Innovative “Alternative” Therapies for Chronic Lyme Disease

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Disclosure Statement

I do not have any financial arrangements, or affiliations with any commercial entities whose products, research or services may be discussed in these materials.
Goals/Objectives:

- To understand the multisystem nature and vicious cycle of chronic Lyme disease/CFS/fibromyalgia (FM) and myalgic encephalomyelitis (ME)

- To understand that immune dysfunction, inflammation and TH1-TH2 immune shift are key components in such disorders and understand how to identify significant immune dysfunction

- To understand how immune modulatory therapies can improve diagnostic accuracy, result in symptomatic improvement and significantly increase the likelihood of successful long-term success

- To understand why failure to address these immune abnormalities are common causes of diagnostic and treatment failure and identify potentially beneficial immune modulatory treatments
Questions/Goals?

- Can immune dysfunction be a key to diagnosing chronic Lyme disease?
- Can immune modulation be a key to successful therapy?
Can be very difficult to differentiate syndromes such as CFS/ME/FM and Lyme disease or other chronic infectious illness

CFS/ME describes symptoms; fibromyalgia (FM) describes physical signs and Lyme disease (LD) names one cause of CFS/FM/ME
Small amount of organism can stimulate huge amounts of immune modulatory cytokines and toxins

Antibiotics alone unlikely to fix

TH1-TH2 shift
  - Increased inflammation but decreased ability to fight intracellular infections
Immune Dysregulation (TH1-TH2)
Most patients with chronic (stage III) Lyme disease are generally asymptomatic for a variable time period (months, years)?

Tests can be labeled as inaccurate because they are positive in “asymptomatic” patients?

Do most people carry Borrelia? How about Babesia? Reason for epidemic of obesity, HTN and diabetes?

Maybe a bigger problem than even “WE” believe?
An emotional or physiologic triggering event often occurs under the backdrop of a chronic Lyme infection, which can set into motion a vicious cycle of pathophysiology with immune dysfunction being at the heart of the problem.

Each problem may trigger other problems.

Measurable hypothalamic, pituitary, immune, hormonal and coagulation dysfunction.

After months or years, see significant immune breakdown of TH1 and overstimulation of TH2

May never become symptomatic or continued to be misdiagnosed as other conditions

The longer the duration, generally the worse the immune dysfunction, the worse the symptoms and the more treatment resistant

Coinfections make symptoms worse and harder to treat
Antibiotics as sole therapy rarely results in long-term improvement.

Need multisystem treatment that addresses:
- Immune dysfunction
- Coagulation defect
- Hormonal deficiencies (Hypothalamic/pituitary/thyroid/adrenal)
- Gastrointestinal
- Pain
- Sleep
- Detoxification
- Molds
- Mitochondrial dysfunction
- Nutritional deficiencies
Fast growing infections are generally most susceptible to antibiotics; borrelia has a very slow replication rate with stationary phase and production of persister cells.

LD is slow growing with periods of little or no growth.

- Most antibiotics only work on bacteria in growth phase.
- The slower the growth, the longer it takes to kill.
- Doubling rates for Staph and Strep are about 20 minutes; Borrelia takes 12-24 hours (35-75 times longer--can be much longer when antibiotics are introduced).
- The standard 10-14 days of antibiotics needed to reliably clear most “regular” infections would require the antibiotic to be present 24 hours per day for 1½ to 3 years for the same curative potential.
Immune dysregulation induced by Borrelia and other coinfections can not only impact the ability to diagnose based on indirect methods that require an intact immune system (especially in late-stage), but also the symptomatology and treatment success.

Identification of immune dysfunction can help aid in proper diagnosis

Immune modulatory therapies can improve diagnostic accuracy, result in symptomatic improvement and significantly increase the likelihood of successful long-term outcomes in even the sickest patients.

With later stages, borrelia infection suppresses the production of interferon gamma, which is needed for a robust TH1 (intracellular) immune response including activation of natural killer (NK) cell activity and conversion from IgM to IgG antibodies with a prolonged IgM response (explains high incidence of IgM + WB?)

In contrast, the TH2 T cell response results in an inefficient IL-4 dominated response with the production of non-cytolytic IgM antibodies.

The TH1 response mainly addresses intracellular and extracellular infections while the TH2 response is largely limited to extracellular infections.

