

Treating Pain and Inflammation Naturally – Part 9: The Microbiome Arrives to Prime Time in Primary Care, Implications for the Anti-Dysbiotic Treatment of Fibromyalgia

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Abstract: Building upon previous reviews in this *Journal*, this new review discusses advances in our understanding of natural/nonpharmacologic treatments for disorders of pain and inflammation by extending the information detailed in Part 6, discussing the role of the microbiome and dysbiosis in musculoskeletal disorders of persistent pain and inflammation. Following the introduction, a survey of the history of and recent developments in the study of the microbiome and dysbiosis will be provided; thereafter, fibromyalgia will be used as an example of dysbiosis-induced disease, exemplifying dysbiotic mitochondriopathy along with microbe-induced microglial activation as the cause of central sensitization and pain amplification.

INTRODUCTION

Previous articles in this now 9-part series have detailed fatty acid biochemistry and the role of diet¹, clinical applications of combination fatty acid therapy², nutritional alleviation of pain³, phytonutritional and nutritional inhibition of the inflammatory NFκB pathway⁴, specific interventions against allergic inflammation⁵, the importance of dysbiosis in the genesis of chronic inflammation and natural treatments against dysbiosis⁶, integrative management of rheumatoid arthritis⁷, and an updated review of the anti-inflammatory diet (“Part 8”).⁸ Also reviewed in 1994 was the assessment and management of genetic hemochromatosis and other forms of iron overload, which are clinically important causes of joint disease, diabetes, liver and heart disease.⁹ While those reviews remain accurate and valuable, we as clinicians and researchers need to continually advance our understanding of the origins of and solutions to our patients’ pain and suffering so that we can provide the best possible healthcare.

The previous review of dysbiosis published in this *Journal* in 2006 (Part 6, op cit) remains among the best clinical reviews of the topic and has served as the basis for a recently updated monograph¹⁰, parts of which will be summarized here as specifically relevant to the dysbiosis-induced disease fibromyalgia. Amazingly, dysbiosis has emerged from scientific obscurity within the past few years; once rarely considered, now dysbiosis and other imbalances of the microbiome have taken their rightful place in center stage in our models of diseases ranging from atopic dermatitis to diabetes mellitus and from psoriasis to Parkinson’s disease.

DYSBIOSIS—FROM OBSCURITY TO “THE FUTURE PRACTICE OF MEDICINE”

These days, everyone is talking about microbiome, dysbiosis, and “leaky gut” or increased intestinal permeability. Many years ago when I published my first books^{11,12} and articles¹³ detailing “dysbiosis”, the word could hardly be found in the Medline index, the topic was controversial at best and ethereal at worst, the term “microbiome” (first published in French in 1949 and in English in 1988) was virtually unknown, and I spent most of the time and space in my lectures and articles substantiating and defending the condition’s existence. In the preparation of my dysbiosis lecture at a major functional medicine conference in 2010, I found that only 180 Medline articles indexed the term “dysbiosis”, and now—slightly less than five years later—more than 1,200 articles index that term. Obviously, the dysbiosis concept has become better known to the point of actually being popular, but this does not mean that clinicians understand what to do with it. A recent article from the June 2015 issue of *Nature Medicine* perfectly summarized this discrepancy between microbiota research and clinical action: “*In the three years since the completion of the first phase of the Human Microbiome Project, the number of scientific papers linking the microbes that live in our gut to diseases ranging from diabetes and colitis to anxiety and depression has grown exponentially. Yet, these tantalizing connections have yielded few benefits from a therapeutics standpoint.*”¹⁴ Thus, despite the bloom in research and the exponential public awareness of dysbiosis, much progress still needs to be made in order to help clinicians—and ultimately patients—better appreciate, assess, optimize and maintain microbial health—eubiosis. Recent articles have promoted the concepts of “microbiome management” and the treatment of dysbiosis as

playing major roles in “the future practice of medicine” but have failed to provide clinically actionable information. The basic science and clinical research data on these various phenomena is crystal clear and intellectually sound but is rarely delivered in a manageable manner so that time-pressured clinicians can perceive the information in an interconnected context that expedites clinical application in patient assessment and treatment. Dysbiosis is an important concept, but doctors cannot treat concepts; we have to define, describe, and deconstruct the microbes, molecules, and mechanisms into their components, then rebuild a conceptual scaffold and intellectual structure that becomes a useful tool that, with study and experience, can be used in a clinical setting to effective benefit.¹⁵

