

# Recovery Potential for MS, ALS, Alzheimer's and Parkinson's Diseases

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THE SUMMIT ON NEURODEGENERATIVE DISORDERS



# CONTINUING MEDICAL EDUCATION COMMERCIAL DISCLOSURE REQUIREMENT

I, William E. Code, have no commercial relationships to disclose.

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# Presentation Overview

Most of our neurodegenerative diseases are triggered or aggravated by toxic chemicals and neurotoxins. Specific strategies of testing, treatment and recovery will be presented. Case presentations will be included to assist with clinical application. Dr. Code's new book, *Solving the Brain Puzzle*, will be available as an additional resource.

# Learning Objectives

1. Immediate use of clinical information from the literature regarding MS, ALS, Alzheimer's and Parkinson's Diseases.
2. Lab investigations useful in complex patient evaluation and follow-up.
3. Specific nutrients for mitochondrial recovery and toxic removal will be discussed.

# Blood flow in brain is critical

1. Provides oxygen, glucose, lipids, amino acids.
2. Eliminates soluble proteins, including  $\beta$ -amyloid and metabolites, and other toxins (eg. Heavy metals and pesticides).
3. Obeys Poiseuille's law: flow related to the fourth power of the radius of the vessel.
4. Protects vascular endothelium which is the blood brain barrier (BBB).

# MS patients mortality and comorbidities

US DOD claims database of 15,684 MS patients and 78,420 non-MS patients:

All-cause mortality 2.9 fold higher, secondary infection, CNS diseases, respiratory and circulatory.

Comorbidities:

- Ischemic stroke 3.8 X
- Suicide attempt 2.4 X
- Ulcerative colitis 2 X
- Cancer 2.2 X

Capkun, Gorana, et al. "Mortality and Comorbidities in Patients with Multiple Sclerosis Compared with a Population without Multiple Sclerosis: An Observational Study Using the US Department of Defense Administrative Claims Database." *Multiple Sclerosis and Related Disorders*, vol. 4, no. 6, 2015, pp. 546–554., doi:10.1016/j.msard.2015.08.005.

## High risk of cardiovascular diseases after diagnosis of MS (Sweden)

Incidence rate ratio for:

- MI = 1.85
- Stroke = 1.71
- Heart failure = 1.97
- Atrial fibrillation = 0.63

Increased risk particularly prominent for women.

Jadidi, Elham, et al. "High Risk of Cardiovascular Diseases after Diagnosis of Multiple Sclerosis." *Multiple Sclerosis Journal*, vol. 19, no. 10, 2013, pp. 1336–1340., doi:10.1177/1352458513475833.

## Role of mercury toxicity in hypertension, cardiovascular disease and stroke.

Houston, Mark C. “Role of Mercury Toxicity in Hypertension, Cardiovascular Disease, and Stroke.” *The Journal of Clinical Hypertension*, vol. 13, no. 8, Nov. 2011, pp. 621–627., doi:10.1111/j.1751-7176.2011.00489.x.



# Statins and Brain Illness

- Double risk of PD
- Increases memory problems including AD

Huang, Xuemei, et al. “Statins, Plasma Cholesterol, and Risk of Parkinsons Disease: A Prospective Study.” *Movement Disorders*, vol. 30, no. 4, 2015, pp. 552–559., doi:10.1002/mds.26152.

Can lifestyle changes reverse coronary heart disease?

Confirmed, yes, may bring about regression of even severe CAD after only one year, without lipid lowering drugs.

Ornish, D., et al. “Can Lifestyle Changes Reverse Coronary Heart Disease?” *The Lancet*, vol. 336, no. 8708, 1990, pp. 129–133., doi:10.1016/0140-6736(90)91656-u.

"The vascular system is crucial to health -- it's how oxygen and other nutrients are delivered to cells, and how toxins are removed. Any damage to the vascular system is a serious threat to the organism. It's clear now that the vascular system is certainly involved in the development of ALS."

