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Neuroinflammation in fibromyalgia and CRPS is multifactorial

Littlejohn[1] 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.

Littlejohn[1] notes that "chronic pain was more strongly associated with lipopolysaccharide–stimulated proinflammatory cytokines"; 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 (FM) and complex regional pain syndrome (CRPS). The gastrointestinal tract is the most abundant source of lipopolysaccharide (LPS, endotoxin), systemic absorption of which is increased by SIBO and increased intestinal permeability. In 1999, Pimentel et al[2] showed that oral administration of antibiotics lead to alleviation of pain and other clinical measures of FM. In 2004, Pimentel et al[3] showed that among 42 fibromyalgia patients, all 42 FM patients (100%) showed laboratory evidence of SIBO, severity of which correlated positively with severity of FM. In that same year, Wallace and Hallegua[4] showed that eradication of SIBO with antimicrobial therapy lead to clinical improvements in FM patients in direct proportion to antimicrobial efficacy. In 2008, Goebel et al[5] documented that patients with FM 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 powerfully pro-inflammatory 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 sensitization.

Vitamin D deficiency is prevalent in chronic pain patients and promotes pain sensitization[7], systemic inflammation, intestinal hyperpermeability, myalgia and bone pain (osteomalacia). Human clinical trials have shown that vitamin D supplementation can alleviate inflammation[8], intestinal hyperpermeability[9], FM pain[10] and other neuromusculoskeletal pain. Vitamin D reduces experimental microglial activation[11], a component of neuroinflammation and central sensitization.

Mitochondrial dysfunction in FM[12] and CRPS[13] can be triggered by gastrointestinal dysbiosis via LPS, D-lactate, and hydrogen sulfide; mitochondrial dysfunction exacerbates and perpetuates microglial activation and glutaminergic neurotransmission[14] and thereby promotes pain sensitization centrally while also contributing to muscle pain peripherally.[15] Treatment of mitochondrial dysfunction with ubiquinone alleviates biochemical and clinical manifestations of FM.[12]

Thus, neuroinflammation in FM and CRPS has biological contributions, including but not limited to gastrointestinal dysbiosis, vitamin D deficiency, and mitochondrial dysfunction. These independent contributions commonly coexist in FM and CRPS patients, and each of these is additive/synergistic with the others in the promotion of peripheral and central hyperalgesia. Neuroinflammation likely has a neurogenic component[1], but 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.

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Competing interests: Dr Vasquez has lectured for Biotics Research Corporation, a nutraceutical company in the USA.
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PMID: 26935282

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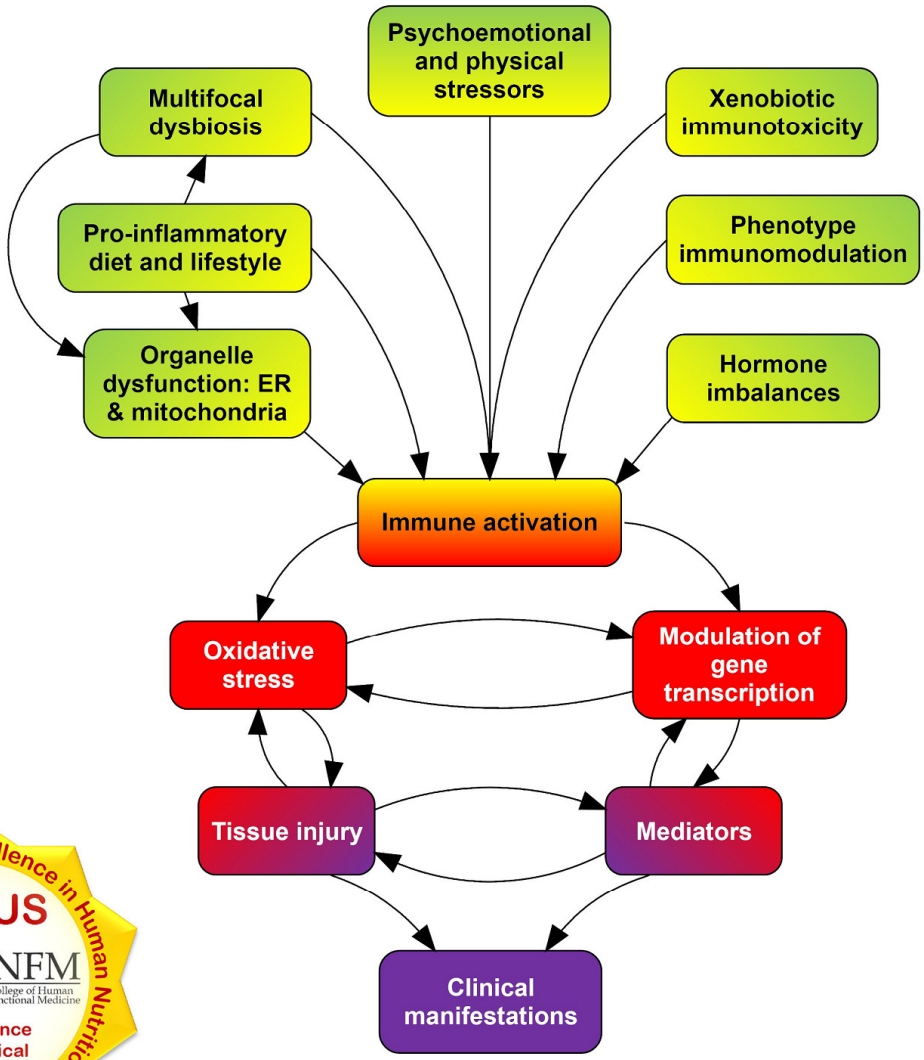

Dr. Alex Vasquez

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Integrative Pain Management

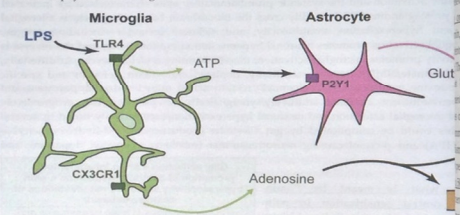
Chapter 3: Concepts and Therapeutics in (Nondrug) Musculoskeletal Care and Integrative Pain Managem

Persistent inadequacies in nutrition education/training among physicians

Introduction: Despite the acknowledged importance of diet in the prevention of obesity, diabetes, hype and other components of cardiometabolic syndrome/disease, physicians are consistently and syste untrained in nutrition. A few exemplary citations are summarized per the following:

What do resident physicians know about nutrition? (J Am Coll Nutr 2008 Apr[29]): "OBJECTIVE:

the resultant changes in neurotransmission that lead to pain sensitivity and changes i behavior." In this work, I show that fibromyalgia is a unique combination of dysbiosi mitochondrial impairment; both of these components need to be treated effectively a to alleviate the brain inflammation—unique—in fibromyalgia. "Glial activation with is different from and worse than glial activation or mitochondrial impairment by itse together exacerbates both while also causing a vicious cycle that promotes emotional/psychiatric changes.



Microglial LPS reception leads to (extracellular) ATP elaboration, which stimulates astr which increases glutaminergic neurotransmission: "Upon LPS stimulation, microglia rapi astrocytes. Astrocytes subsequently release glutamate, and this leads to increased excitatory glutamate receptor-dependent mechanism." Illustration and quote from: Béchade C, Cantau control of neuronal activity. *Front Cell Neurosci.* 2013 Mar 28;7:32[387]

Verified in animal models and likely contributory to clinical pain syndromes such as fib that bacterial endotoxin/LPS can also contribute to central sensitization. This concep be further substantiated in a following section on clinical pain syndromes and more so specific to fibromyalgia[388] or general to rheumatology.[389] The basic pathophysiology depicted below and itemized with citations thereafter.

Bacterial LPS → microglial activation → astrocyte hyperglutaminogenesis → neurocor

[387] Béchade C, Cantaut-Belarif Y, Bessis A. Microglial control of neuronal activity. *Front Cell Neurosci.* 2013 Mar 28;7:32 doi: 10.33 journal.frontiersin.org/article/10.3389/fncel.2013.00032/abstract. Copyright © 2013 Béchade, Cantaut-Belarif and Bessis. *Front Cell N* under terms of Creative Commons Attribution License, which permits use/distribution/reproduction in other forums, provided original
[388] Vasquez A. *Fibromyalgia in a Nutshell: A Safe and Effective Functional Medicine Strategy*. 2012, and later versions.
[389] Vasquez A. *Functional Medicine Rheumatology* v3.5. 2014, and later versions.

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ally accurate—is provided: ions while providing insight omyalgia—reducing the effects portance: Excess glutaminerg ain, myofascial pain and myo odegeneration. Our therapeutic ing microglial activation, 2) hel min D, alkalinization (increase ain citrate which is converted to nesium retention, thereby allevi effects of glutamate/NMDA r activation by promoting conse botanicals that act as ligands fo steine may be elevated in the s e syndrome and fibromyalgia nd benefit of folate and vitamin B12 allevi to NMDA receptor activation resulting in and neurotoxicity.[569]

se in combination with other vitamins, espec balamin, or methylcobalamin—cyanocobala ant content of cyanide.

rally, or 1-2 mg per week by injection t, or methylcobalamin—cyanocobalamin is a nt of cyanide.

The phosphorylated form (P5P) can also be used be given to magnesium status/supplemen ation should always be used with magnesium d 2 mg/d have been shown to significantly mon and well-tolerated in the treatment of migra n causes elevated homocysteine and promotes re Chapter 1.

00-1,500 mg thrice daily: Doses of NAC 4.85 g nt of SLE.

l factors: High coffee intake (>5 cups per da such as methotrexate, metformin, niacin and atients. Metformin is well-known to cause vitam c neuropathy" and promote depression and anxi n (approximately 2.6 g choline[8]). Eat 275 mg of choline; thus, if the goal is to g r day of granulated lecithin.