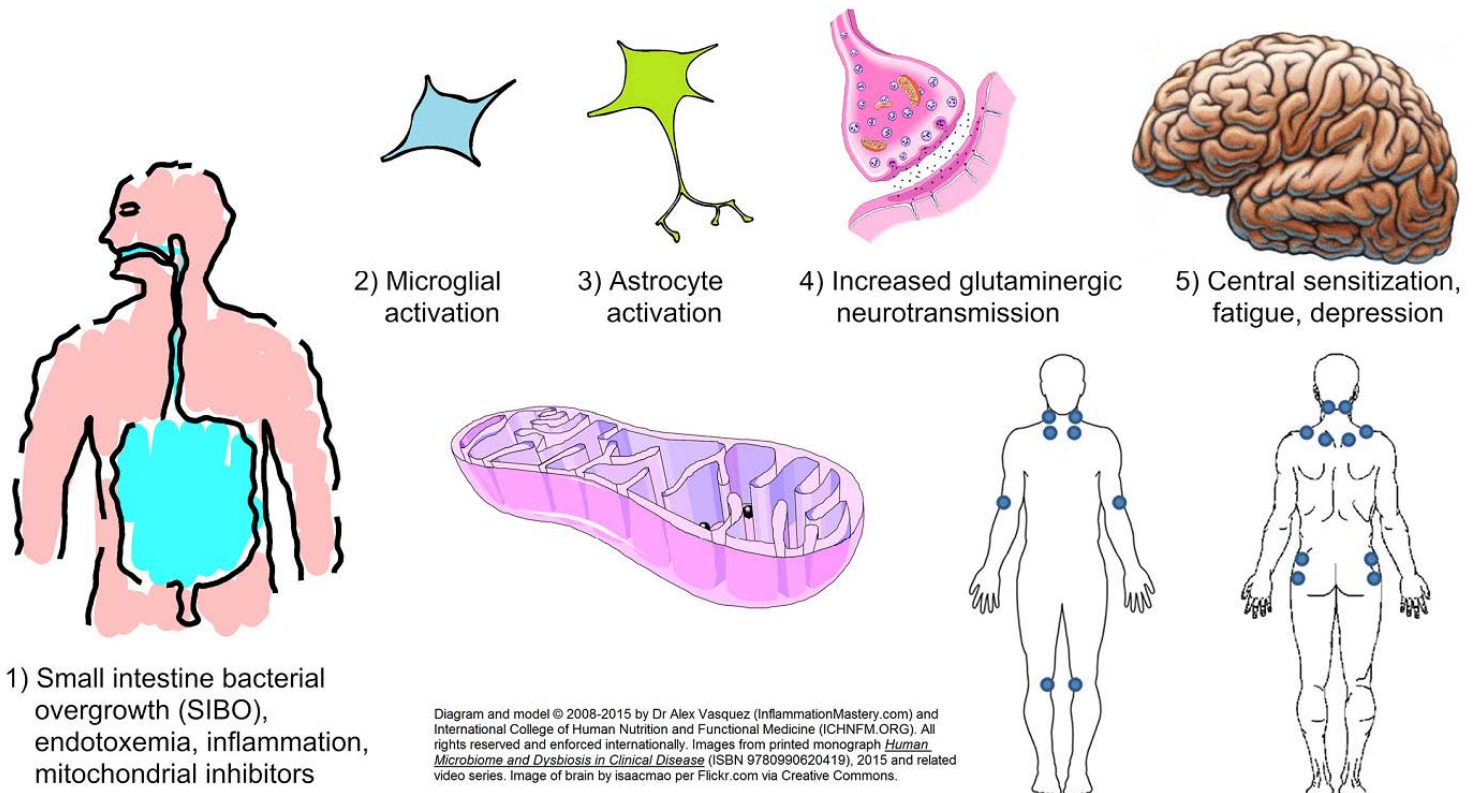
FIBROMYALGIA—DRUG DEFICIENCY OR DYSBIOSIS-INDUCED CENTRAL SENSITIZATION AND MITOCHONDRIAL DYSFUNCTION?

