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

Alex Vasquez DC ND DO FACN

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 diet, clinical applications of combination fatty acid therapy, nutritional alleviation of pain, phytonutritional and nutritional inhibition of the inflammatory NFkB pathway, specific interventions against allergic inflammation, the importance of dysbiosis in the genesis of chronic inflammation and natural treatments against dysbiosis, integrative management of rheumatoid arthritis, and an updated review of the anti-inflammatory diet (“Part 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. 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 monograph, 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 and articles 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.”

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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) astrocye 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 (ICHNF.M.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: int/humnutrfunctmed.org/videos/2015_fibromyalgia_dysbiosis.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 Association22, “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.


Affiliations and Disclosures: Dr Alex Vasquez is Director of Programs at International College of Human Nutrition and Functional Medicine based in United States and Spain and has served as a researcher and lecturer for Biotics Research Corporation.

REFERENCES:
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
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
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, and UCB, and AstraZeneca. Dr Arnold has received grants/research support from Eli Lilly and Company, Pfizer, and AstraZeneca. She is a consultant for Eli Lilly and Company, Pfizer, and Wyeth Pharmaceuticals. She 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
Course Introduction: Updated November 14, 2016—this document is periodically revised so please refresh this document from its online location http://www.ichnfm.org/course-microbiome-dysbiosis to receive any updates—thank you.

- Course overview: This course provides core knowledge in the basic science and molecular biology of dysbiosis as well as the evidence-based clinical interventions used for effective health optimization and disease treatment. Students/attendees will gain a detailed understanding of the pathophysiology, clinical presentations, and therapeutic interventions. Consideration and contextualization includes the four components of evidence-based medicine/healthcare (clinical expertise, patient preference, research evidence, resource availability/socioeconomic context) to aid the data-analysis and treatment decision-making processes.
- Topic overview: New information on the “human microbiome” and “dysbiosis” is being published on a weekly basis, and healthcare providers and the general public alike are all becoming more aware of the role of microbes in human health and disease. Clinicians need a structured understanding of this material in order to take effective clinical action and in order to separate the helpful from the hype-ful with regard to clinical assessments and therapeutic interventions.
- Clinician instructor overview: Dr Vasquez (“DrV”) has been intensely studying this field since the mid-1990s when he first started studying functional medicine; what started out as a clinical and intellectual interest soon became a personal interest when DrV fell ill with a dysbiosis-induced disease. Later in clinical practice, DrV achieved impressive and sometimes amazing results by addressing the microbial component of persistent inflammatory disorders such as psoriasis, rheumatoid arthritis, and other forms of autoimmunity. DrV’s landmark paper “Nutritional and Botanical Treatments Against “Silent Infections” and Gastrointestinal Dysbiosis, Commonly Overlooked Causes of Neuromusculoskeletal Inflammation and Chronic Health Problems” (Nutr Perspectives 2006) is one of the most popular clinical papers detailing these topics, consistently ranked in the top 1% of papers on academia.edu with more than 6,000 downloads. DrV previously taught this information for the Institute for Functional Medicine, where he was faculty for more than 10 years.

Instructor: Alex Vasquez DC ND DO FACN

- Biographical sketch: Dr Alex Vasquez holds three doctoral degrees as a graduate of University of Western States (Doctor of Chiropractic, 1996), Bastyr University (Doctor of Naturopathic Medicine, 1999), and University of North Texas Health Science Center, Texas College of Osteopathic Medicine (Doctor of Osteopathic Medicine, 2010). Dr Vasquez is the author of many textbooks, including Integrative Orthopedics (2004, 2012), Integrative Rheumatology (2006, 2014), Musculoskeletal Pain: Expanded Clinical Strategies (published by the Institute for Functional Medicine, 2008), Chiropractic and Naturopathic Mastery of Common Clinical Disorders (2009), Integrative Medicine and Functional Medicine for Chronic Hypertension (2011), Migraine Headaches, Hypothyroidism, and Fibromyalgia (2012), and Mitochondrial Nutrition and Endoplasmic Reticulum Stress in Primary Care (2014). “DrV” has also written more than 100 letters and articles for professional magazines and medical journals such as British Medical Journal (BMJ), TheLancet.com, Annals of Internal Medicine, and others.
of Pharmacotherapy, Journal of Clinical Endocrinology and Metabolism, Journal of the American Medical Association (JAMA), Alternative Therapies in Health and Medicine, Journal of the American Osteopathic Association (JAOA), Nutritional Perspectives, Journal of Manipulative and Physiological Therapeutics (JMPT), Current Allergy and Asthma Reports, Integrative Medicine, Nature Reviews Rheumatology, and Arthritis & Rheumatism, the Official Journal of the American College of Rheumatology. Dr Vasquez lectures worldwide to healthcare professionals and provides expert consultations to physicians and patients internationally. The former Editor of Naturopathy Digest and a reviewer for Journal of Naturopathic Medicine and Autoimmune Diseases and PLOS One and Alternative Therapies in Health and Medicine, Dr Vasquez is currently the Editor of International Journal of Human Nutrition and Functional Medicine®. All of DrV's books and several articles are available at amazon.com/author/alexvasquez and ichnfm.academia.edu/AlexVasquez and Pubmed respectively.

Course Content and Criteria for Successful Completion/Passing—Outline and Checklist: The material in this program is provided in written/text formats as well as audio-video presentations. Participation in any forums or live discussions is optional/ancillary and not included in the core CE/CME program.

1. Pretest—sampling of material: CE/CME standards encourage the use of a pretest to assess the preexisting “learning gap” and to allow before and after comparison to assess the post-instruction attainment of knowledge. The pretest also allows students/attendees to become familiar with the software interface, test system compatibility on multiple devices, and the terminology, concepts, level of detail, and clinical applications of the information. No minimum passing score is required; students/attendees are encouraged to take the test without studying, preferably prior to reading the clinical monograph.

2. Monograph: The text portion of the clinical monograph contains 144 pages with 635 footnotes/citations, providing 70,500 words not including diagrams, footnotes, textboxes and exercises. Rounding to 71,000 words to include diagrams and textboxes, and using 12,000 words per hour as the standard per Distance Education Accrediting Commission: 71,000 words of text / 12,000 words per hour = 5.9 hours = 6 hours awarded for the reading of this textbook, including diagrams, textboxes, and some of the footnotes. The entire text of the clinical monograph is available within the ICHNFM learning interface at NutritionAndFunctionalMedicine.org; because of the simplicity of the interface and also for ease of reading and speed of access on mobile devices, the online text has a simple format without color, graphics, and footnotes. (For chiropractic credits, all hours need to be clocked within the online learning interface.) For those who want to purchase the complete monograph in book format, several options are available per preference of speed of shipping, grayscale printing vs full-color printing, and—new in 2016—digital ebook formats within the larger textbooks:
   - Full-color: https://www.createspace.com/5518130 with discount code: Q4QKVJBX
   - Black/white printing: https://www.createspace.com/5520172 with discount code: 9BZJ32PJ
   - Full retail with immediate shipping: http://www.amazon.com/dp/0990620417/
   - Textbooks & digital ebooks: The monograph is also included in Chapter 4 of Inflammation Mastery 4th Edition and in the 2-volume set of the same work published as Textbook of Clinical Nutrition and Functional Medicine, Volume 1; both of these books are available discounted from ICHNFM.ORG and in ebook/digital format from major online bookstores such as Amazon.com (via the free Kindle software for phone, iPad, and computer) and Barnes&Noble.