Effects are weak/modest; likely more relevant hat promote loss of betaine in urine.

activation of latent myofascial trigger points in human n patients with chronic low back pain. *J Trace Elem Me* ound fluid in patients with fibromyalgia and chronic fatig

hopenia and fibromyalgia. *PLoS One*. 2015 Apr 22;10(4 nflammation and neurotoxicity of homocysteine in migraine

Homocysteine and Insulin Resistance in Patients with Hypothyroi

FUNCTIONAL INFLAMMOLOGY

Chapter 5.1—Functional Inflammology Protocol for Metabolic Inflammation: Migraine & Fibromyalgia

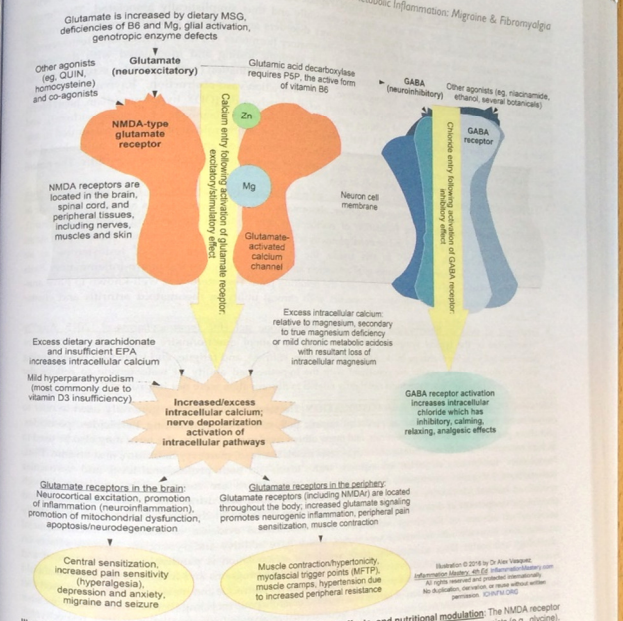

Illustration of the NMDA-type glutamate receptor, its activation, effects, and nutritional modulation: The NMDA receptor is activated by glutamate, QUIN, and other substances which act as agonists (e.g., homocysteine) or co-agonists (e.g., glycine). Different forms of the NMDA receptor exist; thus, the image presented here is a generalized version that is conceptually accurate (rather than all-inclusive; for more details see reviews[871]) and clinically relevant. Neuroexcitatory glutamate is converted to neuroinhibitory GABA by the enzyme glutamic acid decarboxylase, which shows vitamin B6 dose-responsiveness in its reduction of glutamate levels. Magnesium and zinc (and perhaps copper) retard the passage of calcium through this channel, thereby mitigating some of the effects of NMDAr activation. Quenching nitric oxide (for example with hydroxocobalamin), which would otherwise trigger glutamate release, and dousing glial activation are important considerations not included in this illustration. For updates and additional information and explanations, see videos and articles at www.inflammationmastery.com/pain

[871] Vyklicky et al. Structure, function, and pharmacology of NMDA receptor channels. *Physiol Rev*. 2014;63 Suppl 1:S191-203

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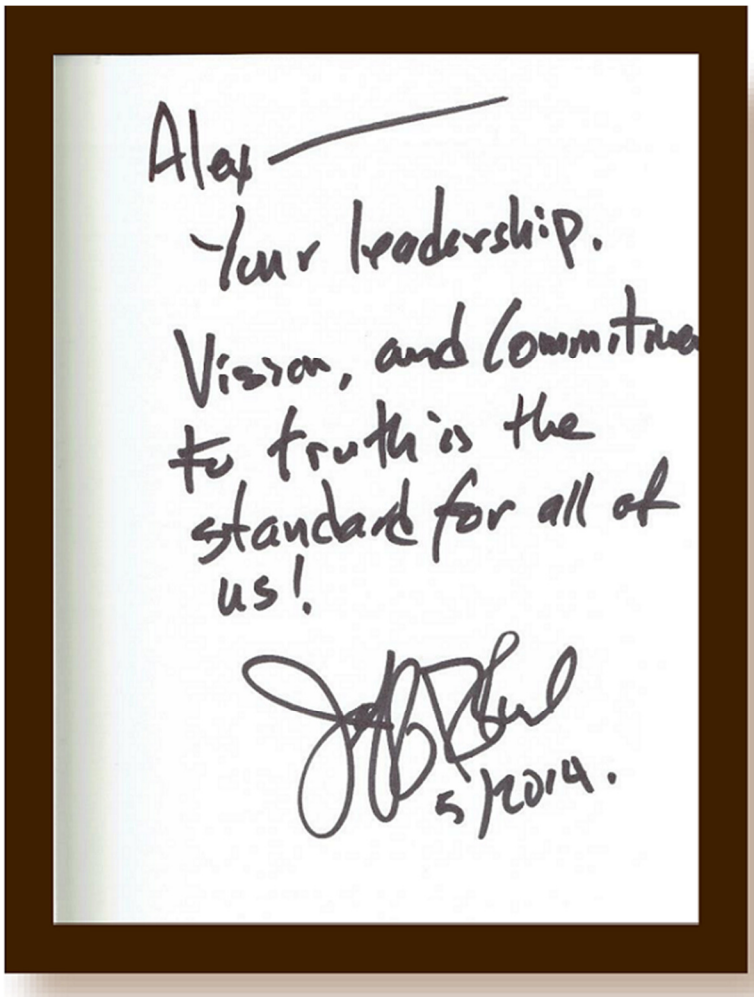
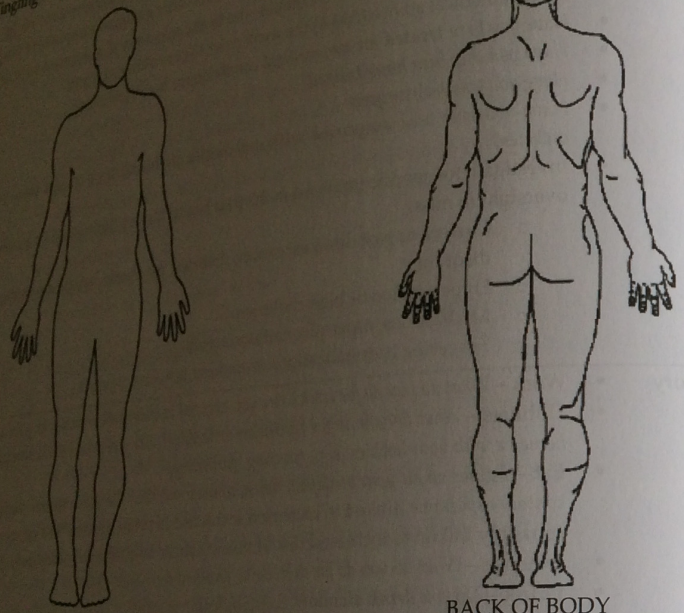
INFLAMMATION MASTERY & FUNCTIONAL INFLAMMOLOGY



Pictured above—Personal inscription from Dr. Jeffrey Bland at a book signing event for his book *Disease Delusion*: My inclusion of Dr Bland's personal note above is not meant to imply that he is endorsing this book; he might very well reject any or all of it. Further, this inclusion does not imply that he carries those same sentiments beyond the day that he wrote them to me in May of 2014. Rather, my inclusion signifies our mutual respect as colleagues, and my personal respect for his thought and demeanor, and his influence on my life and work. I have respectfully honored him in this book as the founder of what most clinicians in America know as Functional Medicine, and I have developed and extended my own version of his concept—that disease states are malleable rather than destined—to the clinical management of inflammatory disorders under the name of Functional Inflammology. Importantly and personally—but not paradoxically if one understands the true goals of mentorship, affiliation, and friendship—due to the support of friends and colleagues, this book also represents a departure from concern that I had for endorsement from or agreement with other people, professions, universities, or organizations. In this book, I have presented the truth as I see it—without apology—and without any filtering other than as the limitations imposed by time, space, my own abilities, and limitations imposed by human physiology. This work—now published as *Inflammation Mastery, 4th Edition* —has been "in progress" since its origin as course notes for Orthopedics and Rheumatology which I taught at Bastyr University in Seattle in 2000-2001 and through its previous publications in many books starting with *Integrative Orthopedics* (2004) and *Integrative Rheumatology* (2006) and peer-reviewed articles in journals ranging from *Annals of Pharmacotherapy* to *Alternative Therapies in Health and Medicine*. In addition to spanning more than 16 years, this work has also spanned various countries and cultures—including Houston, Fort Worth, Austin (Texas), Seattle (Washington), Portland (Oregon) in the United States, then to Bogota, Colombia and Barcelona, Spain. I consider this volume to be my highest presentation of truth, accuracy, and clinical application that I could humanly muster while maintaining my own health, relationship, and other obligations. I will always remain open to correction and the updating of this work as the weight of evidence indicates. The goals of healthcare should be the optimization of physical health and psychosocial-intellectual freedom.

Patients can be asked to localize and describe their pain/discomfort on drawings such as these. Examples of descriptions:

- Numb
- Hypersensitive
- Tingling
- Shooting pain
- Electrical pain
- Stabbing pain
- Burning pain
- Dull ache
- Muscle weakness



FRONT OF BODY

BACK OF BODY

...es below, indicate which pain/discomfort you are referring to and then quantify it by placing an "X" on

...f pain: _____

...pain at all — Worst pain imaginable

...ain: _____

...in at all — Worst pain imaginable

Review of Systems—checklist: Patients/clients are asked to provide more information by the arrow "→", also at the bottom of each page, and/or whereever more detail is warranted. This form can be completed by the clinician and/or by the client.

GENERAL HEALTH	Very rare-None	Occasional-Mild	Intermittent-Moderate	Frequent-Severe
Fatigue, lack of energy, lack of stamina	❑ 0	❑ 1	❑ 2	❑ 3
Need to decrease or alter activities of daily living due to fatigue, pain, or illness	❑ 0	❑ 1	❑ 2	❑ 3
Insomnia, lack of sleep	❑ 0	❑ 1	❑ 2	❑ 3
Excessive tiredness and increased need for sleep	❑ 0	❑ 1	❑ 2	❑ 3
Tired and/or not hungry after waking	❑ 0	❑ 1	❑ 2	❑ 3
Pain at night, night sweats	❑ **0**	❑ **1**	❑ **2**	❑ **3**
Enlarged lymph nodes	❑ **0**	❑ **1**	❑ **2**	❑ **3**
Frequent infections	❑ 0	❑ 1	❑ 2	❑ 3
Undesired weight loss	❑ 0	❑ 1	❑ 2	❑ 3
Undesired weight gain, difficulty losing weight	❑ 0	❑ 1	❑ 2	❑ 3
Cold hands or feet	❑ 0	❑ 1	❑ 2	❑ 3
Compulsive/binge eating, increased appetite	❑ 0	❑ 1	❑ 2	❑ 3
Decreased appetite	❑ 0	❑ 1	❑ 2	❑ 3
Hypoglycemia, low blood sugar	❑ 0	❑ 1	❑ 2	❑ 3
Allergies to food or environment	❑ 0	❑ 1	❑ 2	❑ 3
Sensitivity to fumes, chemicals, odors, exhaust	❑ 0	❑ 1	❑ 2	❑ 3
Have you been tested for iron disorders?	❑ NO	❑ YES	❑ ?	
Past diagnosis of serious illness or chronic health condition such a systemic disease, cancer, HIV, mental condition, heart disease, infection, kidney problems, or other condition	❑ NO	❑ YES→		

MUSCLES and JOINTS	Very rare-None	Occasional-Mild	Intermittent-Moderate	Frequent-Severe
Pain, swelling, or limited motion in joint(s)	❑ 0	❑ 1	❑ 2	❑ 3
Pain, swelling, or weakness in muscle(s)	❑ 0	❑ 1	❑ 2	❑ 3
Cramps in muscles, grind teeth at night?	❑ 0	❑ 1	❑ 2	❑ 3
Other problem, concerns, or questions in this area?	❑ NO	❑ YES→		

HEAD and MIND	Very rare-None	Occasional-Mild	Intermittent-Moderate	Frequent-Severe
Headaches	❑ 0	❑ 1	❑ 2	❑ 3
Feeling of pressure inside head	❑ 0	❑ 1	❑ 2	❑ 3
Faintness, loss of consciousness	❑ 0	❑ 1	❑ 2	❑ 3
Dizziness	❑ 0	❑ 1	❑ 2	❑ 3
Seizures, epilepsy	❑ **0**	❑ **1**	❑ **2**	❑ **3**
Difficulty thinking or processing information; confusion	❑ 0	❑ 1	❑ 2	❑ 3
Difficulty with concentrating or maintaining attention	❑ 0	❑ 1	❑ 2	❑ 3
Poor memory	❑ 0	❑ 1	❑ 2	❑ 3
Difficulty speaking or talking, slurred speech	❑ 0	❑ 1	❑ 2	❑ 3
Hyperactivity	❑ 0	❑ 1	❑ 2	❑ 3
Learning difficulties, dyslexia	❑ 0	❑ 1	❑ 2	❑ 3
Other problem, concern, or question in this area?	❑ NO	❑ YES→		