The persistent widespread body pain that characterizes fibromyalgia has peripheral (e.g., mitochondrial and inflammatory) and central (i.e., brain and spinal cord) origins. Central sensitization describes the phenomenon characterized by increased sensitivity in the brain and spinal cord to pain signals and signals interpreted as pain which would not otherwise be perceived as such. Peripheral abnormalities seen in fibromyalgia include mitochondrial dysfunction, intestinal hyperpermeability, systemic inflammation, DNA damage, oxidative stress; obviously these abnormalities do not originate from within the central nervous system but are generated from elsewhere in the body.

The “drug deficiency model of fibromyalgia” postulates that the condition is idiopathic and therefore necessarily treated with pharmaceutical drugs. According to the American Pain Society in May 2015, fibromyalgia is a “chronic” pain disorder that originates from the brain and spinal cord and requires treatment with analgesic drugs.¹⁶ Despite the mountain of research substantiating the integrated model of the microbial and metabolic origins of fibromyalgia¹⁷, science writers funded by drug companies describe central sensitization as idiopathic and necessarily treated with pain-relieving drugs; noteworthy is the fact that all of the FDA-approved drugs for fibromyalgia are expensive (range \$100-200 per month per drug) and have adverse effects including weight gain, seizures, life-threatening allergic reactions, hepatic toxicity, depression, suicide, and other causes of injury and death.¹⁸

The “microbial and metabolic model of fibromyalgia” shows that small intestinal bacterial overgrowth (SIBO) which is common in clinical practice is notably more common—up to 100% in some studies—in patients with fibromyalgia and that the severity of SIBO correlates with the severity of fibromyalgia, thereby supporting a dose-dependent causal relationship. Central sensitization can result from exposure to microbial molecules such as bacterial endotoxin and the resulting inflammatory response which triggers Toll-like receptor 4 (TLR4) in the brain’s microglial cells, causing astrocytes to promote excitatory glutaminergic neurotransmission¹⁹ which promotes pain perception, depression, central fatigue, and neurodegeneration. Consistent with this model is the finding that microbial metabolites from gastrointestinal bacteria such as hydrogen sulfide (H₂S) and D-lactate can induce mitochondrial dysfunction, as can bacterial lipopolysaccharide (LPS, endotoxin). This model explains why fibromyalgia patients respond to treatments that support mitochondrial function (e.g., coenzyme Q10 300 mg/d²⁰) as well as treatments that directly address the small intestine bacterial overgrowth (SIBO).²¹

Image caption—SIBO leads to secondary central sensitization and mitochondrial dysfunction in fibromyalgia: 1) Bacterial endotoxin from small intestine bacterial overgrowth (SIBO) and increased intestinal permeability leads to the systemic release of inflammatory cytokines and prostaglandins, which readily cross the blood-brain barrier. LPS can activate TLR4 on microglial cells, which are also triggered by inflammatory mediators. 2) Microglial activation leads to 3) astrocyte activation and the 4) resultant increased glutaminergic neurotransmission, which promotes 5) central sensitization to pain, also depression and central fatigue. Bacterial endotoxin and metabolites such as H₂S and D-lactate impair mitochondrial performance, leading to the mitochondrial dysfunction that is well known to characterize fibromyalgia and which leads to muscle pain, fatigue, and exercise intolerance. Diagram and model © 2008-2015 by Dr Alex Vasquez (InflammationMastery.com) and International College of Human Nutrition and Functional Medicine (ICHNFM.ORG). All rights reserved and enforced internationally. Image of brain by IsaacMao per Flickr.com via Creative Commons. Additional details are in *Human Microbiome and Dysbiosis in Clinical Disease* and in an online video: intjhumnutrfunctmed.org/videos/2015_fibromyalgia_dysbiosis.html