Berislav V Zlokovic, MD, PhD

Mary Hayley and Selim Zilkha Chair in Alzheimer's Disease Research

Director, Zilkha Neurogenetic Institute

Chair and Professor of Physiology & Neuroscience

Keck School of Medicine, USC

# Berislav V. Zlokovic, USC

- Up to 45% of all dementias are wholly or partly due to age-related small vessel disease of the brain.
- Early work on ALS, now focused on AD.
- Focuses on brain endothelium, the BBB as how its injury impacts ALS, MS, Parkinson's and Alzheimer's.

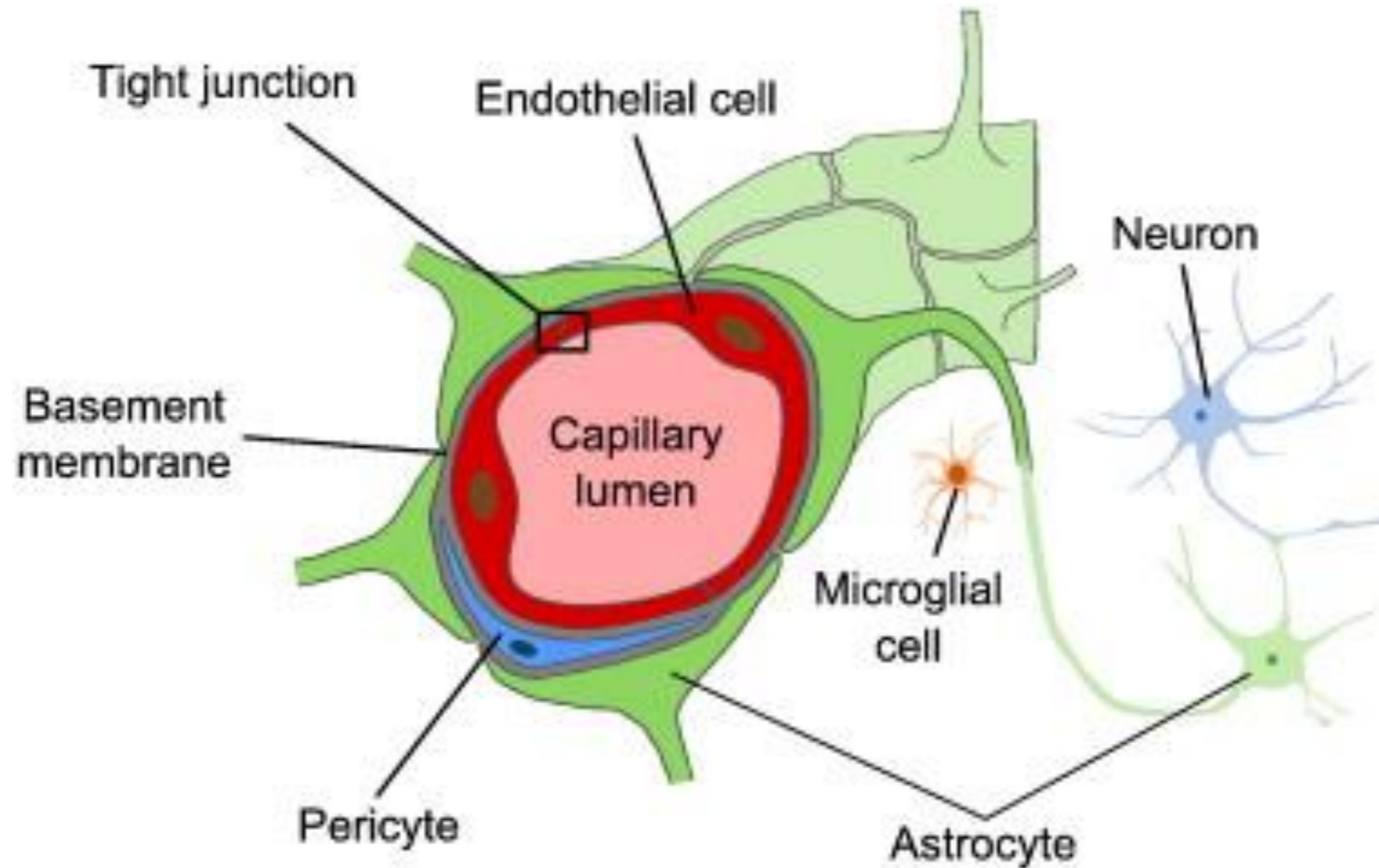
Zlokovic, Berislav V. "The Blood-Brain Barrier in Health and Chronic Neurodegenerative Disorders." *Neuron*, vol. 57, no. 2, 2008, pp. 178–201., doi:10.1016/j.neuron.2008.01.003.