Additional notes or comments:

Interpretation of iron status based on serum ferritin (in descending order)	
Ferritin	**Categorization and management**
≥ 800 mcg/L	Practically diagnostic of severe iron overload[643]: Repeat tests; rule out inflammation or occult pathology. Initiate phlebotomy and consider liver biopsy or MRI.
≥ 300 mcg/L	Probable iron overload; clear predisposition to iron accumulation[644]: Repeat tests; rule out inflammation or occult pathology. In men, initiate phlebotomy and consider liver biopsy or MRI.[645]
≥ 200 mcg/L	*In women:* Probable iron overload; clear predisposition to iron accumulation[646]: Repeat tests, rule out inflammation or occult pathology. In women, initiate phlebotomy and consider liver biopsy or MRI.[647] *In men:* High-normal *unhealthy* iron status with increased risk of myocardial infarction[648]: Rule out inflammation or occult pathology. No follow-up is mandated, yet blood donation and/or abstention from dietary iron are recommended preventative healthcare measures.
≥ 160 mcg/L	*In women:* Abnormal iron status[649]: Repeat tests, rule out inflammation or occult pathology. Consider phlebotomy and liver biopsy or MRI.
≥80-120 mcg/L	High-normal unhealthy iron status[650,651]: No follow-up is mandated; blood donation and abstention from dietary iron are suggested preventative healthcare measures. A subset of patients with restless leg syndrome (RLS, a condition also causally associated with intestinal bacterial overgrowth dysbiosis) have impaired transport of iron into the brain and therefore require slightly elevated ferritin/iron levels (up to 120) to enhance cerebral iron uptake.
40-70 mcg/L	**Optimal iron status for most people**[652,653]
< 20 mcg/L	Iron deficiency: Search for occult gastrointestinal blood loss with endoscopy or imaging assessments in adults; refer to gastroenterologist.[654,655]

[643] Milman N, Albeck MJ. Distinction between homozygous and heterozygous subjects with hemochromatosis using iron status markers and receiver operating characteristic (ROC) analysis. *Eur J Clin Biochem* 1995; 33: 95-8. See also Milman N. Iron status markers in hereditary hemochromatosis: distinction between individuals being homozygous and heterozygous for the hemochromatosis allele. *Eur J Haematol* 1991;47:292-8

[644] Olynyk JK, Bacon BR. Hereditary hemochromatosis: detecting and correcting iron overload. *Postgrad Med* 1994;96: 151-65

[645] "Therapeutic phlebotomy is used to remove excess iron and maintain low normal body iron stores. ... initiated in men with serum ferritin levels of 300 microg/L or more and in omen with serum ferritin levels of 200 microg/L or more, regardless of the presence or absence of symptoms." Barton JC, McDonnell SM, Adams PC, Brissot P, Powell LW, dwards CQ, Cook JD, Kowdley KV. Management of hemochromatosis. Hemochromatosis Management Working Group. *Ann Intern Med* 1998 Dec 1;129(11):932-9

[646] Barton JC, Edwards CQ, Bertoli LF, Shroyer TW, Hudson SL. Iron overload in African Americans. *Am J Med* 1995; 99: 616-23

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[648] Salonen JT, Nyyssonen K, Korpela H,et al. High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. *Circulation* 1992; 86: 803-11

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[650] Lauffer, RB. *Iron and Your Heart*. New York: St. Martin's Press, 1991: 79-8, 83-88, 162

[651] Sullivan JL. Iron and the sex difference in heart disease risk. *Lancet*. 1981 Jun 13;1(8233):1293-4

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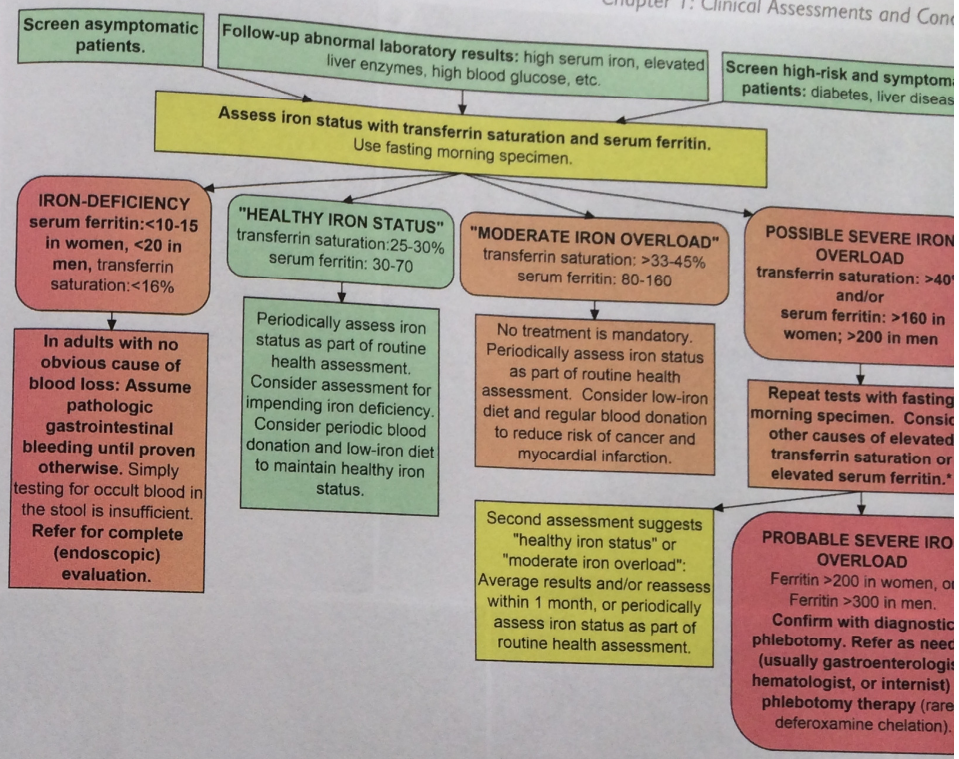
[653] Lauffer, RB. *Iron and Your Heart*. New York: St. Martin's Press, 1991: 79-8, 83-88, 162

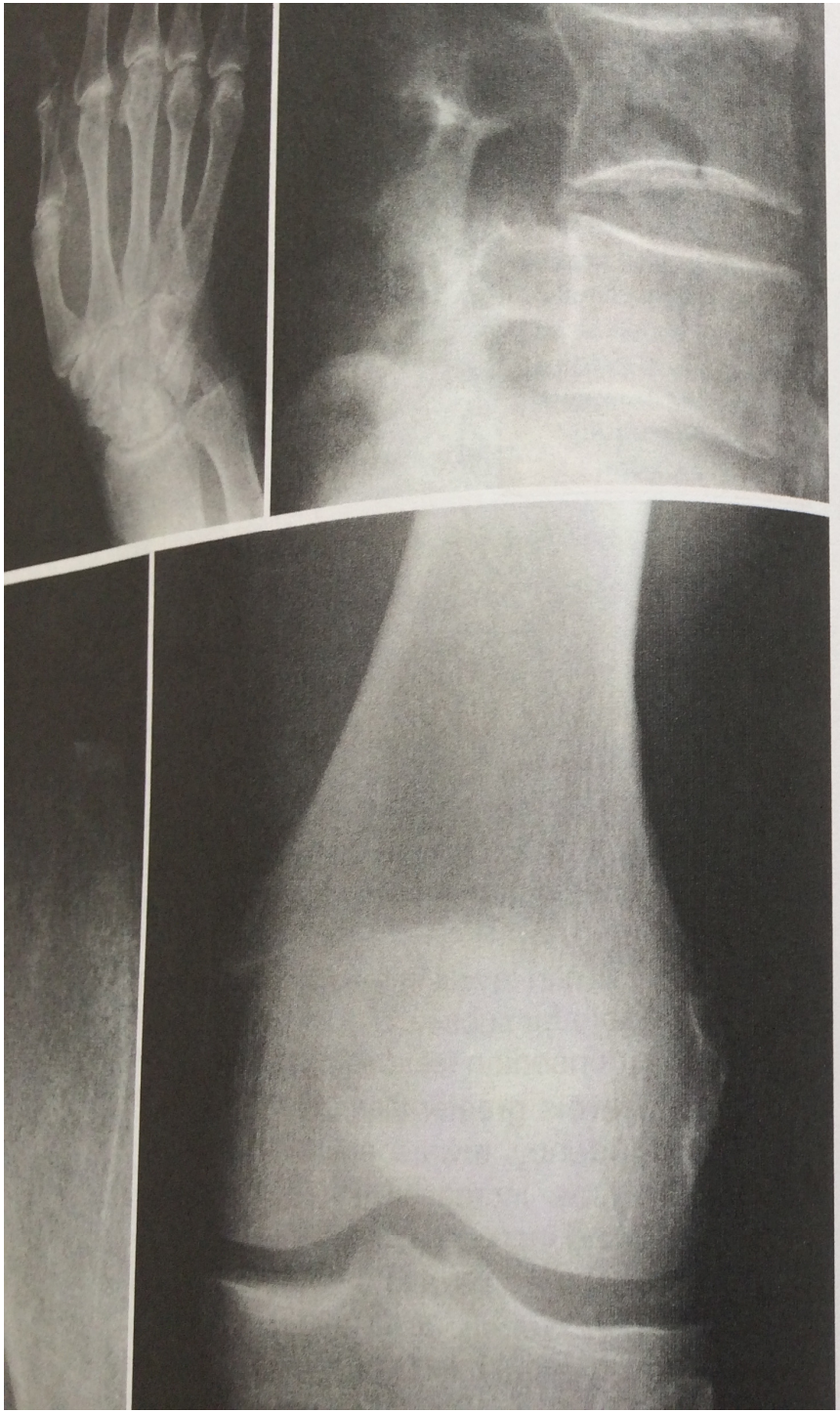
[654] Rockey DC, Cello JP. Evaluation of the gastrointestinal ... "Endoscopy revealed a clinically ... iciency anemia, ...

[655] ...



Guide to Patient Management Based on Iron Status:

- Deficiency: Adult patients with iron deficiency must generally be presumed to have occult gastrointestinal loss and should therefore be referred for gastrointestinal endoscopy; this is consistent with the standard o in medicine.
- Optimal: Ferritin levels between 40-70 mcg/L are generally optimal for most men and women; up to 120 is reasonable for subsets of patients with restless leg syndrome, perhaps also those with recalcitrant depre and/or Parkinsonian features to allow sufficient iron entry into the brain for maximal dopamine productior
- Excess: Levels greater than 200 mcg/L in a woman or 300 mcg/L in a man are suggestive of iron ov and/or tendency toward accumulation and are physiologically unnecessary and medically unjusti particularly as increased iron stores correlate with increased cancer mortality, increased cardiova mortality, and increased all-cause mortality.
- Overload: Diagnosis and treatment for iron overload can occur simultaneously with diagnostic/thera phlebotomy. Genetic testing and liver biopsy are generally inefficient expenditures of financial and r resources; genetic testing is largely irrelevant in the presence of the hemochromatosis phenotype otherwise inexplicable iron accumulation) while liver biopsy exposes the patient to unnecessary trea delays, risk, and expenses. Identification of idiopathic or genotropic iron overload requires testing of g relatives.