After the course is completely developed and deployed, the several hundred updated presentation slides will be available for discounted purchase as a printed bound book (presentation slides are not distributed electronically, because unethical persons will pirate the material); again, attendees will have access to low-cost discount pricing to cover printing/shipping costs.
Neuroinflammation in fibromyalgia and CRPS is multifactorial

Alex Vasquez

In his Review article (Neurogenic neuroinflammation in fibromyalgia and complex regional pain syndrome, *Nat. Rev. Rheumatol.* 11, 639–648; 2015)1, Geoffrey Littlejohn ascribes neuroinflammation to a “neurogenic” origin, presumably triggered by pain and stress. However, attribution of neuroinflammation and central sensitization to a primary neurogenic origin is premature without integrating the well-documented coexistence of small intestine bacterial overgrowth (SIBO, one type of gastrointestinal dysbiosis), vitamin D deficiency, and mitochondrial dysfunction.

Littlejohn1 notes that chronic pain has been associated with lipopolysaccharide (LPS)–stimulated proinflammatory cytokines (particularly IFN-γ and TNF); however, he does not pursue this line of thought to connect it to relevant literature showing clear evidence of gastrointestinal dysbiosis and increased intestinal permeability in patients with fibromyalgia and complex regional pain syndrome (CRPS). The gastrointestinal tract is the most abundant source of LPS, systemic absorption of which is increased by SIBO and increased intestinal permeability. In 1999, Pimentel et al.2 showed that oral administration of antibiotics led to alleviation of pain and other clinical measures of fibromyalgia. In 2004, Pimentel et al.3 showed that among 42 fibromyalgia patients, all (100%) showed laboratory evidence of SIBO, severity of which correlated positively with severity of fibromyalgia. In that same year, Wallace and Hallegua4 showed that eradication of SIBO with antimicrobial therapy led to clinical improvements in fibromyalgia patients in direct proportion to antimicrobial efficacy. In 2008, Goebel et al.5 documented that patients with fibromyalgia and CRPS have intestinal hyperpermeability; mucosal “leakiness” was highest in patients with CRPS, indicating a strong gastrointestinal component to the illness. In 2013, Reichenberger et al.6 showed that CRPS patients have a distinct alteration in their gastrointestinal microbiome characterized by reduced diversity and significantly increased levels of Proteobacteria. LPS from Gram-negative bacteria is powerful proinflammatory and is known to trigger microglial activation via Toll-like receptor 4; experimental studies have shown that LPS promotes muscle mitochondrial impairment, peripheral hyperalgesia, and central sensitization7.

Vitamin D deficiency is prevalent in chronic pain and fibromyalgia patients and promotes pain sensitization, myalgia, and bone pain (osteomalacia)8. Human clinical trials have shown that vitamin D supplementation can alleviate inflammation, intestinal hyperpermeability9, fibromyalgia pain10 and other neuromusculoskeletal pain. Vitamin D reduces experimental microglial activation11, a component of neuroinflammation and central sensitization.

Mitochondrial dysfunction, noted in fibromyalgia12 and CRPS13, may be triggered by gastrointestinal dysbiosis via LPS, lactate, hydrogen sulfide, and inflammation; mitochondrial dysfunction exacerbates and perpetuates microglial activation and glutaminergic neurotransmission14, thereby promoting pain sensitization centrally while also contributing to muscle pain peripherally15. Treatment of mitochondrial dysfunction with ubiquinone alleviates many biochemical and clinical manifestations of fibromyalgia16.

Thus, neuroinflammation in fibromyalgia and CRPS has biological contributions including gastrointestinal dysbiosis, vitamin D deficiency, and mitochondrial dysfunction. These independent contributions commonly coexist, and each of these is additive/synergistic with the others in the promotion of peripheral and central hyperalgesia. The consistent pain-alleviating benefits of treatments for intestinal dysbiosis (antibiotics), vitamin D deficiency (supplementation) and mitochondrial dysfunction (ubiquinone) establish that these painful conditions are multifactorial and maintained by ongoing physiologic insults, each of which is treatable.

Alex Vasquez is at the International College of Human Nutrition and Functional Medicine, Calle Balmes 184, 08012, Barcelona, Spain. E-mail: avasquez@ichnfm.org

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3. **Videos**: Professionally produced and edited presentations are delivered via the learning management system (LMS) online interface. Passing this section and receiving CE/CME credit requires achieving a minimum score of 70%. Students/attendees are allowed to take the test up to five times; the highest score is used for evaluation.

4. **Certifying examination**: Students/attendees print or download the Certificate of Achievement and documentation/certification of CE/CME hours after completing parts 1, 2, 3 described above plus the exam:
   - **Exam for Certificate of Completion (required)**: Approximately 50 questions (approximately 2 questions per hour of instruction) demonstrating familiarity and competence
   - **Exam for Certificate of Excellence (optional)**: Approximately 50 questions (approximately 2 questions per hour of instruction) demonstrating deeper knowledge and greater mastery of the material

<table>
<thead>
<tr>
<th>Items</th>
<th>Topics, Objectives, Clinical Applications</th>
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<tr>
<td>1. Pretest</td>
<td>Online pretest: allows new students/attendees to interact with the information, concepts, and vocabulary and also to appreciate the level of knowledge acquisition that is expected, so that the appropriate amount of time and effort will be spent with the reading and lecture materials.</td>
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| 2. Clinical monograph | Text materials are available online and in printed formats: The entire text of the clinical monograph—*Human Microbiome and Dysbiosis in Clinical Disease*—is available within the ICHNFM learning interface; because of the simplicity of the interface and also for ease of reading and speed of access on mobile devices, the online text has a simple format without color, graphics, and footnotes. (For chiropractic credits, all hours need to be clocked within the online learning interface.) For the complete printed monograph, several options are available per preference of speed of shipping, grayscale printing, or full-color printing:  
   1. Full-color, slower shipping: https://www.createspace.com/5518130; discount code: Q4QKVJBX  
   2. Black/white (cheaper) printing, slower shipping: https://www.createspace.com/5520172; discount code: 9BZJJ2PJ  
   4. The monograph is also included in Chapter 4 of *Inflammation Mastery 4th Edition* and in the 2-volume set of the same work published as Textbook of Clinical Nutrition and Functional Medicine, Volume 1; both of these books are available discounted from ICHNFM.ORG and in ebook/digital format from major online bookstores such as Amazon.com (via the free Kindle software for phone, iPad, and computer) and Barnes and Noble. |