Montagne, Axel, et al. "Pericyte Degeneration Causes White Matter Dysfunction in the Mouse Central Nervous System." *Nature Medicine*, vol. 24, no. 3, May 2018, pp. 326–337., doi:10.1038/nm.4482.

## Cause and prevention of demyelination in a model MS lesion:

- Demyelination can occur in relative absence of lymphocytes.
- Distinctive characteristics suggest a tissue energy deficit.
- Triggered demyelination lesions in the rat spinal dorsal column with microinjection of LPS.
- Lesions preceded by early period of hypoxia.
- Oligodendrocyte numbers decreased at site shortly after.
- Raising inspired oxygen to 80% normobaric significantly reduced or prevented the demyelination.

Desai, Roshni A., et al. "Cause and prevention of demyelination in a model multiple sclerosis lesion." *Annals of Neurology*, vol. 79, no. 4, 2016, pp. 591–604., doi:10.1002/ana.24607.



Swank, R. L. "Subcutaneous Hemorrhages in Multiple Sclerosis." *Neurology*, vol. 8, no. 6, Jan. 1958, pp. 497–497., doi:10.1212/wnl.8.6.497.

# Glymphatics

The glymphatic system (or glymphatic clearance pathway, or paravascular system) is a functional waste clearance pathway for the central nervous system that functions best during sleep.

Xie, L., et al. “Sleep Drives Metabolite Clearance from the Adult Brain.” *Science*, vol. 342, no. 6156, 2013, pp. 373–377., doi:10.1126/science.1241224.

Jessen, Nadia Aalling, et al. “The Glymphatic System: A Beginner’s Guide.” *Neurochemical Research*, vol. 40, no. 12, July 2015, pp. 2583–2599., doi:10.1007/s11064-015-1581-6.

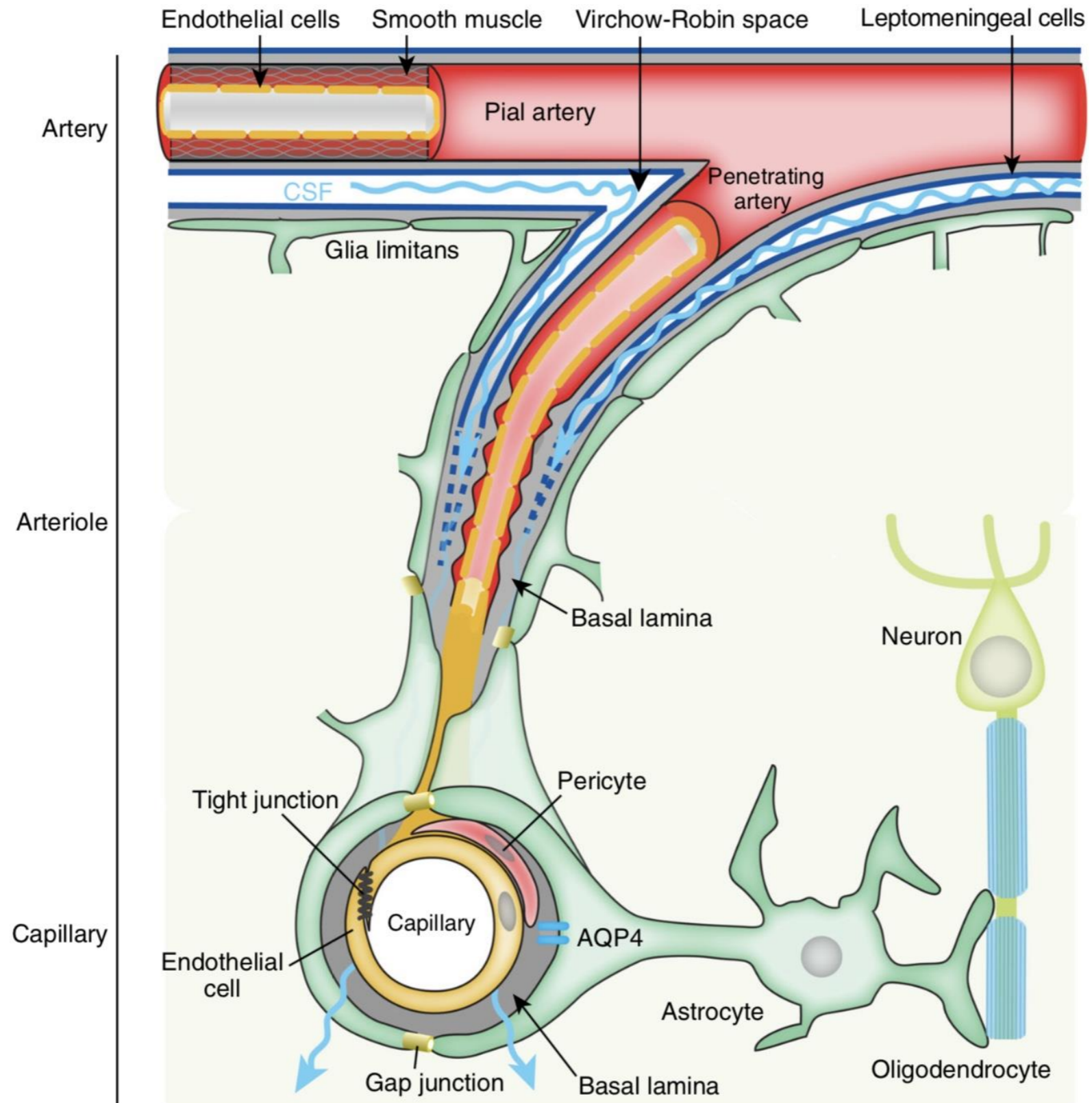
Louveau, Antoine, et al. “Structural and Functional Features of Central Nervous System Lymphatic Vessels.” *Nature*, vol. 523, no. 7560, Jan. 2015, pp. 337–341., doi:10.1038/nature14432.