- Thyroid assessment: may show hyperthyroidism or hyp
  in patients with iron overload.
- Bone marrow biopsy: unnecessary and archaic in this set
- Liver biopsy: traditionally considered the "gold stand
  clearly unnecessary for the diagnosis, which can be estab
  phlebotomy, which is the treatment of choice.[656] **Life-s**
  should never be denied or delayed for lack of liver b
  iron overload.[657]
- Genetic testing, such as for the HFE mutation: This
  situations; these tests should be reserved for research p
  especially children—of index cases. The only value th
  supporting a diagnosis in a patient with elevated se
  phlebotomy; however, a negative result is meaningles
  compatible with iron overload. If the diagnosis is estab

Establishing the diagnosis: Any ***one*** of the following three is sufficient:

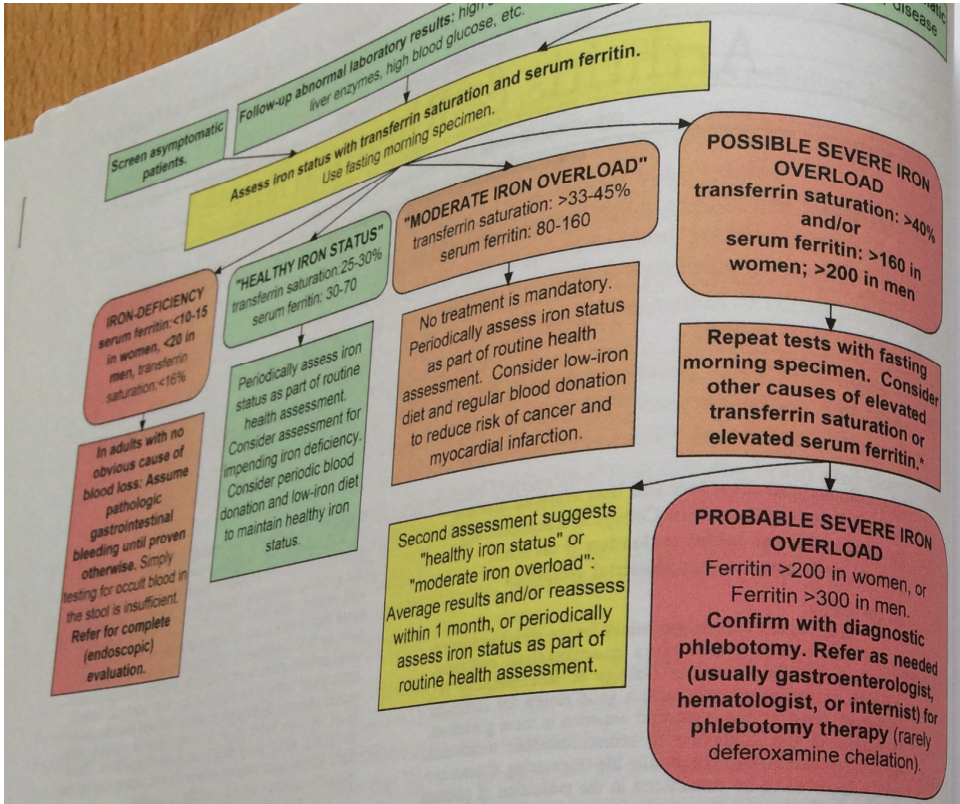
- Diagnostic liver biopsy shows heavy iron deposits.
- Characteristic laboratory findings (ferritin >200 in women or >300 in men) ***and*** the ability to resist intractable anemia with serial/weekly phlebotomies.
- Characteristic MRI of liver ***and*** the ability to tolerate serial/weekly phlebotomies.

Complications:

- Patients diagnosed *and effectively treated* before the onset of
- The most common causes of premature mortality in undia
  failure, liver failure, infections and/or complications of dial

Clinical management:

- Treatment for severe iron overload is iron-removal therapy
  therapeutic phlebotomy—is the treatment of choice. Defe
  who refuse or cannot withstand phlebotomy (i.e.,
  less effective, much more ex



Algorithm for the comprehensive management of iron status: The above flow-chart delineates patien management per iron status.

Basic treatments for severe iron overload:

- **Iron-removal therapy is mandatory:** Phlebotomy therapy is generally performed weekly or twice-weekly deferoxamine chelation is reserved for patients who do not withstand phlebotomy (due to cardiomyopathy, severe anemia, or hypoproteinemia) or may be used concurrently with phlebotomy in some patients. Periodically assess hematologic and iron indexes. Continue with weekly iron removal therapy until patient reaches mild iron-deficiency anemia, then decrease frequency and continue phlebotomy as needed (e.g., 4 times per year).

Laboratory tests and physical examination: Assess general physical condition and hepatic, cardiac, endocrine, and general health status.

Confirm diagnosis: Liver biopsy ("gold standard") or diagnostic phlebotomy; perhaps MRI.

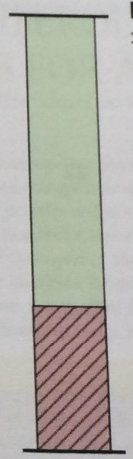
Assess liver status: Liver biopsy or perhaps MRI. Cirrhosis indicates increased risk of hepatocellular carcinoma and reduced life expectancy. Consider liver ultrasound, serum liver enzyme measurement, and serum alpha-fetoprotein o screen for hepatocellular carcinoma every 6 months. Hepatoma surveillance is mandatory in cirrhotic patients.

mplement dietary modifications and nutritional therapies: Avoid iron supplements, multivitamin supplements ith iron, iron-fortified foods, liver, beef, pork, alcohol, and excess vitamin C. Ensure adequate protein intake to place protein lost during phlebotomy. Diet modificatio
ioxidant therapy.

25(OH)D: serum 25(OH) vitamin D

Overview and interpretation:

- **Vitamin D deficiency is a common cause of musculoskeletal pain**[170,1] deficiency is a significant risk factor for cancer, autoimmunity, diabete chronic pain and physical disability.[173,174,175]
- Measurement of serum 25(OH) vitamin D (or empiric treatment with vitamin D3 per day for adults) is indicated in patients with chronic m particularly low-back pain.[176] Optimal vitamin D status correlates wit levels of 50 – 100 ng/mL (125 - 250 nmol/L)—see our review article fo levels greater than 100 ng/mL are unnecessary and increase the risk o



Excess vitamin D
> 100 ng/mL (250 nmol/L) with hyper

Optimal range
50 - 100 ng/mL (125 - 250 nmol/L)

Insufficiency range
< 20- 40 ng/mL (50 - 100 nmol/L)

Deficiency
< 20 ng/mL (50 nmol/L)

Interpretation of serum 25(OH) vitamin D levels. Modified *Alternative Therapies in Health and Medicine* 2004 and Vas *Pain: Expanded Clinical Strategies* 2008.

Advantages:

- Accurate assessment of vitamin D status.

Limitations:

- Patients with certain granulomatous conditions such as sarcoid and patients taking certain drugs such as thiazide diuretics (hy develop hypercalcemia due to "vitamin D hypersensitivity" or patients require frequent monitoring of serum calcium while t supplements.

Comments:

- **Routine measurement and/or empiric treatment with vitami routine component of patient care.**[178]
- Periodic assessment of 25(OH)D and serum calcium are requi and safety of treatment, respectively.
- I'm increasingly convinced of the merit of measuring 1,25-di for the initial assessment of patients with inflammatory/auto

Vitamin D, 1,25 + 25-Hydroxy					
Test	Low	Normal	High	Reference Range	Units
Calcitriol(1,25 Di-Oh Vit D)			115.8	10.0-75.0	pg/mL
Vitamin D, 25-Hydroxy		53.1		30.0-100.0	ng/mL

Cmp14+Egfr					
Test	Low	Normal	High	Reference Range	Units
Glucose, Serum		90		65-99	mg/dL
Bun		20		6-20	mg/dL
Creatinine, Serum		0.93		0.76-1.27	mg/dL
Egfr If Nonafricn Am		104		>59	mL/min/1.73
Egfr If Africn Am		120		>59	mL/min/1.73
Bun/Creatinine Ratio			22	8-19	1
Sodium, Serum		142		134-144	mmol/L
Potassium, Serum		4.8		3.5-5.2	mmol/L
Chloride, Serum		99		97-108	mmol/L
Carbon Dioxide, Total		26		18-29	mmol/L
Calcium, Serum		9.7		8.7-10.2	mg/dL

Cbc/Diff Ambiguous Default					
Test	Low	Normal	High	Reference Range	Units
Wbc		5.8		3.4-10.8	x10E3/uL
Rbc		5.26		4.14-5.80	x10E6/uL

Ldh					
Test	Low	Normal	High	Reference Range	Units
Ldh		123		121-224	IU/L

Homocyst(E)Ine, Plasma					
Test	Low	Normal	High	Reference Range	Units
Homocyst(E)Ine, Plasma		10.7		0.0-15.0	umol/L

Laboratory results for a 39yoM with psoriasis and psoriatic arthritis: Abnormally increased conversion of 25-OH-cholecalciferol to 1,25-d(OH-cholecalciferol is due expression of 25-hydroxyvitamin D3-1alpha-hydroxylase (1-OHase) in inflammatory tissue/cells. Note that serum calcium is normal, so no immediate threat is present (i.e., hypercalcemia) but of course the clinician has the responsibility to ❶ monitor periodically, ❷ inform the patient of symptoms of hypercalcemia such as headache and abdominal pain, and ❸ search for any predictive risk factors such as renal insufficiency or occult leukemia/lymphoma that could precipitate hypercalcemia. Assessment for hyperparathyroidism (eg, iPTH) is reasonable but not completely necessary; likewise, cancer screening is not absolutely indicated, as it would be in the case of idiopathic hypercalcemia. Also noted is the elevated homocysteine, common in patients with psoriasis; increased cell turnover—dermal hyperproliferation—likely contributes to draining/catabolizing nutrients such as folate. Since this patient's 25-OH-D is plenty sufficient, I had the patient temporarily reduce/discontinue vitamin D supplementation to reduce risk of hypercalcemia given that he is clearly vitamin D sufficient.

CME
CONTINUING MEDICAL EDUCATION

THE CLINICAL IMPORTANCE OF VITAMIN D (CHOLECALCIFEROL): A PARADIGM SHIFT WITH IMPLICATIONS FOR ALL HEALTHCARE PROVIDERS

Alex Vasquez, DC, ND, Gilbert Manso, MD, John Cannell, MD

Alex Vasquez, DC, ND is a licensed naturopathic physician in Washington and Oregon, and licensed chiropractic doctor in Texas, where he maintains a private practice and is a member of the Research Team at Biotics Research Corporation. He is a former Adjunct Professor of Orthopedics and Rheumatology for the Naturopathic Medicine Program at Bastyr University. **Gilbert Manso, MD**, is a medical doctor practicing integrative medicine in Houston, Texas. In practice for more than 35 years, he is Board Certified in Family Practice and is Associate Professor of Family Medicine at University of Texas Medical School in Houston. **John Cannell, MD**, is a medical physician practicing in Atascadero, California, and is president of the Vitamin D Council (Cholecalciferol-Council.com), a non-profit, tax-exempt organization working to promote awareness of the manifold adverse effects of vitamin D deficiency.