**Global Objectives and Clinical Importance:**
- Discuss the role of microbial molecules and metabolites in the generation of disease and how to assess and intervene for prevention and treatment of microbe-induced disease
- Identify the pathologic mechanisms/effects/consequences of microbial colonization and know how to assess and intervene for prevention and treatment of dysbiosis-induced disease
- Describe the pathophysiology and treatment of dysbiosis-mediated disease
- Describe the importance, assessment, consequences, and provisional treatment of microbial colonizations
- List the 4 main components of evidence-based medicine:
  1. Published research, including review articles and case reports/series
  2. Physician experience and training
  3. Patient preference
  4. Socioeconomic context, available resources

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<tr>
<th>3. Videos</th>
<th>Video #1: Course Introduction &amp; Clinical Impact of Microbial Molecules: Introduction to the human microbiome and dysbiosis; terms and definitions, clinical relevance and contextualization</th>
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**Objectives and Clinical Importance:**
- Be able to define and explain the clinical significance of: Dysbiosis, eubiosis, and the associated terminology in immunology, microbiology, and pathophysiology
- Define and explain the clinical significance of: Dysbiosis, Eubiosis, total microbial load (TML), total inflammatory load (TIL), probiotics, prebiotics, synbiotics, increased intestinal permeability (AKA: intestinal hyperpermeability, leaky gut)
- Explain: The role of multifocal polydysbiosis in metabolic and inflammatory diseases
- Analyze/Interpret: Laboratory results for significance and/or lack thereof, demonstrating judicious analysis
- Demonstrate: Knowledge of the means by which microbial molecules and metabolites such as LPS, H2S, and D-lactate lead to various clinical presentations directly or by contributing to complex diseases

**Clinical narrative**: The information in this presentation is critically important to begin the process of deciphering the enigma of “dysbiosis” into its component and manageable parts. Consistent with the “molecular basis of disease”, our understanding of dysbiosis-induced disease is founded on the appreciation of the effects of microbial metabolites and molecules and the varied pathophysiologic responses/consequences (reviewed in the next video) per patient. By understanding the major molecules involved, we as clinicians can...
Video #2: Physiologic and Pathologic Mechanisms of Dysbiosis

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<th>Objectives and Clinical Importance:</th>
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<tr>
<td>• Be able to define and explain the clinical significance of: Dysbiosis, eubiosis, and the associated terminology in immunology, microbiology, and pathophysiology</td>
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<tr>
<td>• Explain: Major pathways activated (e.g., LTR, NFκB) by microbial molecules and the clinical consequences (e.g., nonspecific inflammation, impaired Cyp450)</td>
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<td>▪ TLR4—activated by LPS from Gram-negative bacteria</td>
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<td>▪ TLR2—activated by exotoxin and cell wall debris from Gram-positive bacteria</td>
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<td>▪ NFκB—activated by a wide range of microbial and ROS signals</td>
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<td>▪ NLRP3 inflammasome—activated by a wide range of DAMP and PAMP</td>
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<td>▪ TLR4—activated by LPS from Gram-negative bacteria</td>
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<tr>
<td>▪ NLRP3 inflammasome—activated by a wide range of DAMP and PAMP</td>
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Clinical narrative: The information in this presentation helps “bridge the gap” between the vague concept of “microbiome” first to molecules and then to pathophysiologic pathways and responses that lead to the clinical manifestations, which are described in their prototype form in the next video.

Video #3: Prototypic Clinical Patterns of Dysbiosis-Induced Disease

<table>
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<th>Objectives and Clinical Importance:</th>
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<tr>
<td>• Explain and demonstrate appropriate clinical management of the dysbiotic component of the listed prototypic conditions:</td>
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<tr>
<td>▪ Dysbiotic encephalopathies:</td>
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<td>▪ Hepatic encephalopathy</td>
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<td>▪ D-lactic acidosis</td>
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<td>▪ Autobrewery syndrome—one of the irrefutable prototypes of dysbiosis wherein an intestinal overgrowth of yeast ferments dietary carbohydrate into ethanol, allowing persons to become inebriated “drunk” with alcohol despite no intentional/direct/oral intake of alcoholic beverages.</td>
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<td>▪ Fibromyalgia—this pain syndrome is well-known to be caused by SIBO, which results in mitochondrial dysfunction and activation of the NLRP3 inflammasome, resulting in neuroinflammation and central sensitization to pain</td>
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<td>▪ Atopic dermatitis / eczema—well-known to be proximally triggered by bacterial inflammogens and an IgE-mediated response to skin bacteria, especially Staphylococcus aureus</td>
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<td>▪ Insulin resistance and type-2 diabetes—causatively linked with an inflammatory dysbiosis as well as possible dermal overgrowth of Staphylococcus aureus</td>
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<tr>
<td>▪ Psoriasis—well-known, thanks largely to the work of Dr Patricia Noah and colleagues, to be triggered by multifocal polydysbiosis</td>
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<td>▪ Bowel-associated dermatitis arthritis syndrome, short-bowel syndrome—a very elegant model of the effects of SIBO, resulting in multicomponent pathophysiology including generalized inflammation, immune-complex pathophysiology resulting in arthritis/dermatitis/vasculitis, and also cell-mediated bacterial allergy</td>
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<tr>
<td>▪ Analyze/Interpret: Laboratory results for significance and/or lack thereof; judicious analysis</td>
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<tr>
<td>▪ Identify: Actionable alterations in microbial patterns, phenotypes of dysbiosis-induced disease</td>
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<tr>
<td>▪ Implement: Treatment plans consistent with the 4 main components of evidence-based medicine</td>
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<tr>
<td>▪ Must be able to name and clinically apply a 3-pronged treatment plan addressing each of the 3 main components of dysbiosis</td>
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Clinical narrative: The information in this presentation completes the next step in our translation of molecules via pathophysiologic responses to various “patterns of inflammation” that distill into various clinical prototypes; by appreciating these prototypes, clinicians can see the clinical presentation of various patterns of dysbiosis-induced disease.

Video #4: Clinical Approach: Testing Microbes vs Treating Dysbiosis and How the Clinical Approach to Dysbiosis Differs from the Approach Used to Treat Infectious Disease

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Clinical narrative: The information in this presentation completes the next step in our translation of molecules via pathophysiologic responses to various “patterns of inflammation” that distill into various clinical prototypes; by appreciating these prototypes, clinicians can see the clinical presentation of various patterns of dysbiosis-induced disease.
Objectives and Clinical Importance:

- **Explain:** Major concepts in dysbiosis-induced disease and specifically explain the relative importance of laboratory testing and microbial identification in the treatment of dysbiosis-induced disease
  - What are the strengths and limitations of laboratory assessment for patients who may have dysbiosis but who do not have evidence of clinical infection?
  - What is the overall clinical value, and what are the adverse effects of excessive laboratory testing?
  - What are the financial and ethical implications of overseas laboratory testing, as well as the judicious use of laboratory testing which turns out to be inaccurate due to faulty methodology and false advertising?

- **Identify:** Microbe-disease associations from the perspective of dysbiosis rather than from the perspective of classic Microbiology or Infectious Disease

Clinical narrative: The information in this presentation provides opportunity and contextualization to enable a broader perspective on the assessment and treatment of microbe-induced disease; most physicians inexperienced with dysbiosis-induced disease will assume that microbe-induced disease requires microbiologic testing and microbe-specific antibiotics—this is not generally and not always true, and the appropriate approach depends on the clinical disease and the suspected microbes, ie, requires knowledge and judgement rather than the reflexive “shoot from the hip approach” of antibiotic prescribing.