Cook, Michelle Schoffro. *The brain wash: a powerful, all-Natural program to protect your brain against Alzheimers, chronic fatigue syndrome, depression, Parkinsons, and other diseases.* J. Wiley & Sons Canada, 2007.

# Glymphatics

- Function mainly during sleep.
- May be a biological need for sleep across species.
- Failure of lymphatic function may contribute to pathology in neurodegenerative conditions.





Jessen, Nadia Aalling, et al. "The Glymphatic System: A Beginner's Guide." *Neurochemical Research*, vol. 40, no. 12, July 2015, pp. 2583–2599., doi:10.1007/s11064-015-1581-6.

# Detoxification Lifestyle

1. Avoidance of environmental toxicants such as heavy metals, persistent organic pollutants (eg. glyphosate) and EMF.
2. Mobilization or elimination of toxicants by loss of excess fat and use of saunas, chelation and exercise.
3. Optimal GI health (microbiota).
4. Excellent nutrition and hydration.
5. Attention to stress and resilience (improved relations).
6. Adequate sleep and relaxation.

Cline, John C. "Nutritional Aspects of Detoxification in Clinical Practice." *Alternative Therapies*, May 2015, pp. 54–62.

Avoid GMO foods and glyphosate, which is used as a desiccant on wheat, potatoes, sweet potatoes, beet and sugar cane. Glyphosate is known to:

- Cause changes in microbiome per its antibiotic effect.
- Act as a mitochondrial toxin.
- Deactivate vitamin D3.
- Impair liver detoxification by interfering with P450 pathways.

Samsel, Anthony, and Stephanie Seneff. "Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance." *Interdisciplinary Toxicology*, vol. 6, no. 4, 2013, doi:10.2478/intox-2013-0026.

# Electromagnetic Hypersensitivity

Biological effects of dirty electricity with emphasis on diabetes and MS.

Havas, Magda. “Electromagnetic Hypersensitivity: Biological Effects of Dirty Electricity with Emphasis on Diabetes and Multiple Sclerosis.” *Electromagnetic Biology and Medicine*, vol. 25, no. 4, 2006, pp. 259–268., doi:10.1080/15368370601044192.



Gut microbial diversity associated with reduced arterial stiffness in women.