SIBO leads to secondary central sensitization and mitochondrial dysfunction in fibromyalgia: © 2008-2015 by Dr Vasquez, ICHNFM.ORG. Brain by IsaacMao/Flickr.com. Video: intjhumnutrfunctmed.org/videos/2015FMDysbiosis.html

CONCLUSION

Dysbiosis and disorders of the human microbiome need the attention and skill of clinicians in order to alleviate disorders of pain (eg, fibromyalgia), inflammation (eg, rheumatoid arthritis and ankylosing spondylitis), metabolic impairment (eg, diabetes mellitus) and neurologic dysfunction (eg, depression and peripheral neuropathy). Per an article titled “The Human Microbiome and the Future Practice of Medicine” published on September 15, 2015 in *JAMA—Journal of the American Medical Association*²², “The study of the human microbiota has substantial potential for improving the management of human health and disease.” Similarly, *British Journal of General Practice* published an editorial titled “The microbiome: what it means for medicine” in March 2014²³, concluding that “Harnessing the microbiome to treat disease and maintain health is thus the next step in the journey into a new era of medicine.” Fibromyalgia perfectly exemplifies a disabling clinical disorder which obligates clinicians to appreciate that anti-dysbiotic treatments and effective microbiome management are—like mitochondrial nutrition and mitochondrial medicine²⁴—ready for prime time in primary care clinical practice. Additional substantiation is provided in an online video available titled “The Microbial and

Metabolic Origins of Fibromyalgia” available at intjhumnutrfunctmed.org/videos/2015FMDysbiosis.html.

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REFERENCES:

1. Vasquez A. Reducing Pain and Inflammation Naturally—Part 1: New Insights into Fatty Acid Biochemistry and the Influence of Diet. *Nutritional Perspectives* 2004 Oct: 5-14
2. Vasquez A. Reducing Pain and Inflammation Naturally—Part 2: New Insights into Fatty Acid Supplementation and Its Effect on Eicosanoid Production and Genetic Expression. *Nutritional Perspectives* 2005 Jan: 5-16
3. Vasquez A. Reducing Pain and Inflammation Naturally—Part 3: Improving overall health while safely and effectively treating musculoskeletal pain. *Nutritional Perspectives* 2005: 34-44
4. Vasquez A. Reducing Pain and Inflammation Naturally—Part 4: Nutritional and Botanical Inhibition of NFkappaB,