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OBJECTIVES

Upon completion of this article, participants should be able to do the following:

1. Appreciate and identify the manifold clinical presentations and consequences of vitamin D deficiency
2. Identify patient groups that are predisposed to vitamin D hypersensitivity
3. Know how to implement vitamin D supplementation in proper doses and with appropriate laboratory monitoring

Reprint requests: InnoVision Communications, 169 Saxony Rd, Suite 103, Encinitas, CA 92024; phone, (760) 633-3910 or (866) 828-2962; fax, (760) 633-3918; e-mail, alternative.therapies@innerdoorway.com. Or visit our online CME Web site by going to http://www.alternative-therapies.com and selecting the Continuing Education option.

While we are all familiar with the important role of vitamin D in calcium absorption and bone metabolism, many doctors and patients are not aware of the recent research on vitamin D and the widening range of therapeutic applications available for cholecalciferol, which can be classified as both a vitamin and a pro-hormone. Additionally, we also now realize that the Food and Nutrition Board's previously defined Upper Limit (UL) for safe intake at 2,000 IU/day was set far too low and that the physiologic requirement for vitamin D in adults may be as high as 5,000 IU/day, which is less than half of the >10,000 IU that can be produced endogenously with full-body sun exposure.[1,2] With the discovery of vitamin D receptors in tissues other than the gut and bone—especially the brain, breast, prostate, and lymphocytes—and the recent research suggesting that higher vitamin D levels provide protection from diabetes mellitus, osteoporosis, osteoarthritis, hypertension, cardiovascular disease, metabolic syndrome, depression, several autoimmune diseases, and cancers of the breast, prostate, and colon, we can now utilize vitamin D for a wider range of preventive and therapeutic applications to maintain and improve our patients' health.[3] Based on the research reviewed in this article, the current authors believe that assessment of vitamin D status and treatment of vita-

Vasquez A et al. The clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers. *Altern Ther Health Med* 2004 Sep-Oct: This article indexed on Medline at ncbi.nlm.nih.gov/pubmed/15478784 and is archived by the author online ICHNFM.ORG/faculty/vasquez/profile.html and https://ichnfm.academia.edu/AlexVasquez

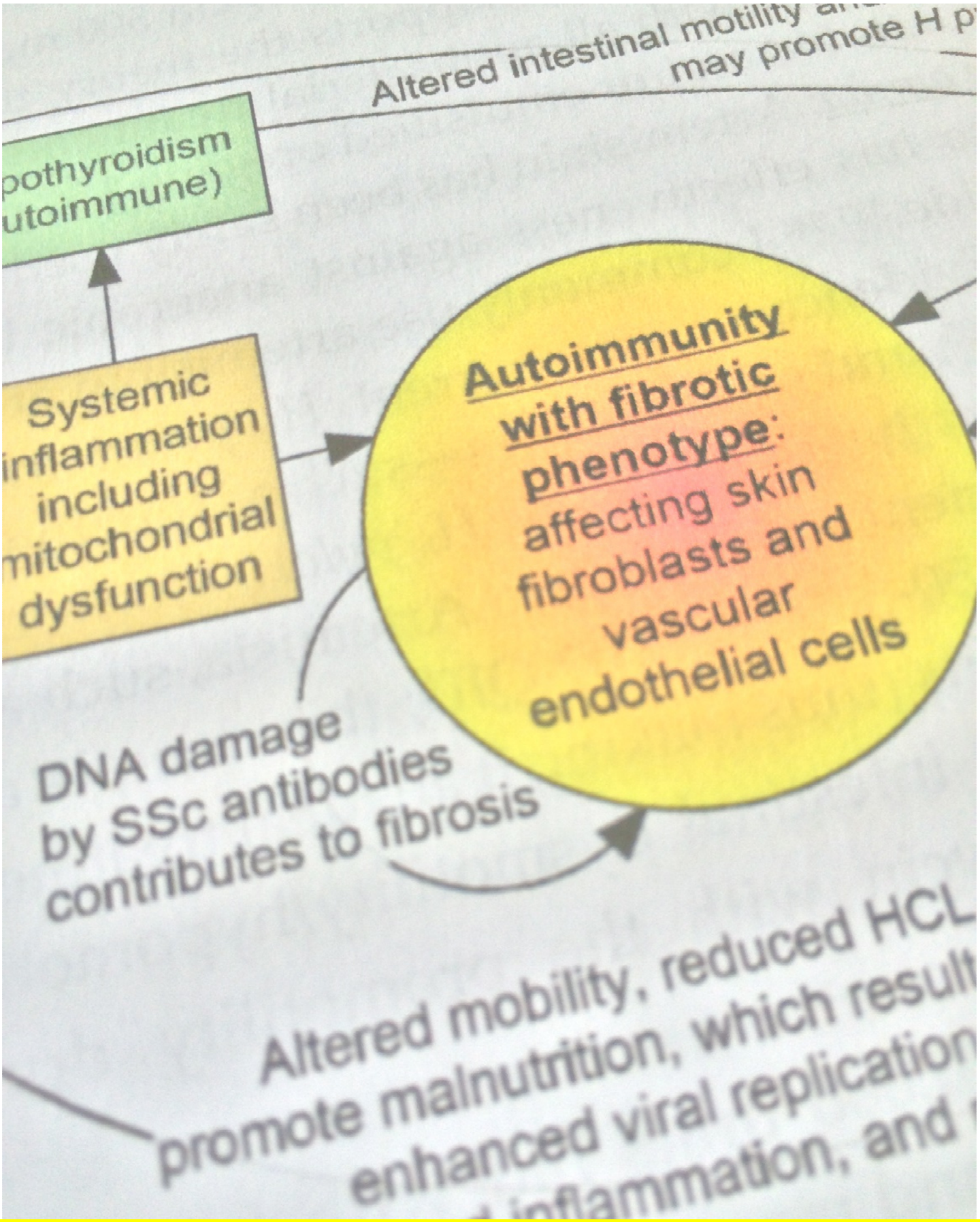
Notices: The intended audiences for this book are health science students and doctorate-level licensed medical clinicians. This book has been written with every intention to make it as accurate as possible, and each section has undergone peer-review by an interdisciplinary group of clinicians. In view of the possibility of human error and as well as ongoing discoveries in the biomedical sciences, neither the author nor any party associated in any way with this text warrants that this text is perfect, accurate, or complete in every way, and all disclaim responsibility for harm or loss associated with the application of the material herein. Information and treatments applicable to a specific *condition* may not be appropriate for or applicable to a specific patient; this is especially true for patients with multiple comorbidities and those taking pharmaceutical medications, which are generally associated with multiple adverse effects and drug/nutrient/herb interactions. Given that this book is available on an open market, lay persons who read this material should discuss the information with a licensed medical provider before implementing any treatments and interventions described herein.

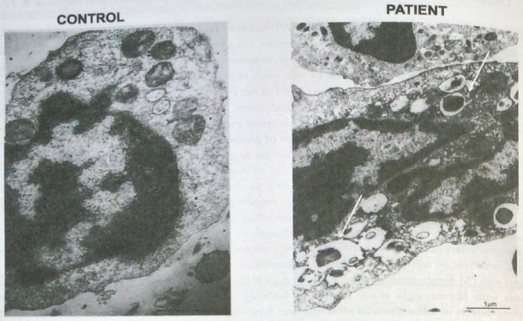
Reviews of previous and recent works:

- "Thank you most kindly for your incredible dedication and kindness in sharing your knowledge with us. I am due to start med school next semester and thanks to you and all those who have taught you, I'll be way ahead of the curve." *Premedical/Medical student 2015*
- "Dr Vasquez, I have followed your work extensively and admire your intellect and passion. Thank you for your passion for teaching with integrity!" *Chiropractic doctor 2015*
- "I just wanted to tell you how much I appreciate the information I have received from you. I am still digesting most of it. I feel I have learned quite a bit already yet also feel I have barely scratched the surface." *Doctor and Graduate student under Dr Vasquez, 2013*
- "Dr. Vasquez, Thank you for all you do. **Your conference was simply amazing**. No one wanted to leave the room. I met medical professionals and very interesting lay people who were stimulated and invigorated to change their lives and the lives of others. **I am in awe at your intellectual integrity and veracity.** Best of luck to you in all of your future endeavors." *Medical physician and ICHNFM 2013 Conference Attendee*
- **2014 review of Functional Inflammology, Volume 1: "A truly comprehensive text on the vast subject of inflammation. I consider this book to be an essential addition to any health care practitioner who wishes to operate within the realm of Function Medicine. Please be aware that this book is dense in its content, and its 700 plus pages are full of deeply insightful information. I think Dr. Vasquez is one of the most prolific functional medicine contributors and books such as this should cement his reputation as such."**
- "I attended the last ICHNFM conference in Portland (and am still basking in the amazing information received)." *Email from Clinical Oncology Dietitian, in late February 2014*
- "Thanks for a fantastic conference!" *ICHNFM 2013 Conference Attendee*
- "Your discourse today reflected not only your passion and commitment to the wellness of our planet but most importantly the clarity and sincerity of your spirit/ heart/ mind. Always good to be with you and look forward to seeing you soon. Hope we can spend more time then." *Medical physician attendee 2014*
- "I was so refreshed by the 'unfiltered excellence.' What humanness. Breaths of fresh air." *ICHNFM 2013 Attendee*
- "Keep in mind Alex, that humanity is a better place because of you. I know you can't undo it all, but think about how many people would be worse off if it wasn't for your wonderful knowledge being shared with all us docs. Things that I have learned from you have changed peoples' lives for the better." *Naturopathic physician, 2014*
- "Just got back to Guam. Great experience at the International Conference on Human Nutrition and Functional Medicine. Exciting concepts on functional medicine. Thanks Dr. Alex Vasquez and team!" *ICHNFM 2013 Conference Attendee*
- "Already waiting in line to buy next year's ticket! **Dr. Vasquez you crushed it!** The future is looking fun already ☺" *ICHNFM 2013 Conference Attendee*
- "Had an incredible time at the 2013 International Conference on Human Nutrition and Functional Medicine. Got to meet some amazing people and hear from some of the top researchers/health professionals about human nutrition and functional medicine approaches. It was definitely worth every penny and can't wait to go back next year!" *ICHNFM 2013 Conference Attendee*
- "I miss you! Your confidence in a program you believed in. I miss your live classes where we would get off topic on a clinical pearl. I miss your way of teaching in a laid back atmosphere that made me feel comfortable, not intimidated. I just needed to let you know, this program is not the same, I am almost done, otherwise, I would have bailed out! I am grateful for the last 18 months I did have with you at the helm. ... You ignited in me my passion for learning again. You sparked the minds of all of us with your enthusiasm. Don't ever let anyone take that away. It has given birth to your new endeavor, and we will follow where you lead. Enjoy your new surroundings and celebrate your new beginnings. I know I look forward to what is ahead." *Doctor and Graduate student under Dr Vasquez, 2013*
- "Wonderful conference! Thanks so much." *ICHNFM 2013 Conference Attendee*
- "Really wonderful conference! Lots of material ready to implement Monday morning! **Congrats to Alex Vasquez on a herculean job very well done**!" *ICHNFM 2013 Conference Attendee*
- "Thanks for a great conference. I really enjoyed all of the speakers, but your lectures were by far the most useful for implementing ideas into my clinical practice. And the most entertaining." *ICHNFM 2013 Conference Attendee*
- "Thank you for your life-changing work." *Physician, 2011*
- "I want Dr. Vasquez to know that I have just received his book, *Chiropractic and Naturopathic Mastery of Common Clinical Disorders*. **It is a treasure. The best book in my library.** Thank you for the contribution that you are giving to the world of health care." *Clinician, 2010*
- "I appreciate the resources you offer the profession. I use your books and articles regularly." *Doctor, 2011*
- "Dr. Vasquez, I greatly appreciate your efforts. I am a student at ___, 8th trimester, and would like to express my gratitude for your research and works. After coming across your texts in the library**, I quickly found your insight and explanations of the current health care crisis, and in depth coverage and algorithms for inflammatory**

diseases as a profound inspiration and call to action. I appreciate your attention to detail, and have been taken back several times by the potency and meaning of your sentences. Thank you for your hard work, I will enjoy these books and will surely share with those that have the same drive for true and competent patient care." *Health Sciences Student, 2008*