Video #5: Dysbiosis by Location—The Mouth

Objectives and Clinical Importance: This is the first video in the series on “dysbiosis by location” which is Dr Vasquez’s unique approach to understanding and addressing multifocal polydysbiosis—dysbiosis that occurs in multiple locations via multiple microbes.

- Be able to define and explain the clinical significance of:
  - Halitosis—minor problem or major clinical indicator?
  - Systemic diseases associated with orodental dysbiosis and gingivitis
  - Specific microbial association with rheumatoid arthritis and the exact molecular mechanism
  - Clinical means for optimizing orodental heath
  - Bacterial translocation from the gingival mucosa

- Know the strengths and limitations per the research for the following treatments:
  - Nutritional therapy, especially with folate, ubiquinone, vitamin D
  - Scaling and planing
  - Flossing
  - “Oil pulling”
  - Antiseptic mouthwashes

Clinical narrative: The information in this presentation fills some very important gaps in medical education specifically and the education of most clinicians generally; the mouth is one of the most commonly excluded locations from clinical education, having been resigned to the specialty of the dental profession. We now appreciate that orodental health is an indicator and influencer of systemic health, with powerful implications for the pathogenesis of rheumatoid arthritis. Students/attendees should be able to name the exact microbe and molecule connecting orodental dysbiosis with rheumatoid arthritis.

Video #6: Dysbiosis by Location—The Sinuses and Respiratory Tract

Objectives and Clinical Importance:

- Be able to define and explain the clinical significance of:
  - Dysbiosis of the nares is linked with the following diseases/disorders:
    - ANCA vasculitis, formerly Wegener’s granulomatosis—what is the microbe and what is the exact molecule that lead to vasculitis?
    - Chronic rhinosinusitis—notice the current understanding of this condition, specifically that it is a perfect fit with Dr Vasquez’s description of dysbiosis, namely that “persons with dysbiosis-induced disease commonly present with a pathologic inflammatory response to nonpathogenic microbes”
    - Atopic dermatitis—what microbe is the main trigger, how do we rid it from the nares? What other steps need to be taken? What are the instructions and cautions with the following treatments:
    - Clinical interventions—know the implementation and cautions of the following
      - Antibiotic therapy, such as with cephalaxin, trimethoprim/Bactrim
      - Antimicrobial therapy with dilute hypochlorite
      - Antimicrobial therapy with 5% iodine or mupirocin
      - Saline lavage of the sinuses—what is the main caution, what is the name of the most worrisome pathogen, and what are the means to prevent this infection?

Clinical narrative: The information in this presentation brings the nose/nares/sinuses into clinical perspective with regard to systemic/dermal/vasculitic diseases; clinicians will learn several different evidence-based approaches to treating dysbiosis-induced disease that originates from the nares and sinuses.
### Video #7: Dysbiosis by Location—Genitourinary Tract

**Objectives and Clinical Importance:**
- Be able to define and explain the clinical significance of: Dysbiosis, eubiosis, and the associated terminology in immunology, microbiology, and pathophysiology
- **Explain:** The role of multifocal polydysbiosis in metabolic and inflammatory diseases
- **Analyze/Interpret:** Laboratory results for significance and/or lack thereof; judicious analysis
- **Identify:** Actionable alterations in microbial patterns, phenotypes of dysbiosis-induced disease
- **Demonstrate:** Familiarity with the published research, especially the work of Noah and colleagues as well as Rashid and Ebringer
- **Implement:** Treatment plans consistent with the 4 main components of evidence-based medicine

**Clinical narrative:** The genitourinary tract is known to be a common location of infection-induced systemic inflammation as appreciated with classic Reiter’s syndrome, which is now termed reactive arthritis. Likewise, available evidence points to the genitourinary tract as a source of microbe-induced immunostimulation in persistent arthritis, such as rheumatoid arthritis.

### Video #8: Dysbiosis by Location—Blood, Tissue, Parenchymal Dysbioses

**Objectives and Clinical Importance:** Be able to define and explain the clinical significance of:
- Bacterial translocation to the blood from the gastrointestinal tract
- Bacterial translocation to the blood from the gingival mucosa
- Laboratory findings directly or indirectly consistent with bacterial translocation
- L-form bacteria
- **Bonus:** Discuss the role of tissue dysbiosis in the genesis and pharmacologic antimicrobial management of chronic low-back pain

**Clinical narrative:** The information in this presentation provides an eye-opening experience for clinicians by showing the presence of live bacteria in the blood and tissues of patients with common and chronic conditions such as diabetes type-2 (bacterial translocation from the gastrointestinal tract) and low-back pain (bacterial intervertebral disc infection, responsive to drug antimicrobial treatment)

### Video #9: Dysbiosis by Location—Skin and Environmental Dysbiosis

**Objectives and Clinical Importance:** Be able to define and explain the clinical significance of:
- Exposure to air-borne microbial immunogens
- IgE-mediated “allergic”-type responses to dermal bacteria in atopic dermatitis

**Clinical narrative:** The information in this presentation shows how microbes outside of the body—in the nearby environment and on the skin—can contribute to systemic and/or dermal inflammatory disease; students/attendees should demonstrate skill in the use of various treatments and assessments related to the material in this section (written and video)

### Video #10: Dysbiosis by Location—Prototypes of Gastrointestinal Dysbiosis

**Objectives and Clinical Importance:** Be able to define and explain the clinical significance of the following microbes along with strategies (as needed) for treatment:
- **Gamma strep, Enterococcus; Group A streptococci,**
- **Staphylococcus aureus**
- Segmented filamentous bacteria (SFB)
- Aeromonas hydrophila
- Citrobacter rodentium, freundii
- Hafnia alvei
- Helicobacter pylori
- Klebsiella pneumoniae
- Pseudomonas aeruginosa
- Proteus mirabilis
- Blastocystis hominis
- Dientamoeba fragilis
- Endolimax nana
- Entamoeba histolytica
- Giardia lamblia
- Candida, yeasts

- **Explain:** All clinical aspects of the following major prototypes and patterns of gastrointestinal dysbiosis:
  - Insufficiency dysbiosis
  - Bacterial overgrowth, small intestinal bacterial/microbial overgrowth (SIBO/SIMO)
  - Immunosuppressive dysbiosis—eg, mucosal immunosuppression due to glitoxin
  - Hypersensitivity/allergic dysbiosis—bacterial allergy and IgE-mediated allergic responses to bacteria
  - Inflammatory dysbiosis—classically exemplified by reactive arthritis
### Amoebas, cysts, protozoas, and other parasites

- Metabolic/dysmetabolic dysbiosis—classically exemplified by diabesity as well as by fibromyalgia
- Neurotoxic dysbiosis—classically exemplified by D-lactate acidosis
- Neuroinflammatory dysbiosis—e.g., Bickerstaff brainstem encephalitis resulting from gastroenteritis

**Clinical narrative:** The information in this presentation again helps bring specificity and discernment to huge topic; in this case “gastrointestinal dysbiosis” which exists in discrete patterns, which can overlap; by appreciating each different prototype of gastrointestinal dysbiosis, clinicians will be better able to identify these patterns among patients in clinical practice and will—with study and experience—be able to appreciate when these patterns co-exist and overlap concomitantly.