- the Major Intracellular Amplifier of the Inflammatory Cascade. A Practical Clinical Strategy Exemplifying Anti-Inflammatory Nutrigenomics. *Nutritional Perspectives* 2005 July: 5-12
5. Vasquez A. Reducing Pain and Inflammation Naturally—Part 5: Improving neuromusculoskeletal health by optimizing immune function and reducing allergic reactions: a review of 16 treatments and a 3-step clinical approach. *Nutritional Perspectives* 2005 Oct: 27-40
 6. Vasquez A. Reducing Pain and Inflammation Naturally—Part 6: Nutritional and Botanical Treatments against “Silent Infections” and Gastrointestinal Dysbiosis, Commonly Overlooked Causes of Neuromusculoskeletal Inflammation and Chronic Health Problems. *Nutritional Perspectives* 2006 Jan: 5-21
 7. Vasquez A. Reducing Pain and Inflammation Naturally—Part 7: Rheumatoid Arthritis as a Prototypic Pattern of Inflammation. *Nutritional Perspectives* 2009 July: 27-40
 8. Vasquez A. Revisiting the five-part nutritional wellness protocol: the supplemented Paleo Mediterranean diet. *Nutritional Perspectives* 2011 Jan: 19-25
 9. Vasquez A. High body iron stores: causes, effects, diagnosis, and treatment. *Nutritional Perspectives* 1994 Oct. See also: Vasquez A. Musculoskeletal disorders and iron overload disease: comment on the American College of Rheumatology guidelines for the initial evaluation of the adult patient with acute musculoskeletal symptoms. [Letter] *Arthritis & Rheumatism* 1996; 39:1767-8
 10. Vasquez A. Human Microbiome and Dysbiosis in Clinical Disease. *International College of Human Nutrition and Functional Medicine* 2015. ISBN 978-0990620419
 11. Vasquez A. Integrative Rheumatology. *Integrative and Biological Medicine Research and Consulting*, 2006. Updated in 2014 as *Naturopathic Rheumatology v3.5*, ISBN 978-0990620426.
 12. Vasquez A. *Musculoskeletal Pain: Expanded Clinical Strategies*. Institute for Functional Medicine, 2008. Updated in 2014 as *Naturopathic Rheumatology v3.5*, ISBN 978-0990620426.
 13. Vasquez A. Multifocal dysbiosis: Pathophysiology, relevance for inflammatory and autoimmune diseases, and treatment with nutritional and botanical interventions. *Naturopathy Digest* 2006 Jun http://www.ichnfm.org/faculty/vasquez/reprints/2006_multifocal_dysbiosis.html
 14. de Vrieze J. Microbiome models, on computers and in lab dishes, see progress. *Nature Medicine* 2015 June; 21: 543–544 www.nature.com/articles/nm0615-543
 15. Vasquez A. Translating Microbiome (Microbiota) and Dysbiosis Research into Clinical Practice: The 20-Year Development of a Structured Approach that Gives Actionable Form to Intellectual Concepts. *IJHNF: International Journal of Human Nutrition and Functional Medicine* 2015: v3q2; p1 http://www.ichnfm.org/publications/content/epub/IJHNF_2015_first/
 16. American Pain Society. Fibromyalgia Has Central Nervous System Origins. May 16, 2015. <http://americanpainsociety.org/about-us/press-room/fibromyalgia-clauw>
 17. Vasquez A. Fibromyalgia in a Nutshell: A Functional Medicine Approach. 2012. Updated in 2014 in *Naturopathic Rheumatology v3.5*.
 18. “Dr Clauw has received grants/research support from Pfizer and Forest Laboratories. He is a consultant and a member of the advisory boards for Pfizer, Eli Lilly and Company, Forest Laboratories, Cypress Biosciences, Pierre Fabre Pharmaceuticals, UCB, and AstraZeneca. Dr Arnold has received grants/research support from Eli Lilly and Company, Pfizer, Cypress Biosciences, Wyeth Pharmaceuticals, Boehringer Ingelheim, Allergan, and Forest Laboratories. She is a consultant for Eli Lilly and Company, Pfizer, Cypress Biosciences, Wyeth Pharmaceuticals, Boehringer Ingelheim, Forest Laboratories, Allergan, Takeda, UCB, Theravance, AstraZeneca, and sanofi-aventis. Dr McCarberg has received honoraria from Cephalon, Eli Lilly and Company, Endo Pharmaceuticals, Forest Laboratories, Merck & Co, Pfizer, and Purdue Pharma. The FibroCollaborative group was sponsored by Pfizer.” “Editorial support was provided by Gayle Scott, PharmD, of UBC Scientific Solutions and funded by Pfizer.” Clauw DJ, Arnold LM, McCarberg BH; FibroCollaborative. The science of fibromyalgia. *Mayo Clin Proc.* 2011 Sep;86(9):907-11
 20. Béchade C, Cantaut-Belarif Y, Bessis A. Microglial control of neuronal activity. *Front Cell Neurosci.* 2013 Mar 28;7:32
 21. Cordero MD, Alcocer-Gómez E, Culic O, et al. NLRP3 inflammasome is activated in fibromyalgia: the effect of coenzyme Q10. *Antioxid Redox Signal.* 2014 Mar 10;20(8):1169-80
 22. Wallace DJ, Hallegua DS. Fibromyalgia: the gastrointestinal link. *Curr Pain Headache Rep.* 2004 Oct;8(5):364-8
 23. Relman DA. The Human Microbiome and the Future Practice of Medicine. *JAMA.* 2015 Sep 15;314(11):1127-8
 24. Allen-Vercoe E, Petrof EO. The microbiome: what it means for medicine. *Br J Gen Pract.* 2014 Mar;64(620):118-9
 25. Vasquez A. Mitochondrial medicine arrives to prime time in clinical care: nutritional biochemistry and mitochondrial hyperpermeability (“leaky mitochondria”) meet disease pathogenesis and clinical interventions. *Altern Ther Health Med.* 2014 Winter;20 Suppl 1:26-30