- "I never told you this, but whenever I need to research a particular disease, **besides going on Pubmed and checking some classic Pathophysiology and Clinical Nutrition books, I use your books and I find them extremely well organized, concise, and up-to-date and with the functional/integrative medicine thinking I enjoy and believe it is the future of Health Care**." *Nutrition Research Consultant and University Faculty in Europe, 2009*
- "Thanks so much. You are a great asset to our profession." *Doctor, 2010*
- "As a 7th trimester student quickly approaching 8th trimester and student clinic, I know I will be utilizing your books often. **Your "Chiropractic and Naturopathic Mastery of Common Clinical Disorders" book is referenced very frequently by many clinicians and faculty members at [our university]. Your work is highly regarded**, and I look forward to clinically utilizing the information I will obtain from your writings." *Health Sciences Student, 2011*
- "I am a chiropractic student at ___ Chiropractic College. I just wanted to drop a quick line thanking you for your thorough and accessible textbook Integrative Orthopedics. We are using it in our Differential Diagnosis class, and **it is the best book I've come across in Chiropractic College bar none. The writing is concise, informative and refreshingly eloquent. The material is super practical. I hope you continue putting out great resources.**" *Health Sciences Student, 2011*
- "I appreciate the resources you offer the profession. **I use your books and articles regularly**." *Doctor, 2011*
- "**Your Integrated Orthopedics book is magnificent**. I wish all textbooks were structured and as thoughtful as that one." *Health Sciences Student, 2008*
- "By reading the introduction I realize that calling it an orthopedics book; does not do it justice. **It is far more than that. It looks to me that you have created, or are creating, the bible of Integrative Orthopedics and physical medicine**. *Physician, 2007*
- "First of all let me say how honored I am that you have allowed me to review this work. You have done an amazing job! In my opinion **every healthcare provider SHOULD have this on their bookshelf**." *Physician, 2007*
- "Your work on Chapter 12: Hip and Thigh is very good. The chapter is inclusive of the typical pathologies seen in private practice and I particularly liked the separation of juvenile from adult pathologies. Your choice of tests to assess hip and thigh pathology on page 320 is very nice and inclusive. I appreciate your use of algorithms and find them very useful in teaching and in practice. In general, **I thought this chapter represents a quality, state of the art presentation**!" *Clinician and Professor in Clinical Sciences, 2007*
- "I saw your books in a colleague's office and was really impressed. Really appreciate the thoroughness you've put into them." *Doctor, 2010*
- "**It is with great interest and fascination that I have been reading your material both in your two books (Integrative Orthopedics and Integrative Rheumatology) and online. I consider myself very fortunate to have come across your work**, as many of the basic elements of health which you discuss I never learnt or even heard about while in chiropractic college." *Doctor, 2010*
- "I appreciate the resources you offer the profession. I use your books and articles regularly." *Doctor, 2011*
- "**I'm so pleased with your books and was inspired to let you know they have already been incredibly useful! Good index; well organized algorithms. Sometimes I buy educational material and it just sort of sits there... Your books now live on my main desk. Thanks**." *Physician and Journal Editor, 2009*
- "I just wanted to let you know how much I am enjoying reading **your book Integrative Rheumatology. It is having an extremely positive impact in the way I view health and am having a tough time putting it down. It is very inspirational.** I have long felt that it is very important to set a good example for your patients and now try my best to be one for my future patients. I like how you stress this in your book. In order to be the best example for my patients I am going to need to address some problems with my own health. I look healthy from the outside but I have been suffering from fatigue for about 4 years. It has a very negative impact on my health. People say that doing the same thing and expecting different results is the definition of insanity so I think it is time that I attempt to make some changes. ... **Thanks again for writing such a great book. I feel it is a must have for anyone in a musculoskeletal practice**." *Health Sciences Student, 2010*
- "My name is [recent graduate], and I've been a fan of your books since I was in chiropractic college at [university] campus. Dr. [Author, Presenter] made your book, Integrative Rheumatology, required reading for his 9th quarter nutrition class. I never looked back, and have since purchased Chiropractic & Naturopathic Mastery of Common Clinical Disorders as well as Chiropractic Management of Chronic Hypertension." *Doctor, 2010*
- "I saw your books in a colleague's office and was really impressed. Really appreciate the thoroughness you've put into them." *Doctor, 2010*





Blood cells in FM patients show mitochondrial destruction (mitophagy), smaller size and lower number of mitochondria: Structure of blood mononuclear cells (BMCs, cells of the immune system) from FM patients. The healthy/control BMCs show mitochondria with a normal structure. Autophagosomes (indicated by arrows), where mitochondria are destroyed (the process of mitophagy [*mito*=mitochondria, *phagy*=consumption], are noted in the BMCs of patients with FM. [Bar = 1 micrometer]. This open-access image is respectfully attributed to the brilliant research published by these researchers Cordero MD, De Miguel M, Moreno Fernández AM, Carmona López IM, Garrido Maraver J, Cotán D, Gómez Izquierdo L, Bonal P, Campa F, Bullon P, Navas P, Sánchez Alcázar JA. Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients. *Arthritis Res Ther.* 2010;12(1):R17 arthritis-research.com/content/12/1/R17

Mitophagy: The body's inherent mechanism for the destruction of dysfunctional mitochondria

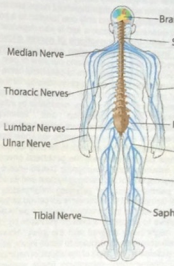
Concept: Autophagic destruction of mitochondria is termed "mitophagy" and is the body's inherent mechanism for eliminating superfluous or dysfunctional mitochondria; this generally has a protective and life-sustaining effect. However, in the case of fibromyalgia wherein the mitochondrial dysfunction is persistent, prolonged mitophagy contributes to failure of adequate energy production and thereby contributes to clinical manifestations of fatigue, dyscognition, and impaired exercise/activity performance. Further, the consistent documentation of significant mitophagy in patients with fibromyalgia proves the biological/organic/real/pathophysiologic character of the illness and refutes the pharmacocentric paradigm which holds that the condition is of psychogenic or neurologic origin and thus to be treated with so-called "antidepressants" and/or analgesic drugs, respectively.

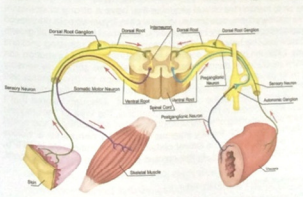
- "The removal of damaged mitochondria that could contribute to cellular dysfunction or death is achieved through process of mitochondrial autophagy, i.e. mitophagy." Novak I. *Antioxid Redox Signal.* 2011
- "Mitochondrial number and health are regulated by mitophagy, a process by which excessive or damaged mitochondria are subjected to autophagic degradation." Rambold. *Cell Cycle.* 2011
- **"Autophagy can be beneficial for the cells by eliminating dysfunctional mitochondria, but massive autophagy can promote cell injury and may contribute to the pathophysiology of FM."** Cordero. *Arthritis Res Ther.* 2010

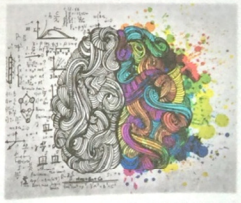
- **Pain in fibromyalgia originates peripherally and is amplified centrally: The pain of fibromyalgia originates from the muscles[252] secondary to stimulation by oxidative and inflammatory mediators and is excessively** amplified in the brain and spinal cord; another possible peripheral contribution to pain inputs is degeneration of nerve fibers in the skin.[253] To risk redundancy for clarity: **FM pain originates *peripherally* in the muscles**

(and likely in the skin as well, at least in some patients) and is amplified *centrally* in the spinal cord and brain. Following reception and amplification of the original muscular pain, the peripheral "receptive field" grows both in size and intensity/hypersensitivity to include the skin, so that various skin inputs are perceived as pain; the two main types of dysfunctional pain sensitivity/sensations are allodynia (reception of nonpainful stimuli as pain) and hyperalgesia (extended duration and increased intensity of pain).

- Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input (*Pain.* 2009 Sep[254]): "Lidocaine injections increased local pain thresholds and decreased remote secondary heat hyperalgesia in FM patients, emphasizing the important role of peripheral impulse input in maintaining central sensitization in this chronic pain syndrome; similar to other persistent pain conditions such as irritable bowel syndrome and complex regional pain syndrome."

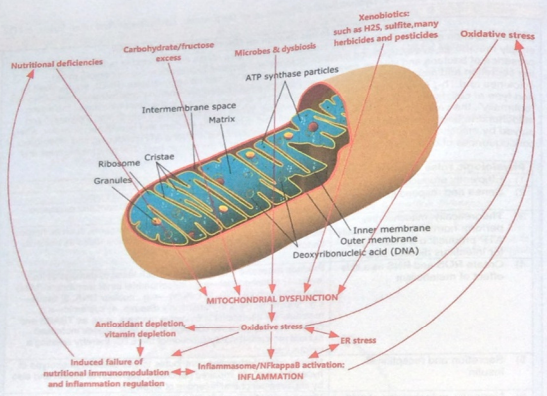






More than 400 years of the history and development of neuroanatomy and neurophysiology represented in four images: These four images in sequence represent the history and development of the fields of neuroanatomy and neurophysiology, ❶ starting with the drawing by Descartes in the 1600s, ❷ the tracing of nerves throughout the body, ❸ what might be called the

findings suggest that some patients with chronic pain labeled as fibromyalgia have unrecognized SFPN, a distinct disease that can be tested for objectively and sometimes treated definitively." Oaklander et al. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. *Pain.* 2013 Nov;154(11):2310-6
[254] Staud et al. Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input. *Pain.* 2009 Sep;145(1-2):96-104



Schematic overview of mitochondrial dysfunction's major causes and consequences: Notice the presence of vicious cycles whereby cause becomes consequence, and then consequence becomes cause. Several dietary, nutritional, botanical, pharmaceutical/microbiologic, and sociopolitical interventions are obvious from the diagram.

