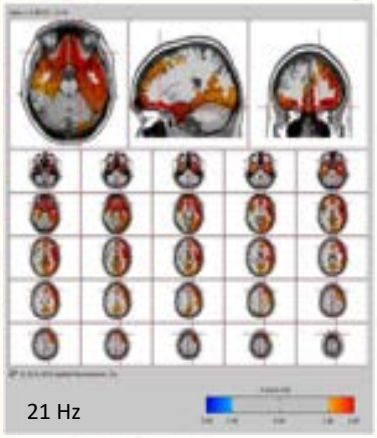
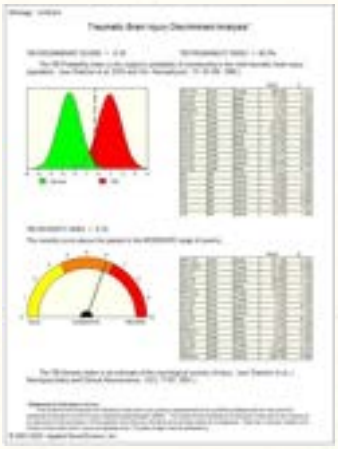
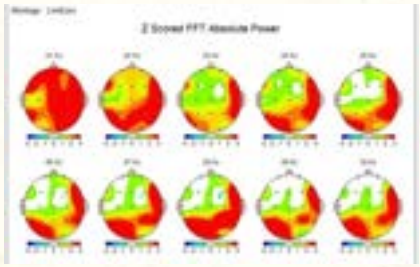
Sample QEEG Outputs



3-D LORETA & Neuronavigator Imaging



Peer-reviewed measurement of TBI presence and severity



Brain maps of activity measured by wave frequencies (1-30Hz) compared to normal database by Standard Deviations

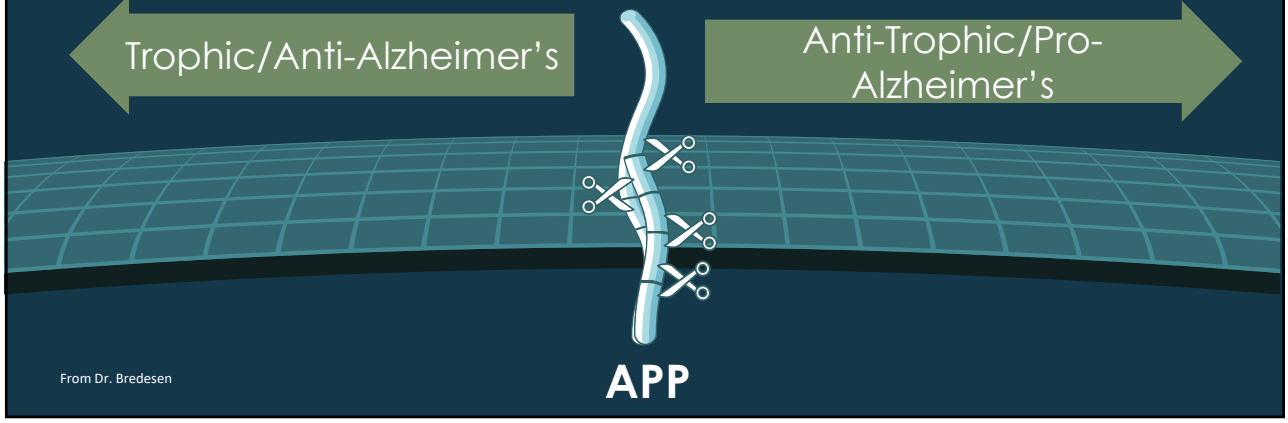
9

Framework for understanding root causes of neurodegeneration

$$p(AD) \propto \int \frac{\sum(synaptoclastic\ signaling)}{\sum(synaptoblastic\ signaling)} \approx \int \frac{\sum[inflammatory\ mediators + toxins]}{\sum[energetics + trophic\ support]}$$

Trophic/Anti-Alzheimer's

Anti-Trophic/Pro-Alzheimer's



From Dr. Bredesen

10

Factors that can affect Brain Health

1. Trophic

- Circulation – blood pressure, hypercoagulability, delivery of oxygen, lymphatics
- Hormones – cortisol, thyroid, sex hormones, glucose metabolism
- Mitochondrial function
- Sleep & recovery