- New link between gut microbiome and arterial hardening

Menni, Cristina, et al. “Gut Microbial Diversity Is Associated with Lower Arterial Stiffness in Women.” *European Heart Journal*, May 2018, doi:10.1093/eurheartj/ehy226.

## ALS and circulating endotoxins, eg. LPS

Zhang, Rongzhen, et al. “Circulating Endotoxin and Systemic Immune Activation in Sporadic Amyotrophic Lateral Sclerosis (SALS).” *Journal of Neuroimmunology*, vol. 206, no. 1-2, 2009, pp. 121–124., doi:10.1016/j.jneuroim.2008.09.017.

**Obesity and gut dysbiosis promote neuroinflammation, cognitive impairment and vulnerability to AD: new directions and therapeutic implications.**

Daulatzai, Mak Adam. "Obesity and Gut's Dysbiosis Promote Neuroinflammation, Cognitive Impairment, and Vulnerability to Alzheimer's Disease: New Directions and Therapeutic Implications." *Journal of Molecular and Genetic Medicine*, vol. s1, no. 01, 2014, doi:10.4172/1747-0862.s1-005.

## Gut bacteria may play a role in AD: show a direct causal link

Harach, T., et al. “Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota.” *Scientific Reports*, vol. 7, 2017, p. 41802., doi:10.1038/srep41802.



## Vagotomy and subsequent risk of PD

Svensson, Elisabeth, et al. “Vagotomy and Subsequent Risk of Parkinson's Disease.” *FEBS Letters*, Wiley-Blackwell, 17 July 2015, [febs.onlinelibrary.wiley.com/doi/10.1002/ana.24448](https://febs.onlinelibrary.wiley.com/doi/10.1002/ana.24448). Accessed 16 May 2018.

## Direct evidence of PD pathology spread from GI tract to brain in rats.

Holmqvist, Staffan, et al. “Direct Evidence of Parkinson Pathology Spread from the Gastrointestinal Tract to the Brain in Rats.” *Acta Neuropathologica*, vol. 128, no. 6, Sept. 2014, pp. 805–820., doi:10.1007/s00401-014-1343-6.

## Investigation of gut in PD reveals new findings of bacteria:

- Examined GI contents of 72 people with PD and 72 without.
- Those with PD had lower levels of *Prevotella* bacteria.
- This bacterium helps create thiamine and folate and to maintain an intestinal barrier against environmental toxicants.

Scheperjans, Filip, et al. "Gut Microbiota Are Related to Parkinsons Disease and Clinical Phenotype." *Movement Disorders*, vol. 30, no. 3, May 2014, pp. 350–358., doi:10.1002/mds.26069.

# The role of microbiome in CNS disorders

- This microbiome effect on CNS function is manifest in both normal and disease conditions.
- Occurs through neural, endocrine, metabolic and immunological mechanisms eg. HPA axis
- Lower microbiome diversity identified as less healthy and associated with metabolic dysfunction and low-grade inflammation.

Wang, Yan, and Lloyd H. Kasper. “The Role of Microbiome in Central Nervous System Disorders.” *Brain, Behavior, and Immunity*, vol. 38, 2014, pp. 1–12., doi:10.1016/j.bbi.2013.12.015.

# How BBB connects the microbiome and the brain

Microbiome interacts with CNS and can regulate many of its functions.

Bacteria can release factors into systemic circulation or can translocate into blood.

Can alter peripheral immune cells to promote interactions with the BBB.

Both bacteria and their proteins can cross the BBB, alter BBB integrity, and change transport mechanisms.

Microbiome SCFAs can cross the BBB to affect brain function.

Logsdon, Aric F, et al. “Gut reactions: How the blood–brain barrier connects the microbiome and the brain.” *Experimental Biology and Medicine*, vol. 243, no. 2, 2017, pp. 159–165., doi:10.1177/1535370217743766.

# FMT helps MS constipation

Three case reports together.

Two of three went from wheelchair to walking and have persisted for 20 years.

Borody, Thomas J., and Alexander Khoruts. “Fecal Microbiota Transplantation and Emerging Applications.” *Nature Reviews Gastroenterology & Hepatology*, vol. 9, no. 2, 2011, pp. 88–96., doi:10.1038/nrgastro.2011.244.