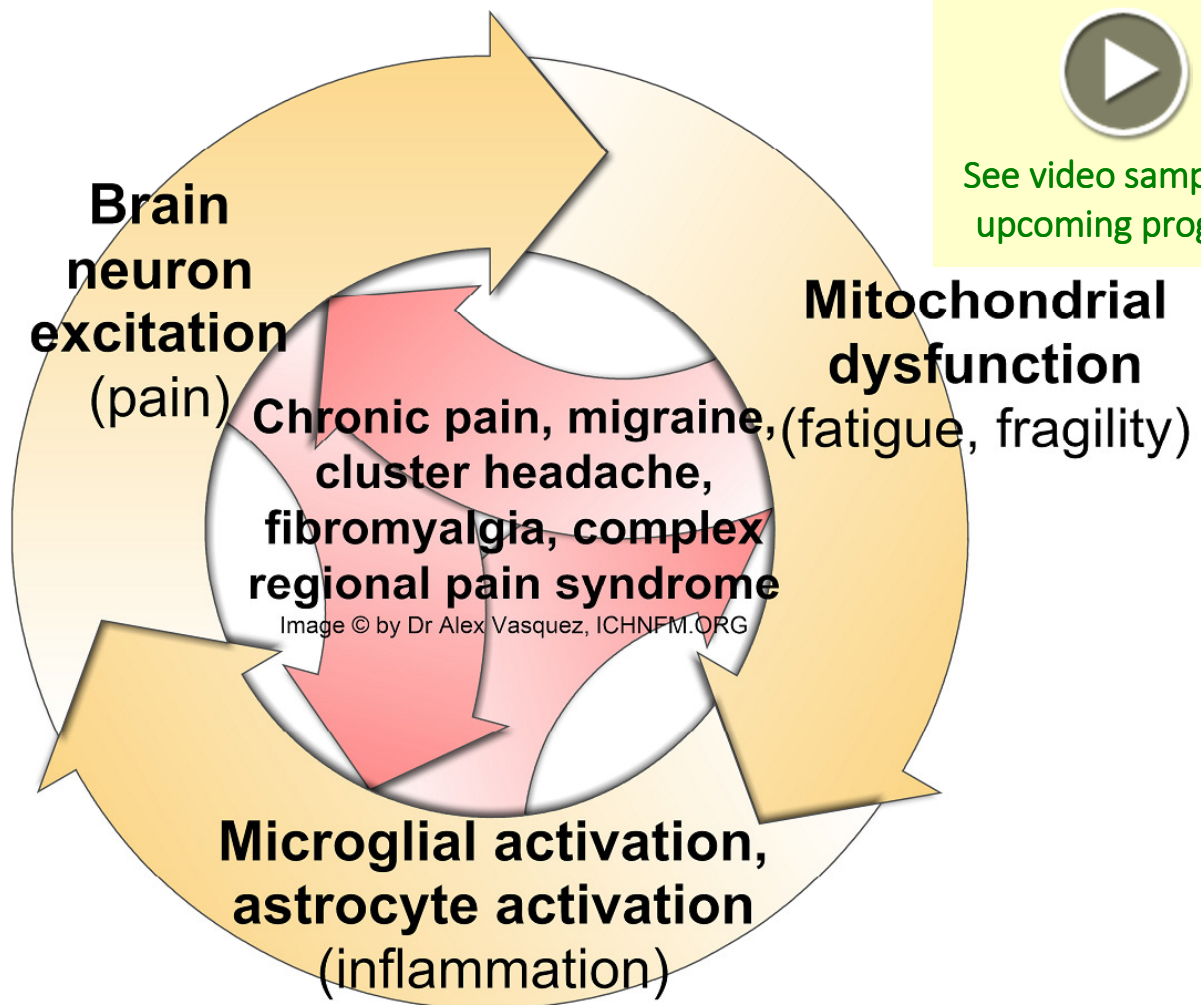
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