Transforming the body to a TH2 “extracellular” dominant response then converting to an intracellular L-form with a downregulated TH1 “intracellular” immune response results in an effective immune evasion strategy that may be the hallmark of transformation to late-stage dissemination.¹,¹⁷,¹⁸
Microscopic Analysis: Dark Field with Immunofluorescent Antibodies

- Test for mainly Borrelia and Babesia
- Very high specificity
- We are finding that it appears that 25-35% of the population has borrelia and/or babesia
- 70-80% of those shown to be infected are “asymptomatic” (unless you take a detailed history)
- Positive test results in asymptomatic patients correlated with TH1 suppression

In house data: Holtorf Medical Group, El Segundo, CA
Microscopic Analysis: dark field with immunofluorescent antibodies

- The majority of the asymptomatic infected patients have low immune function, with low natural killer cell number and function, but they don’t have the elevation in inflammatory markers yet, such as C4a, ECP, HTGF-beta, leptin and immune activation of coagulation (D-dimer, TAT complex, soluble fibrin monomer, prothrombin frag 1 &2, PAI-1, etc.)
- Appears that when these inflammatory markers increase, that is when they become symptomatic
- Possibly aid in prevention of CFS/FM/Chronic Lyme?

In House Data: Holtorf Medical Group, El Segundo, CA
Microscopic Analysis: Dark Field with Immunofluorescent Antibodies

- Our data fits with other unpublished data, such as a study on migrant farm workers—found 20-30% tested positive for Borrelia and/or Babesia by PCR and microscopy.
- Found all but a few percent were asymptomatic.
- Also fits with Stanford study on CFS where patients had immune suppression for, on average, greater than 3 years before they became symptomatic when inflammation kicked-in.

In House Data: Holtorf Medical Group, El Segundo, CA
Multisystem Treatment
(Component Four)

Treat the immune dysfunction along with the Infectious component
Immune Modulating Therapies

- Increase TH1 and decrease TH2
- Boosting NK cell and lowering inflammatory cytokines
  - LDN
  - Peptides (Thymosin alpha-1/Thymosin B4/BPC 157)
  - Heparin
  - Ozone (MAH/Direct/High-dose/10-pass)
  - Leukine/Neupogen
  - Silver
  - Chelation (heavy metals stimulate TH2 and lower TH1)
  - LDA/LDI
  - IVIG (low dose or high dose-give 10-20 iu pitocin IV with each treatment if possible)
  - UVBI
  - Allergy elimination (gluten)
  - Antivirals (The deterioration in HIV is in direct correlation to the TH1/TH2 balance)
  - Antibiotics (do provoked WB, ECP and other immune markers whenever possible)
  - Transfer factors
  - Mushroom extracts
  - Isoprinosine
  - High dose B12
  - Probiotics
  - Antioxidants/Glutathione (low glutathione decreases TH1 and increases TH2)
  - Bee Venom
  - Acupuncture
TH1-TH2 Shift in HIV Determines Progression of Illness

Naltrexone is an opioid competitive antagonist

- At 50 mg, it is used for opioid reversal and treatment of opioid addiction
- At 1.5-6.5 mg it modulates the immune system
  - Reduces inflammation
  - Resets abnormal TH1/TH2 balance
  - Promotes healing
  - Reduces thyroid resistance
  - Promotes weight loss

- At 10-30 mg, it is approved for weight loss with Wellbutrin

- Ultra-low dose at 0.002 mg, it is used with narcotics to increase effect and reduce tolerance, dependence, tachyphylaxis and addiction
Reversible competitive antagonism of LDN transiently blocks the opioid receptor

- This stimulates a positive feedback mechanism to increase production of endogenous opioids (endorphins)

LDN

- LDN blocks the maladaptive neuro-inflammatory cascade that can be associated with chronic infections and other initiating stimuli
- Modulates T and B lymphocyte production
- Shift of immune response from TH2 to TH1
- Promotes healing

20. Donahue RN, McLaughlin PJ, Zagon IS. Low-dose naltrexone targets the opioid growth factor-opioid growth factor receptor pathway to inhibit cell proliferation: mechanistic evidence from a tissue culture model. Experil Biology Med 2011;236(9):1036
Very low incidence of side-effects

Can cause insomnia

- Usually improves after several weeks
- Can take during the day if a problem
- Can use with short-acting narcotics if taken away from narcotic dose (half-life about 4 hours) but do not use with long-acting or potent/high-dose narcotics
- Can use ultra-low dose naltrexone of 0.002 mg

20. Donahue RN, McLaughlin PJ, Zagon IS. Low-dose naltrexone targets the opioid growth factor-opioid growth factor receptor pathway to inhibit cell proliferation: mechanistic evidence from a tissue culture model. Experil Biology Med 2011;236(9):1036
Pilot study (12 FM patients, placebo-controlled, single blind, crossover design)

Primary outcome of self-reported overall FM symptom severity, secondary symptom severity, and mechanical pain testing q two weeks

LDN reduced FM symptoms of FM by 30%

Thirty-two FM patients, randomized, double-blind, placebo-controlled, crossover study

Daily self-reported symptoms: baseline (2 weeks), placebo 4 weeks or LDN 12 weeks and 4 week f/u

LDN reduced FM symptoms of FM by 28.8%

LDN also associated with improved satisfaction with life and improved mood

32% met criteria for response (defined as a significant reduction in pain plus a significant reduction in either fatigue or sleep)

In an open-label study by Horowitz of 1000+ patients with Lyme disease and MSIDS, approximately 75% of patients experienced less fatigue, myalgia, and arthralgia when the naltrexone dose was titrated to 4.5 mg at bedtime.