# MS and your microbiome

MS people have:

1. Reduced diversity of microbiome;
2. Reduced number of some commensals;
3. A few bacteria groups in excess of normal;
4. Testing per DNA, not stool culture.

Branton, W. G., et al. "Brain microbiota disruption within inflammatory demyelinating lesions in multiple sclerosis." *Scientific Reports*, vol. 6, no. 1, 2016, doi:10.1038/srep37344.

# Gut germs appear to play a role in MS

- Some bacteria found more in the gut of MS patients.
- MS prevalent bacteria promote disease-causing immune activity
- Noted in two separate studies:

Pröbstel, Anne-Katrin, and Sergio E. Baranzini. “The Role of the Gut Microbiome in Multiple Sclerosis Risk and Progression: Towards Characterization of the ‘MS Microbiome.’” *Neurotherapeutics*, vol. 15, no. 1, 2017, pp. 126–134., doi:10.1007/s13311-017-0587-y.

Berer, Kerstin, et al. “Gut Microbiota from Multiple Sclerosis Patients Enables Spontaneous Autoimmune Encephalomyelitis in Mice.” *Proceedings of the National Academy of Sciences*, vol. 114, no. 40, Nov. 2017, pp. 10719–10724., doi:10.1073/pnas.1711233114.

# Parkinson's and the gut

- Gut microbes promote  $\alpha$ -synuclein-mediated motor deficits and brain pathology.
- Depletion of gut bacteria reduces microglia activation.
- SCFAs modulate microglia and enhance PD pathophysiology.
- Human gut microbiota from PD patients induce enhanced motor dysfunction in mice.

Sampson, Timothy R., et al. "Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease." *Cell*, vol. 167, no. 6, 2016, doi:10.1016/j.cell.2016.11.018.



# Blood Brain Barrier (BBB) Dysfunction in PD

- Study in human beings with Positive Emissions Tomography (PET).
- Revealed dysfunctional BBB as a causative mechanism in PD.
- Injury aggravated by:
  1. Pesticides
  2. Hypoxic episodes

Kortekaas, Rudie, et al. "Blood-Brain barrier dysfunction in parkinsonian midbrain in vivo." *Annals of Neurology*, vol. 57, no. 2, 2005, pp. 176–179., doi:10.1002/ana.20369.

# Organochlorine insecticides in PD

- Post-mortem study confirms more found in substantia nigra of PD patients versus controls.
- Individual testing now an option

Corrigan, F M, et al. “Organochlorine Insecticides In Substantia Nigra In Parkinsons Disease.” *Journal of Toxicology and Environmental Health, Part A*, vol. 59, no. 4, 2000, pp. 229–234., doi:10.1080/009841000156907.

# FMT Basics

1. Mobilize and soften stool with magnesium.
2. Clean colon to start — two colon irrigations.
3. Ensure safety of healthy donors.
4. Ten implants per rectum over two weeks and two or more follow-up.

## Diet modulation of gut microbiome in MS patients:

- Correct resident microbial commensal community.
- Extensive interplay between the microbiota and the immune system.
- May help heal leaky gut.

Saresella, Marina, et al. “Immunological and Clinical Effect of Diet Modulation of the Gut Microbiome in Multiple Sclerosis Patients: A Pilot Study.” *Frontiers in Immunology*, vol. 8, 2017, doi:10.3389/fimmu.2017.01391.

# Homocysteine

- Marker of methyl group metabolism.
- Elevated levels associated with:
  1. Vascular dysfunction;
  2. Neurodegenerative disease;
  3. Autoimmune diseases.

Schalinske, Kevin L., and Anne L. Smazal. "Homocysteine Imbalance: a Pathological Metabolic Marker." *Advances in Nutrition*, vol. 3, no. 6, Jan. 2012, pp. 755–762., doi:10.3945/an.112.002758.

# Mitochondrial Nutrition Cofactors

- Energy source: glucose or MCTs.
- Key transporter is acetyl carnitine in the brain to move free fatty acids (FFAs) into mitochondria.
- Other transforming molecules include lysine, methionine and serine; vitamins D3, C, B6, B12, folate, trimethyl glycine, biotin and iron.
- Once inside the mitochondria CoQ10, and vitamins C, K, B1, B2, B3, niacin, B6, alpha-lipoic acid and minerals Mg, Zn, S Fe and P.
- ATP molecule needs to be recharged nearly 1,000 times per day.