### Video #11: Dysbiosis by Location—Gastrointestinal Dysbiosis Solutions

<table>
<thead>
<tr>
<th>Objectives and Clinical Importance:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Analyze/Interpret: Laboratory results for significance and/or lack thereof; judicious analysis</td>
</tr>
<tr>
<td>• Identify: Actionable alterations in microbial patterns, phenotypes of dysbiosis-induced disease</td>
</tr>
<tr>
<td>• Demonstrate: Skill in clinical reasoning with the clinical use of the following antimicrobial/eubiotic agents and antidysbiotic interventions specific to the gastrointestinal tract:</td>
</tr>
<tr>
<td>- Dietary modification, including fiber and phytochemical diversity and carbohydrate specificity</td>
</tr>
<tr>
<td>- Nutritional supplementation—for example, what is the role of glutamine (and zinc) in the pathophysiology of 1) intestinal hyperpermeability, 2) inflammatory responses mediated by TLR4 and NFkB, and 3) immunodefensive responses. Also, what nutrients have specific modifying effects on the gastrointestinal microbiome?</td>
</tr>
<tr>
<td>- Oregano</td>
</tr>
<tr>
<td>- Undecylenic acid</td>
</tr>
<tr>
<td>- Berberine</td>
</tr>
<tr>
<td>- Rifaxamin</td>
</tr>
<tr>
<td>- Nystatin</td>
</tr>
<tr>
<td>- Diflucan/Fluconazole</td>
</tr>
<tr>
<td>- Augmentin</td>
</tr>
<tr>
<td>- Azithromycin</td>
</tr>
<tr>
<td>- Metronidazole/Tinidazole</td>
</tr>
<tr>
<td>- Oral Vancomycin</td>
</tr>
<tr>
<td>- Doxycycline</td>
</tr>
<tr>
<td>- Ciprofloxacin</td>
</tr>
<tr>
<td>- Combination botanical medicines—research base and clinical implementation, specifically the relative effectiveness when compared with “standard antimicrobial drug treatment” with rifaxamin, per the recent clinical trial.</td>
</tr>
<tr>
<td>- Name the specific dietary protocol that provides the “best case scenario” for the eradication of dysbiosis and the maintenance of eubiosis</td>
</tr>
</tbody>
</table>

**Clinical narrative:** The information in this presentation empowers clinicians to address gastrointestinal dysbiosis from the “worst case scenario” to the “best possible treatment”, while also facilitating 1) early treatment, starting on day #1, 2) reduced reliance on drug antibiotics, and 3) enhanced skill in prescribing.

### Video #12: Gut-Brain Connection

<table>
<thead>
<tr>
<th>Objectives and Clinical Importance:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Be able to define and explain the specific molecular, metabolic, neurologic, and inflammatory pathways involved in the gut-brain axis:</td>
</tr>
<tr>
<td>- Microbial metabolites and debris</td>
</tr>
<tr>
<td>- Inflammatory pathways activated that alter neurotransmitter synthesis and neurotransmitter reception</td>
</tr>
<tr>
<td>- Mitochondrial consequences</td>
</tr>
<tr>
<td>- Various mechanisms of neurocortical excitation</td>
</tr>
<tr>
<td>- Efferent and afferent signaling via cranial nerve 10</td>
</tr>
<tr>
<td>- Laboratory assessments</td>
</tr>
<tr>
<td>- Concrete clinical examples of pathophysiology and clinical intervention</td>
</tr>
</tbody>
</table>

**Clinical narrative:** The information in this presentation deciphers the complexity of the “gut-brain axis” into comprehensible and actionable components.

### Video #13: Review, Summary of Major Concepts, Preparation for Certifying Exam

<table>
<thead>
<tr>
<th>Objectives and Clinical Importance:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Demonstrate competence in the subject matter by achieving a score of 70% or higher on the final examination</td>
</tr>
<tr>
<td>• Illustrate the ability to make proper clinical decisions based on the cases and information provided</td>
</tr>
</tbody>
</table>
**Course Delivery:** The intellectual content of this course is delivered primarily via two media—printed monograph and online videos. Students/attendees have 120 days (4 months) from the time of entry (following population of all course materials) in order to complete the course. Additional time can be requested.

<table>
<thead>
<tr>
<th>Exam</th>
<th><strong>Multiple Choice Certifying Exam followed by printing of Certificate of Completion:</strong> A second, optional, and more difficult exam is available for attendees who wish to achieve the Certificate of Excellence in this course.</th>
<th>1.5</th>
</tr>
</thead>
</table>

**Total hours 30**

**Accreditations for continuing education / continuing medical education (CE/CME):**
- **CME (medical, pharmacy, and nursing):** Accreditation statements:
  - **AMA PRA Category 1 Statement:** This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Foundation for Care Management (FCM) and International College of Human Nutrition and Functional Medicine (ICHNFM). FCM is accredited by the ACCME to provide continuing medical education for physicians. Physicians may only claim those hours in actual attendance. FCM designates this educational activity for a maximum of 30 AMA PRA Category 1 credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.
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- **Planning committee and disclosures:** Fair and balanced discussion of any proprietary products/services has been provided. Dr. Alex Vasquez has served as a consultant researcher and lecturer for Biotics Research Corporation; he has no financial relationships with laboratory services mentioned. Jeanette Dunn, RN, MSN, EdD, CNS has no financial relationships with products or services mentioned. Lisa Chamberlain, PharmD has no financial relationships with products or services mentioned.

- **Commitments to change—the purpose of continuing medical education (CME):** The general purpose of accredited CME activities is to “bridge the gap” between new information and previous practice routines; new information must be presented to bridge or fill the “knowledge/learning gap” with an emphasis on changing behavior(s) in clinical practice.

  1. Gaining and using a more nuanced and detailed appreciation of the role of the microbiome—in its various main locations as detailed in this course—in various disease states and taking appropriate action with regard to laboratory assessment and clinical intervention.
  2. Appreciating the strength of research supporting the use of nonpharmacologic interventions in the favorable elimination of pathogens and/or promotion of eubiosis; reducing dependency on antibiotic drugs; avoiding the promotion of antibiotic resistance via overuse of antibiotic drugs.
  3. Know the precise interventions for the nonpharmacologic management of dysbiosis per the following: 1) oro-dental dysbiosis, 2) nares dysbiosis, 3) berberine, 4) oregano oil, 5) hypochlorite, 6) 5% topical iodine, 7) scaling and planing, 8) dietary intervention.

- **Chiropractic CE credits:** Perhaps surprisingly, continuing education (CE) accreditation for chiropractic doctors is much more complicated than is CME for medical doctors because each state in the USA plus the provinces of Canada each have their own applications, requirements, limitations, costs, and deadlines. *This course will NOT have chiropractic accreditation for all states, due to costs and logistics (e.g., deadlines) and because not all states allow online/distance education for chiropractic CE.* If your state does not allow online/distance education, please write to your state...
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Because of its obvious relevance to the treatment of “fatigue, stress, and digestive issues”—all topics connected to dysbiosis—the text of this recent publication by Dr Vasquez is included here in the syllabus.