Mitochondria—Re-Introduction and New Perspectives:

- Production of cellular energy in the form of ATP: Mitochondria are organelles ("small organs") within each cell that produce the majority of cellular energy for biochemical reactions and cellular processes. The primary fuel used by cells of the body is ATP—adenosine triphosphate. Everyone who has studied mitochondria—ranging from high-school and undergraduate students of Biology all the way to doctorate-level medical/healthcare professionals—is familiar with the fact that mitochondria make ATP; in fact, for most people, whether they are general public or doctors, this is all they know about mitochondria. New research, however, has shown us that mitochondria have many roles in addition to their ability to produce cellular energy. Most importantly, mitochondria are now known to play important roles in perpetuating chronic inflammation, responding to microbial infections, triggering of cell death, and controlling various metabolic processes.[1,2]
- Perpetuation of chronic inflammation: Most relevant to the focus of this work on clinical conditions related to inflammation is the fact that mitochondria have the ability to trigger inflammatory responses via activation of the nuclear transcription factor kappa-B (NFkB). Transcription factors are intracellular molecules that bind to the genetic material (DNA) in the nucleus of the cell to influence the activation or transcription of specific genes; in this case the transcription factor kappaB is most notorious for its activation of genes that promote inflammatory responses—necessary for short-term responses to injury or infection, but harmful when protracted and nonspecific. In this way, certain types of mitochondrial stimulation/activation/dysfunction can

[1] Pieczenik SR, Neustadt J. Mitochondrial dysfunction and molecular pathways of disease. *Exp Mol Pathol.* 2007 Aug;83(1):84-92
[2] Green DR, Galluzzi L, Kroemer G. Mitochondria and the autophagy-inflammation-cell death axis in organismal aging. *Science.* 2011 Aug 26;333(6046):1109-12

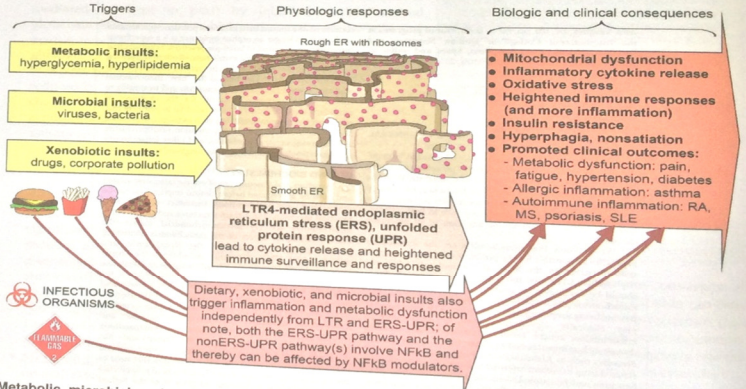
Food-Induced Activation of Toll-like Receptors, Endoplasmic Reticulum Stress, and the Unfolded Protein Response:

An Integrated Model for Understanding Metabolic Inflammation

Metabolic Inflammation: Diet-Induced Metabolic Impairment and Inflammation

In this section, I will describe and give structure to a model for understanding what I have previously described—albeit intuitively—as metabolic inflammation.

Introduction: In my model presented starting in 2012,[65] I began differentiating/describing inflammatory conditions as existing along and within an *overlapping continuum* of ❶ metabolic inflammation, ❷ allergic inflammation, and ❸ autoimmune inflammation. The most basic definition/description of metabolic inflammation is simply that it is a pathophysiologic state of nonacute metabolic disruption/dysfunction combined with a state of chronic/sustained mild/nonacute inflammation. What I have also stated is that "chronic inflammation" as most of us were taught in our Pathology coursework does not—for the most part—exist; except for a few rare diseases, the body does not perpetuate clinically significant states of inflammation. So-called *chronic* inflammation only occurs via a *sustained* inflammatory response. Another newer—and perhaps more direct way—of shattering the outdated paradigm of "chronic disease" is to state that such *diseases* do not exist—only *responses* and *accumulated damage* exist. Clinicians should experiment with the possibilities and implications of exchanging their conception of "chronic diseases" in favor of "sustained responses"; I think they will find the experience to be more illuminating/empowering/engaging than resignation to the chronic disease model and its subsequent indefinite noncurative (poly)pharmacotherapy. The illustration below introduces and summarizes several key concepts.

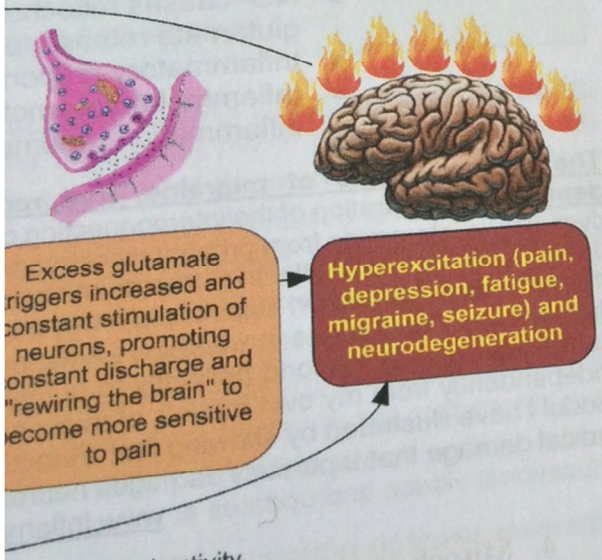


Metabolic, microbial, and xenobiotic insults—often via TLR4—induce endoplasmic reticulum stress (ERS) and the subsequent unfolded protein response (UPR): Consequences include vicious cycles of inflammation, oxidative stress, mitochondrial dysfunction, insulin resistance and hyperphagia—all consistent with sustained sterile nonacute inflammation and metabolic dysfunction/impairment termed here as *metabolic inflammation*.

[65] Vasquez A. *Functional Immunology and Nutritional Immunomodulation: Presentation Slides Part 1.* Publication Date: June 5, 2012, ISBN-13: 978-1477603857

d psychiatric disorders, such as pain and
ectively. The neurons themselves can also
nflammation because the inflammation is
nerve cells. When **brain inflammation** is
ecomes a self-reinforcing cycle, sometimes
consequences; for example, ❶ inflamed
t activate endothelial cells (thereby causing
activation of mast cells and platelets causes
onate metabolites (such as prostaglandins,
itional inflammation and also promote
nation and metabolic impairment seen in
lease of the inflammation-associated and
which causes leakiness of the blood-brain
nflammatory molecules from the blood.[5]

rs more glial activation,
and a vicious cycle



ble to normal activity
s and stressors
motional stress.
o neurons, leading to neuron death: neurodegeneration.

tly show evidence of mitochondrial impairment:
ng 1) defects in CoQ10 synthesis, 2) defects in
(ETC). The majority of these problems can be
lysfunction promotes inflammation in microglia:
al mitochondria promote microglial activation.
Complex #4 in the electron

amplify, and [illegible] neuroinflammation caused by increased neuroactivity—the microglial cells; thus, neurogenic (in this context, including the microglia and astrocytes as components of the brain and spinal cord) neuroinflammation would be expected to participate in seizure disorders and vaccine-induced encephalomyelitis.

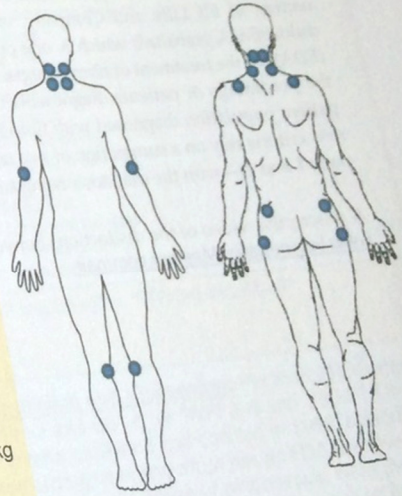
4. ***Image lower right*—The nervous system (represented by artistic brain image) is now appreciated as dynamic and interactive receiver and processor of sensory information**; in modern times, pain processing is appreciated as a dynamic, complex, and interactive process at every level, from ❶ peripheral reception of stimuli (e.g., in the skin or muscles), to the ❷ spinal cord, to the ❸ brainstem, to the ❹ subcortical structures especially the thalamus, to the ❺ cortex. Generally appreciated is that much "spill-over", "misinterpretation", inhibition and amplification" can occur in the spinal cord, brainstem, [illegible] of the brain, so that the [illegible] ion of pain—in the muscles for example in the case of FM—is amplified skin pain, resulting in allodynia (misinterpretation of light touch as pain) intensity and duration). The brain is constantly adapting to input; for ns in various patterns to produce memory. When the brain is constantly the neuron-neuron interconnections to increase pain processing—what cilitates the perception of pain, leading to enhanced pain perception, e.g.,

Diagnosis

- Clinical criteria—description and contrast of the 1990 criteria and the 2010 criteria: Per guidelines published in 1990 by the American College of Rheumatology (ACR), a diagnosis of fibromyalgia can be made in a patient with inexplicable, widespread myofascial pain of at least 3 months' duration; *inexplicable* denotes normalcy of routine laboratory and physical examination findings and failure to find an alternate explanation or diagnosis, while *widespread* denotes bilateral pain above and below the waist not attributable to trauma or rheumatic disease and with pain at 11 of 18 classic tender point locations (see illustration below).

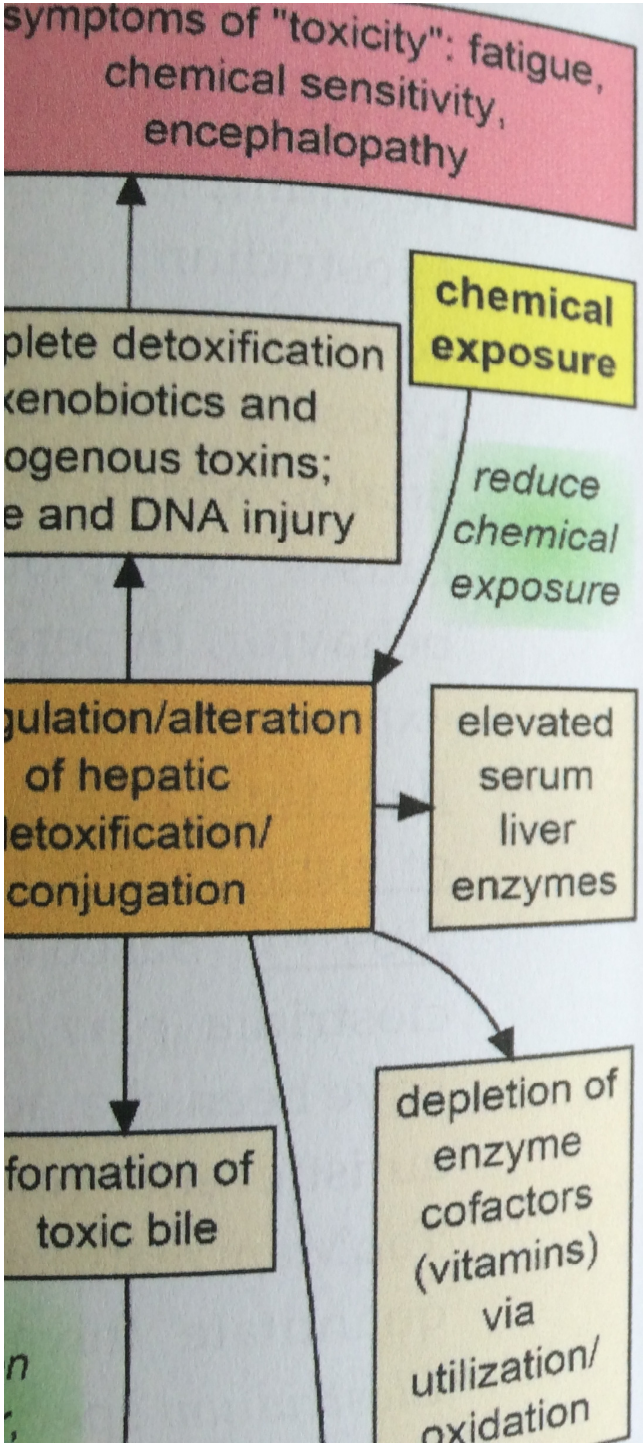
Illustration of the 9 paired locations of FM tender points:
Pain, on digital palpation, must be present in at least 11 of the following 18 tender point sites:
1. Occiput: at the suboccipital muscle insertions.
2. Low cervical: at the anterior aspects of the intertransverse spaces at C5-C7.
3. Trapezius: at the midpoint of the upper border.
4. Supraspinatus: at origins, above the scapula spine near the medial border.
5. Second rib: upper lateral to the second costochondral junction.
6. Lateral epicondyle: 2 cm distal to the epicondyles.
7. Gluteal: in upper outer quadrants of buttocks in anterior fold of muscle.
8. Greater trochanter: posterior to the trochanteric prominence.
9. Knee: at the medial fat pad proximal to the joint line.