Rafflelock, pp. 61-72 in Greenblatt, James, and Kelly Brogan. Integrative therapies for depression: redefining models for assessment, treatment, and prevention. CRC Press, Taylor & Francis Group, 2016.

# Iron Excess

- Remember hemachromatosis.
- Brain iron increases with age
- Higher in men
- Brain iron elevated in neurodegenerative diseases: MS, AD

Bartzokis, George, et al. "Gender and Iron Genes May Modify Associations Between Brain Iron and Memory in Healthy Aging." *Neuropsychopharmacology*, vol. 36, no. 7, Sept. 2011, pp. 1375–1384., doi:10.1038/npp.2011.22.

# Serum C-Reactive Protein (CRP)

- Used as cardiac inflammation indicator.
- Prognostic biomarker in ALS (Amyotrophic Lateral Sclerosis).
- Most famous folks are Lou Gehrig, the Iron Man for the New York Yankees, and Stephen Hawking.
- ALS patients with elevated CRP progress more rapidly.

Lunetta, Christian, et al. "Serum C-Reactive Protein as a Prognostic Biomarker in Amyotrophic Lateral Sclerosis." *JAMA Neurology*, vol. 74, no. 6, 2017, p. 660., doi:10.1001/jamaneurol.2016.6179.



# Benefits of Regular Exercise

- Reduces insulin resistance.
- Increases ketosis which increases BDNF.
- Increases size of hippocampus.
- Improves vascular function.
- Reduces stress and inflammation.
- Improves sleep
- Increases survival of newborn neurons.
- Improves mood.

Bredesen, Dale E., and Joe LeMonnier. *The End of Alzheimers: the First Program to Prevent and Reverse Cognitive Decline*. Thorndike Press, A Part of Gale, a Cengage Company, 2017.

# Exercise and Biome Health

Exercise and gut immune function: evidence of alterations in colon immune cell homeostasis and microbiome characteristics with exercise training.

Cook, Marc D, et al. “Exercise and Gut Immune Function: Evidence of Alterations in Colon Immune Cell Homeostasis and Microbiome Characteristics with Exercise Training.” *Immunology and Cell Biology*, vol. 94, no. 2, 2015, pp. 158–163., doi:10.1038/icb.2015.108.

# The End of Alzheimer's by Dale Breddersen MD

Describes three types of AD:

1. Uses ReCODE program to personalize re: abnormal lab values, eg. homocysteine control.
2. Insulin resistance: ketoflex diet.
3. Chronic mold or Lyme — suggests Schoemaker protocol.

Bredesen, Dale E., and Joe LeMonnier. *The End of Alzheimers: the First Program to Prevent and Reverse Cognitive Decline*. Thorndike Press, A Part of Gale, a Cengage Company, 2017.