Correspondence regarding Cutshall, Bergstrom, Kalish’s “Evaluation of a functional medicine approach to treating fatigue, stress, and digestive issues in women” in Complement Ther Clin Pract 2016 May

1. Description of treatments

The authors state that treatments were “personalized” but provide little data on how or why the treatment was allocated other than to divide patients into two groups for the “adrenal protocols” which are faintly outlined in the footnotes, no dosages are provided as all of the product formulations appear to be proprietary. Table 1 which outlines the “adrenal protocols” shows the treatments to be remarkably similar between the high and low salivary cortisol groups. The authors administered “DHEA drops” and “pregnenolone drops” but the varying dosages of the hormones, administered three times each day, are not provided. Authors need to provide the actual dosages of all treatments, including hormones. When new and innovative treatments are used, the scientific rationale and clinical justification should be provided.

2. Use of hormonal therapy

With regard to the salivary testing used in this study, the authors need to have described the laboratory methodology. The authors state, “A significant increase was seen in mean salivary DHEA concentration, with an initial value of 4.7 (4.8) ng/mL and an end-of-study value of 5.7 (15.4) ng/mL. However, the median DHEA concentration decreased from baseline to end of study (3.1–2.2 ng/mL), which suggests that the mean value may not accurately reflect the effect of the protocol on DHEA levels. In addition, 1 participant had a 36-fold increase in salivary DHEA level, which affected the mean.” Thus, the same marker was found to increase, decrease, and change unreliable. Table 5 of the results shows that Cortisol/DHEA ratio started at 5.2 and resulted at 12 at the end of the study. Consistently throughout the medical literature, respectively higher levels of cortisol and lower levels of DHEA are causally associated with insulin resistance, intra-abdominal obesity, hippocampal atrophy, and bone loss [2] [3]; to the contrary of the bulk of the peer-reviewed literature, these authors present these results as beneficial changes. The “DHEA drops” and “pregnenolone drops” are not described either in dosage or formulation. Pregnenolone is a neurosteroid with clinical benefits including amelioration of fatigue, psychosis, anxiety, and depression [4] [5]. DHEA is well-known to alleviate depression, inflammation, fatigue and to improve quality-of-life measures [6]. DHEA administration raises androgens and estrogens [7], both of which are important in the promotion of various cancers including breast cancer. [8] [9] The authors might have described appropriate serologic and clinical follow-up, risk considerations, as well as limits to the duration of treatment.

3. Accurate description of functional medicine

The authors define functional medicine as “The functional medicine model is focused on restoring optimal functioning of 3 body systems: hormonal, digestive, and detoxification.” The authors’ sweeping statement “Restoring these 3 body systems has positive effects on stress, energy, fatigue, digestive issues, and quality of life” has no citations. The definition of functional medicine provided by these authors is discordant with more authoritative descriptions published by the Institute for Functional Medicine [10] and International College of Human Nutrition and Functional Medicine [11]. The authors use the terminology “adrenal and digestive cleanse protocols” without definition, justification, or citation. In scientific publications, unique statements require substantiation and citation.

4. Controlling for external influences

The authors describe the dates of the study as “September 2014 through April 2015” but did not control for vitamin D levels and sunlight exposure which are known to affect mood and cognition. [12] [13] The severity of depression, pain, and “functional disorders” has been reported to vary seasonally with exacerbations in
5. Disclosure of commercial interests

The authors deny conflict of interest and that “The study sponsors had no involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.” However, the authors do not disclose the identity of the sponsors. One of the authors (Kalish) is a consultant/speaker for a large distributor of nutritional supplements [16] and also a consultant/speaker endorser of the laboratory used in this study [17]; these relationships are not disclosed in the article. According to the authors’ interview [18] and press release [19] regarding their publication, they provide “training in functional medicine” and seminars related to the treatments used in this study.

6. Fecal microbiotic testing; antimicrobial treatments

The authors fail to detail the laboratory methodology for the microbiotic testing and to describe the relevance of such testing and the results. Per the footnote describing the mastic product, the authors do not clearly describe the identity nor the ingredients of this treatment.

While the functional medicine approach to healthcare is science-based, eclectic, and effective [20], research that uses the name “functional medicine” should accurately reflect its definitions and practice. Such research, as with all research, should employ reproducible laboratory methodology, should accurately describe all aspects of treatments, must properly discuss risks of treatments, should use standard testing methods to assess response to treatment as well as safety and disclose commercial interests.

References


Alex Vasquez DC ND DO FACN
Director of the International College of Human Nutrition and Functional Medicine (ICHNFM.ORG) in the United States and Europe. Dr Vasquez lectures and consults internationally and has published more than 100 professional articles and letters and more than 12 books, most recently including Inflammation Mastery Fourth Edition. Dr Vasquez has served as a consultant researcher and lecturer for Biotics Research Corporation.

Alex Vasquez, DC ND DO FACN
Carrer del Bisbe Llagarda 5, 08001, Barcelona, Spain
E-mail address: avasquez@ichnfm.org.

10 June 2016

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VOLUME 2—containing the updated presentation slides—will be sent to all students in the course.

**Human Microbiome and Dysbiosis in Clinical Disease, Volume 2**

An Integrative Functional Medicine approach to understanding and treating microbial imbalances and their clinical consequences

Monographs and Presentation Slides for Continuing Education Program

*Volume 2: Part 5 + Updated Presentation Slides for Videos #1 - #13*

A continuation of the three-part learning system of text, slides, video

**Alex Vasquez, D.O., D.C., N.D., F.A.C.N.**

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Orientation to ICHNFM learning: www.NutritionAndFunctionalMedicine.ORG

Introduction: Welcome to International College of Human Nutrition and Functional Medicine (ICHNFM) and the available free sample course, which provides you an opportunity to see the layout, content samples, and technical delivery.

Learning and Teaching Styles: Among the many considerations that shape the process of knowledge transfer, five of which shape ICHNFM content delivery are the following:

- **Different people have different learning styles, but everyone benefits from a mix of different approaches:** ICHNFM content delivery meets 4 of the 4 main learning styles:
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  2. **Physical / kinesthetic learning:** Printed books allow highlighting, note-taking, drawing, and hand-written exercises and sample exams to provide a physical-tactile component to learning. People get to actually "touch" the information, draw on it, follow the diagrams physically and mentally. Additionally, with mobile learning, attendees/students can review the videos while exercising or while somehow active but not seated in front of a computer.
  3. **Auditory-digital learning:** Learning by hearing words, concepts, and conversations.
  4. **Auditory-tonal learning:** Learning by hearing tones, emphasis, repetition, rhymes, acronyms, voices, emotions.

- **People learn at their own pace, in their own style:** ICHNFM provides flexibility in timing and methods of access.

- **People need time to review and repeat the information:** Our delivery systems allow for review and ruminaton, to allow the information to "sink in"; note that this contrasts with the one-time exposure of conferences, which typically only provide superficial exposure to new material. For detailed information that requires practical application in clinical practice, one-time "conference exposures" are among the worst ways to transmit new material.