Per 1990 ACR guidelines, the diagnosis of FM is supported when at least 11 out of 18 of these locations are painful. Digital palpation should be performed with an approximate force of 4 kg (9 lbs). A tender point has to be painful at palpation, not just "tender."[259]



FM tender points are assessed bilaterally at 9 paired sites: (sub)occiput (below the head at the neckline) cervical spine (lower neck), trapezius and supraspinatus (two of the shoulder muscles), second rib (ar near costosternal [rib-breastbone] junction), lateral epicondyle, gluteal region, greater trochanter, and fat pad of the knees. Tender points are provoked by the clinician's application of approximately 9 po fingertip pressure, which is sufficient to cause blanching of the clinician's nail bed. The tender fibromyalgia are distinguished from myofascial trigger points (MFTP, described by Travell[260]) a counterstrain tender points (described in the osteopathic literature by Jones[261]). Pain must have been

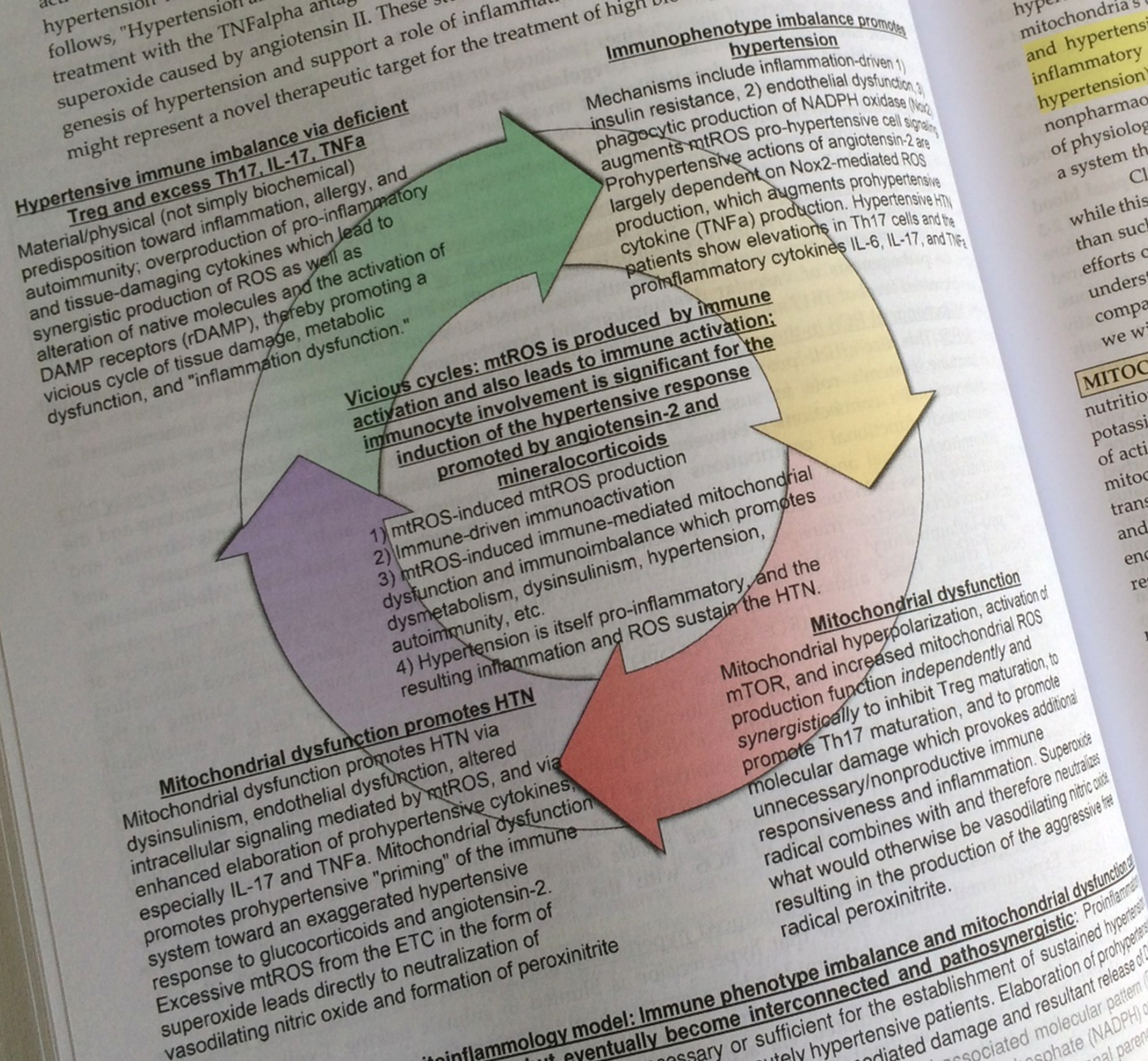
1990 Criteria for the Classification of Fibromyalgia. nfra.net/Diagnost.htm Accessed Nov 2011
Myofascial Pain and Dysfunction. The Trigger Point Manual. Baltimore: Lippincott Williams & Wi
Jones Strain Counterstrain Incorporated, 1995. [ISBN 0964513544]



Gastrointestinal dysbiosis: Assessments

- **History**: Clinicians should suspect gastr constipation/diarrhea, irritable bowel sy sensitivity, severe allergies, and autoim arthritis, and ankylosing spondylitis. Fre by yeast and/or overgrowth of aerobic ba indications for stool testing; however, cl **will have no gastrointestinal symptom *not un*necessary simply because the pat**
- **Breath testing**: Bacterial overgrowth of t **post-carbohydrate hydrogen/methane b** be sufficiently diagnostic.
- **Lactulose-mannitol assay**: The intestinal two tasks: 1) **efficient absorption** of nutr and microbial antigens, and indigestib impairments in nutrient absorption and commonly results in micro- or macro-nu of microbes, antigens, waste products, an

...nide adenosine dinucleotide phosphate (NADPH) oxidase... vicious cycle via which ❶ angiotensin-2 activates NADPH... immune activation (i.e., angiotensin-2 is proinflammatory... and immunocytes-dependent), and ❷ heightened immune... is dependent up... Thus, we see a tripartite... oxidase to produce ROS which the... and its hypertensive effects are ROS-dependent and immunocytes-dependent), ... secretion of IL-17 and TNFa, both of which promote hypertension, and... activation leads to increased secretion of IL-17 and TNFa, both of which promote hypertension... hypertension itself leads to immune activation. These authors articulated part of the vicious cycle as follows, "Hypertension also increased T lymphocyte production of tumor necrosis factor (TNF) alpha, and treatment with the TNFalpha antagonist etanercept prevented the hypertension and increase in vascular superoxide caused by angiotensin II. These studies identify a previously undefined role for T cells in the genesis of hypertension and support a role of inflammation in the basis of this prevalent disease. T cells might represent a novel therapeutic target for the treatment of high blood pressure."



The mitoimmunology and mitoinflammology model: Immune phenotype imbalance and mitochondrial dysfunction are ...pendently (at least initially) but eventually become interconnected and pathosynergistic: Proinflammatory ... experimental models—either necessary or sufficient for the establishment of sustained hypertension ... Th17 cells and serum IL-17 in acutely hypertensive patients. Elaboration of prohypertensive ... simultaneously, immune-mediated damage and resultant release of DAMP... receptor for damaged associated molecular pattern (DAMP)... adenosine dinucleotide phosphate (NADPH) oxidase... ...tic tissues such as renal parenchyma...

- **Therapeutic nutritional immunomodulation...:** we can surmise that the "immune system" and inflammatory responses are necessary... the hypertensive clinical phenotype. Prohypertensive hormones such as glucocorticoids and angio... effect elevated blood pressure through various means, some of which are completely dependent on i... of mitochondrial oxidative stress and the resultant pro-inflammatory immune response; I have te... interdependency "**mitoimmunology**" and "**mitoinflammology**."

Correction of **mitochondrial dysfunction** and **immunophenotype imbalance** are both now... means by which clinicians can modulate dysfunctional pro-hypertensive pathophysiologi... furthermore, we must now appreciate the intimate connection between mitochondrial dysfuncti... the role played by intramitochondrial ROS as cell signaling molecules that promote... hypertension, and autoimmunity) and the immune system, which can now be seen as the... mitochondria's direction. Stated more plainly: Mitochondrial signals (e.g., mtROS) direct the... and hypertensive response of the immune system (which will "over-react" if already i... inflammatory imbalance) to promote harmful inflammation, which I categorize as... hypertension), ❷ allergic, and ❸ autoimmune. These insights provide acce... nonpharmaodependent means by which clinicians can address hypertension via correcti... of physiologic function rather than dependence on pharmacomonkeywrenching—using... a system that is already dysfunctional.

Clinicians have generally considered oxidative stress to be "bad" and antiox... while this is generally true in a quantitative sense, we as intellectually competent clinic... than such broad categories of "good and bad" given that the information is now av... efforts of innumerable named/unnamed researchers, their students, and assistants... understanding, we need to discern the names and characteristics, roles ar... compartmentalization of ROS to better appreciate their participation in health and... we will be better able to help our patients and strengthen the science of our hea...

MITOCHONDRIA/METABOLIC IMPAIRMENT CoQ10 is the most... nutritional/physiological treatment for hypertension; its nearest competitors (... potassium, magnesium, and vitamin D3). Not too many years ago, we were not... of action, and indeed many different antihypertensive actions exist, including... mitochondrial. However, at this time, the mitochondrial mechanism clearly... transfer in the electron transport chain, reducing free radical elaboration; not... and thereby reducing the binding of nitric oxide with superoxide which th... endothelial dysfunction, and the relative/absolute vasoconstriction that... resultant hypertension.

In a personal communication by email in which the current author c... researcher Peter Langsjoen MD FACC (citations[255,256]) about CoQ10's... hypertension, the following reply was received, as quoted in the textb...

Personal communication from Peter H. Lan...

Dear Alex,

In regards to the antihypertensive effect of coenzyme Q10, I do have... The first theory is that coenzyme Q10 (CoQ10) has some influence... some benefit in hypertension. There is one thing that is quite clear, an... vasodilator function because we never see a decrease in blood press... pressures.

My own theory on this subject is that the decrease in blood pres... phenomenon. We have observed that patients with established hy... dysfunction and it is clear that CoQ10 supplementation improves... process requiring a large amount of ATP to re-establish calcium... uncouple. When diastolic function improves, there is a seconda...

[255] Langsjoen PH, Langsjoen AM. Supplemental ubiquinol in patients with advanced co...
[256] Langsjoen P, Langsjoen P, Willis R, Folkers K. Treatment of essential hypertensio...

Inflammation Mastery 4th Edition is now available in digital/ebook format via major bookstores such as Amazon.com and Barnes & Noble.