# MS helped with HBOT

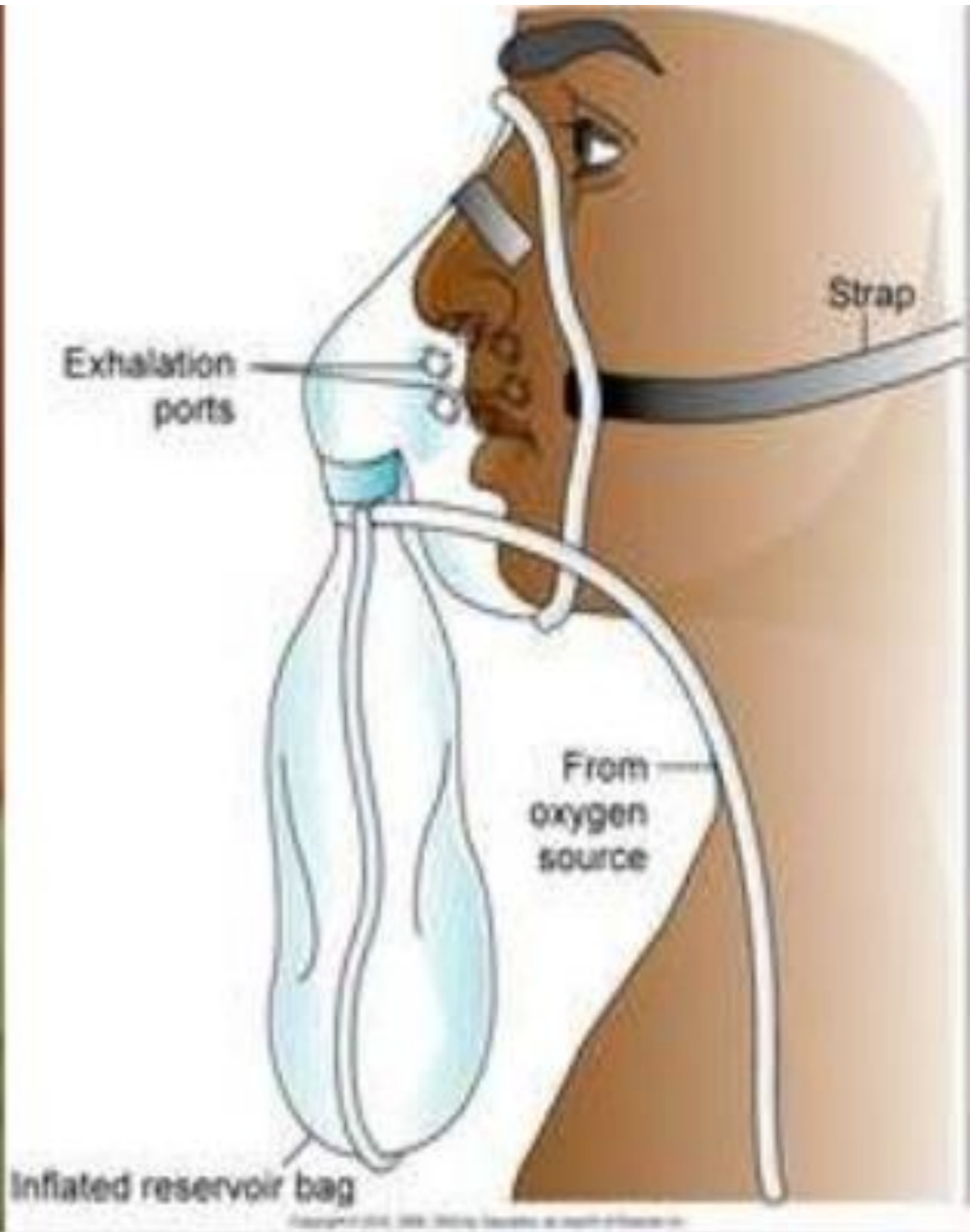
- Benefits persist most of one year.
- Especially helped mobility and bladder.

Fischer, Boguslav H., et al. “Hyperbaric-Oxygen Treatment of Multiple Sclerosis.” *New England Journal of Medicine*, vol. 308, no. 4, 1983, pp. 181–186., doi:10.1056/nejm198301273080402.

# Hyperbaric oxygenation induces antioxidant gene expression

Godman, Cassandra A., et al. "Hyperbaric Oxygen Treatment Induces Antioxidant Gene Expression." *Annals of the New York Academy of Sciences*, vol. 1197, no. 1, 2010, pp. 178–183., doi:10.1111/j.1749-6632.2009.05393.x.

James, Philip B. *Oxygen and the Brain: The Journey of Our Lifetime*. 1st ed., Best Publishing, 2014. ISBN: 978-1-930536-50-0



“I had a stroke a number of years ago, and Dr. Neubauer made a chamber available to me. Although I may have recovered from the stroke spontaneously, I feel that the pressurized oxygen gave me every advantage. I have had this chamber for more than 6 years. I take six treatments per week at 1.35 atmospheres absolute (ATA) for one hour each and have had more than 3,000 exposures. I am 95 years old and work five days a week doing research, lecturing, and writing papers. Oxygen toxicity has never been a problem.”

Teller, Edward. “On Hyperbaric Oxygenation.” *Journal of American Physicians and Surgeons*, vol. 8, no. 4, 2003, p. 97.

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