2. Anti-trophic

- Inflammation & cytokine storms
- Pathogens – viruses, tick borne illness
- Traumatic brain injury
- Toxins – biotoxins / water damaged buildings, chemicals, heavy metals
- Microbiome imbalance – oral, nasal, gut

3. Brain Network Function

- Dysregulated networks & coherence – limbic system, frontal & temporal lobes
- Neurotransmitter balance

11

Optimizing Trophic Factors

Goals of Treatment	Interventions
• **Optimal cerebral blood flow & oxygenation**	• Treatment of POTS • Treatment of hypercoagulability • Hyperbaric oxygen
• Improved mitochondrial function	• Nutraceuticals, NAD / NR • Low & high intensity light therapy
• Insulin sensitivity (HOMA IR < 1.0) • Ketosis (1-4.0mM BHB), metabolic flexibility	• Keto brain healthy diet • Using Continuous Glucose Monitor guidance
• **Optimize sleep & recovery**	• Sleep hygiene, stress management • Oura ring
• **Optimize hormones** – stress, sex, thyroid	• Hormone support
• Optimize micronutrients & trophic factors (e.g., BDNF)	• Micronutrient support (outline which ones)

12

Reducing Anti-trophic factors

Goals of Treatment	Interventions
• Address **mast cell activation** if present	Luteolin, broad MACS protocols
• Improve inflammatory and innate immune system markers / cytokine storms	Polyphenols, curcumin, resveratrol, Pharmaceuticals & nutraceuticals targeted at markers (e.g., **maraviroc** – CCL5 / SCDL40 , **VIP** – C4a / TGF-Beta) Hyperbaric oxygen
• Removing **toxins**	Address environmental exposures – clean indoor air, WDB, chemicals, dental health Detoxification protocols sequenced appropriately
• Addressing infections	Antiviral & tick-borne disease protocols
• Optimize microbiome	Probiotics / prebiotics, food, dental / oral hygiene
• Healing prior injury (e.g., **traumatic brain injury)**	**Hyperbaric oxygen**

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Optimizing Brain Network Functions

Goals of Treatment	Interventions
• Limbic system programs	Dynamic Brain Retraining System Gupta Programme **Vagal Nerve Stimulators** **19 channel Neurofeedback**
• Addressing brain network dysregulation and coherence	19 channel Neurofeedback **High Intensity Light Therapy** Electrical Brain Stimulation **Hyperbaric Oxygen** **Brain Exercises**
• Addressing neurotransmitter deficiencies	Symptom guided neurotransmitter support – pharmaceutical / nutraceutical

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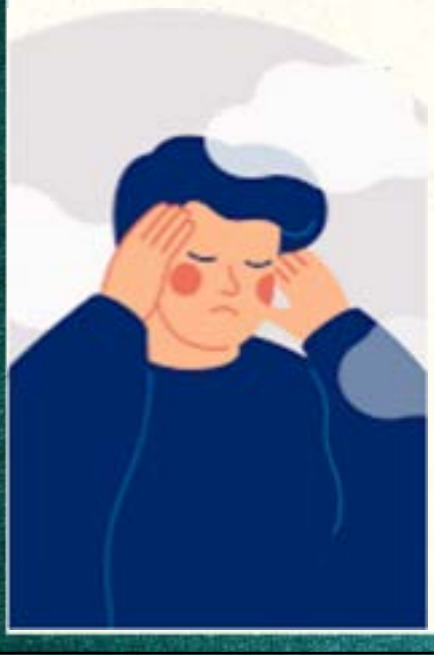

Conclusion

- Brain Fog & Brain Health can be **accurately measured with appropriate tools** including symptom surveys, measurement of cognitive performance as well as functional & anatomical tools
- Taking a **comprehensive approach to root causes of brain health can reveal other factors** that can be addressed in addition to ME/CFS
- There are a **significant toolkit of interventions that can work** with a precision medicine approach!
- Improvement in symptoms can either happen as a result of directly treating the underlying condition versus treatments that address brain issue directly

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Addressing Brain Health Issues in ME / CFS

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