- **People learn via interaction and conversation:** ICHNFM provides opportunities via forums and conversations for students/attendees to learn the material and to gain additional perspectives.

- **People learn by accountability, feedback, and correction:** One of the greatest adages in modern medical education is that "Assessment drives learning." (Leinster S. Assessment in medical training. Lancet. 2003 Nov) Without assessments, students can delude themselves into thinking they understand the material simply because they learn some vocabulary and some new concepts; we all need to be held to high standards so that we can learn material not simply superficially but to some level of practicality and applicability en route to mastery. Great teachers provide this perspective, challenge, and opportunity.

Assessment of clinical competence

Tests of clinical competence, which allow decisions to be made about medical qualification and fitness to practise, must be designed with respect to key issues including blueprinting, validity, reliability, and standard setting, as well as clarity about their formative or summative function. **Multiple choice questions, essays, and oral examinations could be used to test factual recall and applied knowledge,** but more sophisticated methods are needed to assess clinical performance, including directly observed long and short cases, objective structured clinical examinations, and the use of standardised patients. The goal of assessment in medical education remains the development of reliable measurements of student performance which, as well as having predictive value for subsequent clinical competence, also have a formative, educational role.

**Assessment drives learning.** Many people argue that this statement is incorrect and that the curriculum is the key in any clinical course. In reality, students feel overloaded by work and respond by studying only for the parts of the course that are assessed. **To promote learning, assessment should be educational and formative**—students should learn from tests and receive feedback on which to build their knowledge and skills. Pragmatically, assessment is the most appropriate engine on which to harness the curriculum.

THE LANCET • Vol 357 • March 24, 2001
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Important clinical topics:
1. Dysbiosis and the Microbiome
2. Mitochondrial Medicine and Mitochondrial Nutrition in Primary and Specialty Care
3. Nutritional Immunomodulation for the Treatment of Allergy and Autoimmunity
4. Chemical Toxicity, Clinical Disease, and Practical Detoxification

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Translating Microbiome (Microbiota) and Dysbiosis Research into Clinical Practice: The 20-Year Development of a Structured Approach that Gives Actionable Form to Intellectual Concepts

Alex Vasquez DC ND DO FACN

Experience and Perspectives

Many years ago when I published my first books\(^1\)\(^2\) and articles\(^3\) 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. These days, everyone is talking about microbiome, dysbiosis, “leaky gut” (thanks largely to Leo Galland MD), and my 1996 article on “Silent Infections and Gastrointestinal Dysbiosis” has been downloaded at least 4,000 times and is one of the top 1% most popular articles on Academia.edu.\(^4\)

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.”\(^5\)

To the extent that this information is being integrated into clinical practice at all, the current level of practical application is a bit indelicate and cumbersome beyond the most commonly repeated advice of advocating probiotics, avoiding antibiotics, perhaps delving into using botanical antimicrobials and laboratory testing. Breath testing (an insensitive test for only one subtype of gastrointestinal dysbiosis) and microbiologic testing have become popular to the point of overuse as doctors grapple for clinical clues. (Noteworthy in the conversation on functional laboratory testing is that one functional medicine laboratory in particular used inaccurate proprietary microbe-identification methods to extract millions of dollars of patient and physician money only to deliver innumerable wasted hours in patient suffering and...
physician confusion due to misleading and worthless [e.g., "parasite present: taxonomy unavailable"] laboratory information. So, 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 microbiotal health—eubiosis.

**Clinical Importance**

The priority is to understand the role of dysbiosis in clinical disease; patients are suffering day-by-day and hour-by-hour because of microbial colonization, bacterial allergy, reactive arthritis, systemic inflammation, fibromyalgia, insulin resistance, neurocognitive impairments, autoimmunity, and other manifestations of dysbiosis. 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. Personally, I have generally approached clinical care with a sense of urgency, for altruistic reasons and because I know the experience of being persistently ill—in my case, the situation lasted for seven years and still occasionally recurs, as discussed later.

**Dysbiosis-Triggered Illness: Deconstructing the Phenomena and Helping Our Patients**

Dysbiotic illness can ultimately be understood as a manifestation of human intolerance of the total microbial load (TML) and more specifically the total dysbiotic load (TDL) which is only one part of the total inflammatory load (TIL), alternately described as the total impairment load—that is, the total load of physiologic, biochemical, and psychosocial burdens that promote inflammation or any type of metabolic/physiologic/mental impairment. As I have said for many years, dysbiosis is a disease state best described as a "bad relationship" wherein neither the host nor the microbe(s) are unilaterally "at fault" but rather that they are—for a variety of modifyable and nonmodifyable reasons—currently incompatible. Conceptualizing dysbiotic illnesses as a relationship rather than as an infection—an extension of the acute infection model wherein the microbe is presumed guilty gives us three major areas of intervention: 1) immunorestoration, 2) tolerogenic or adaptive, 3) antimicrobial.

**Clinical pathophysiology of dysbiosis-induced disease**: The total microbial load communicates to the human body in general and the innate/adaptive immune systems specifically from various locations via specific molecules, which then are "combinatorially summarized" in conjunction with the patient's physiologic profile—including genetic makeup, nutritional status, xenobiotic load, sleep and stress status—to produce a pattern of clinical manifestations. Doctors are trained to diagnose and treat the resulting prototypic pattern rather than the problems contributing to the pattern. Image from cover and text of Vasquez A. Human Microbiome and Dysbiosis in Clinical Disease. Published, copyrighted ©, trademarked ® by Dr Alex Vasquez and International College of Human Nutrition and Functional Medicine 2015. [ISBN 1512360295 / 9781512360295]
I did not become an expert in dysbiosis entirely by choice; I had to become so in order to literally save my own life and preserve my own health. The year was 1995, the idea of “leaky gut” was new and ridiculed (in contrast to its wide acceptance today), and the entire concept of functional medicine had only been announced just a few years prior. Thanks to mostly to Metchnikoff, the naturopathic profession, a handful of allopathic doctors, and a few scattered and vintage medical articles, we had some vague ideas about dysbiosis but very few details with which to understand it better, let alone treat it effectively. In this case, I am discussing gastrointestinal dysbiosis, which is the prototype but obviously only one of the eight location-based subtypes of dysbiosis.

I remember the exact day and moment that it all started. What began with the typical “brain fog” later progressed to physical inertia, multiple chemical sensitivity / environmental intolerance (MCS/EI), and progressive immediate-onset food allergies, most of which were frustratingly unidentified except for soy lecithin—of note, 1996 was the first year of genetically manipulated (GM) soy in the US. I was also progressively lymphopenic and had remarkable responses to parenteral vitamins, especially vitamin B12 (improved mental clarity) and folic acid (resolution of progressive lymphopenia). At this time, I was finishing chiropractic college, starting naturopathic college, and harvesting gems from every seminar, book, and audiocassette I could find, notably from Bland, Galland, Gaby, and Wright. With new access to the internet, I scoured the earlier versions of Medline and spent my evenings and weekends in the medical libraries at Oregon Health Science University in Portland and University of Washington in Seattle. I started compiling and publishing articles, and my main research interests at the time—other than studying everything nutrition and trying to find solutions to my own mysterious illnesses—were rheumatology and hemochromatosis.

Following graduation and licensure, I opened a clinical practice in Seattle, and later I was also invited to teach Orthopedics and Rheumatology at Bastyr University. The responsibility of teaching these courses gave me reason to dive even deeper into the research and to begin articulating and giving structure to what almost always starts as inklings and impressions. Slowly, I started to understand dysbiosis, its various permutations, and the variances of effect that different microbes could have, either in isolation or in combination—what I would later elucidate as combinatorial dysbiosis and continue to refine on an almost daily and regular basis.

With effort and reflection, obscurity morphed into clarity. If all we had to work with is the laboratory result above, this alone would have been sufficient to explain and solve all my health problems within hours; I have this level of understanding now, but only after studying the topic—not simply for academic reasons or in a cursory manner, but with some sense of personal urgency—for twenty years. The main findings of the results above are the Citrobacter freundii and the Klebsiella pneumoniae, and additional finding on this same result was that of markedly elevated fecal beta-glucuronidase. With years of trial and error and a high degree of certainty based on personal experience backed by a massive review of the research literature, I would interpret the above results as follows:

• **The mental and physical fatigue** I experienced were due mostly to hydrogen sulfide (H2S) produced by the *Citrobacter freundii*. H2S is a mitochondrial toxin and thus a neurotoxin, thereby explaining the fatigue, and it also chelates cobalamin, thereby explaining the response to vitamin B12, indicative of vitamin B12 deficiency, which was also contributing to the fatigue. Constipation was another problem that was not only miserable, but which also promoted the persistence of the dysbiosis and which was caused by the gut-paralyzing effect of H2S.

• **The multiple chemical sensitivity / environmental intolerance (MCS/EI)** was due to impaired cytochrome p450 detoxification secondary to endotoxin in general and the O antigen of Klebsiella pneumoniae in particular. Additively and synergistically, the elevated fecal beta-glucuronidase was deconjugating whatever little cytochrome p450 detoxification was taking place, leading to the inability to clear and thus the accumulation of ambient chemicals and internal toxins that could not be oxidized for conjugation; notice the dual effect of endotoxin-mediated blockade of cytochrome p450 along with increased enterohpatic recycling due to the elevated fecal beta-glucuronidase. The folate deficiency and resultant lymphopenia are presumed due to a combination of malabsorption and increased utilization; at this time I also had an increased lactulose:mannotol ratio and dramatically elevated caffeine clearance with horrid benzoate conjugation.

• **Immediate-onset food allergies** were due to the increased intestinal permeability and immune activation, both of which can be blamed on elevated gastrointestinal endotoxin. During this time, I gained personal physician heal thyself experience with practically innumerable nutrients, botanicals, and a few antimicrobial drugs; I also appreciated—and was ultimately cured by—my (in)famous vitamin C purge: first-morning consumption of two cups of coffee (peristalsis stimulant) and ~30 grams of vitamin C with the resulting osmotic laxative and exaggerated migratory motor complex providing gastrointestinal housecleaning par excellence.

**Conclusions**

With the compilation of personal experiences and ongoing research from thousands of clinicians and basic scientists, we collectively have the knowledge and tools available to assess and alleviate dysbiotic illnesses in their various forms. The twilight of the idiopathic era and the dawn of new possibilities in health and healthcare continue to be progressively illuminated.
History of this publication: This article was written and illustrated by Dr Alex Vasquez; editorial critiques and peer reviews were provided by a quorum of IJHNFM reviewers. Kind review was also provided by external laboratory specialists. Publication does not imply endorsement by all members of IJHNFM Editorial Review Board.

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International College of Human Nutrition and Functional Medicine®

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- Founding principles—ICHNFM was founded in 2013—and launched via the tremendously successful International Conference on Human Nutrition and Functional Medicine in Portland Oregon in September 2013—by an international group of expert clinicians, surgeons, researchers, authors and presenters to provide international and multilingual excellence in scholarship and training in clinical/human nutrition and functional medicine. Further, as an organization founded by experts and for experts, the purpose and infrastructure of the organization is firmly committed to supporting the teaching process ("incentivized and unfiltered excellence") of the instructors/presenters/authors and the learning process of our students/attendees/readers. Additional details are provided online: http://ichnfm.org/about.html

For complete information, see www.ICHNFM.ORG, our social media, and our newsletter:

- Main website and newsletter: ICHNFM.ORG and http://www.ichnfm.org/join_email.html
- Newsletter: http://www.ichnfm.org/join_email.html
- Social media for Conferences (main): https://www.facebook.com/ICHNFM
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Continuing Education: Upcoming events/programs/courses for open-education and for continuing medical education (CME): www.ichnfm.org/cme/

The following list was updated June 16, 2015—see our website, social media, and newsletter for updates. This list is subject to change—see websites and mailings for updates; discounts are distributed by email newsletter

- **Human Microbiome and Dysbiosis in Clinical Disease**: This is a 14-hour Continuing Education program for physicians, pharmacists, nurses and nurse practitioners. The program contains the following 3 major components:
  - The monograph: reading + online exam = 7 hours of continuing education
    - Retail: http://www.amazon.com/dp/0990620417/
    - Full-Color Version: https://www.createspace.com/5518130 with Discount Code: Q4KVJBX
  - Videos: viewing + online exam = 7 hours of continuing education
    - Trailer and proposed location for videos: https://vimeo.com/ondemand/ichnfmmicrobiome1
  - Competency and learning examination:

- **The New Mitochondrial Medicine and Nutrition in Primary and Specialty Care**: This is anticipated to be a Continuing Education program for physicians, pharmacists, nurses and nurse practitioners with a duration (and credit value) of approximately 14 hours. Currently all programs are founded upon these 3 main components:
  - The monograph: reading + online exam = continuing education credits
  - The videos: viewing + online exam = continuing education credits
  - The exam: online exam = continuing education credits

- **Nutritional Immunomodulation**: Similar delivery and content to programs described above.
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- **International College** of Human Nutrition and Functional Medicine®—based in Portland Oregon USA and Barcelona Spain, hosts and co-hosts onsite conferences, online seminars, our professional forum ([www.NutritionAndFunctionalMedicine.org.edu](http://www.NutritionAndFunctionalMedicine.org.edu)) and publications available in print, open access, and/or via other journals. Examples of books and monographs are listed below:
- **International Conference** on Human Nutrition and Functional Medicine®—organized and hosted on a periodic basis, either onsite or online. To see information about our inaugural 2013 conference, see below:
  - 2013 conference overview video: [https://vimeo.com/70825563](https://vimeo.com/70825563)
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**Organization**—Authors are allowed creative flexibility; structure and flow of the article should be intuitive, logical, and clear. We cherish the blend of scholasticism with artistry.

**Grammar**—Grammar should be clear and appropriately structured. Avoid use of passive sentence subjects such as "There are..." and "It is evident..." Brevity is the soul of wit; nonpowerful words and sentences should be omitted. Focus on direct subjects, powerful verbs, accurate and efficient descriptors.

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