23. Horowitz open labeled study HVHAC (2009-2016)
Peptide therapy for immune dysfunction in CFS/FM/Chronic Lyme disease
Peptide Therapy

- Short chain of amino acids
- Generally < 70 AA (> 70 becomes a protein)
- Natural, bioidentical or altered (synthetic)
- Seemingly simple peptides are found to be regulate most every known process and system in the body in a tissue specific manner
- While hormone therapy and optimization were a mainstay of antiaging medicine, it is being understood that regulatory peptides are the master controls of many functions of the body, including hormone production
Currently, peptides are available that have been shown to safely and effectively improve and modulate specific parts of hormone production, immune function, the sleep cycle, the production of inflammatory mediators, DNA replication, cell division and renewal, cancer cell destruction and apoptosis, libido and sexual arousal, tissue healing and specific biological functioning of the brain, skin, eyes and urinary and reproductive systems.
Peptides vs Hormones

- Hormones generally work on nuclear receptors with resultant gene activation and protein synthesis.
- Peptides are generally non-genomic that act on membrane receptors to activate an intracellular signaling cascade.
- Peptide signaling molecules generally have more of a rapid response with less side-effects when compared to hormones.
- Peptides have more precise tissue-selective effects, while hormones have less precise broader effects.
Peptide Classes

- Growth Hormone Secretagogues (GHSs)
- Thymosins (immune modulators)
- Pineal hormones
- Melanocyte Stimulating Hormone (MSH) analogues
- Myostatin Inhibitors
- Others
Peptides

- Thymusins (Thymic peptides) for immune modulation
  - Thymosin Alpha 1 (TA1)
  - Thymosin Beta 4 (Tβ4)
Thymosin Alpha 1 (TA1)

- Immune Effects
  - Stimulates T cell production
  - Assists in the development of B cells to plasma cells
  - Increased mitogen response by lymphocytes
  - Decreased production of proinflammatory cytokines
  - Increased chemotactic response and phagocytosis by neutrophils
  - Normalizes immune balance and response
  - Normalizes immune dysfunction
  - Promotes TH2 to TH1 shift

Thymosin Alpha 1 (TA1)

- Clinical Effects
  - Improved tissue repair and healing
  - Improved host defense to infection
  - Improved microcirculation
  - Improves stress tolerance
  - Inhibits viral replication or growth of cancer
  - Improves cancer defense
  - Increases antioxidant and glutathione production
  - Reverse immunosuppression of CFS/FM/Lyme
  - Reduces inflammation

TA1 Applications

- Approved in over 30 countries
  - Vaccine adjunct\textsuperscript{27}
  - Cancer treatment/chemotherapy adjunct\textsuperscript{27-29}
  - Treatment of Hepatitis B and C\textsuperscript{26,28}
  - Treatment of AIDS\textsuperscript{26}
  - Very low incidence of adverse effects
  - FDA approved under Orphan Drug Program in US
TA1 Effects

- Directly suppresses viral and tumor replication and also increases viral and tumor antigenic expression on cell surface, making them more susceptible to immune destruction
  - Possibly same with Lyme?
  - “Not only activating immuno-effector cells or modulating cytokines expression, TA1 also directly exerted its effects on target cells. It could increase the expression of MHC I and tumor antigens, directly depress viral replication, and increase expression of viral antigens on the surface of target-infected cells, making them more visible to the immune system and less prone to escape from immunosurveillance.”

TA1 Effects

TA1: Dual Mode of Action

- **Immunomodulatory**
  - ↑ T-cell production
  - ↑ IL-2, IFN-γ
  - ↓ IL-4, IL-10

- **Antiviral**
  - ↓ T-cell apoptosis
  - ↓ Viral replication
  - ↓ MHC I

**Mechanism of Action**

- Virally infected cell
  - ↓ Viral replication
  - ↓ T-cell apoptosis

- CD4+ T-cell
  - ↑ T-cell production
  - ↑ IL-2, IFN-γ

- CD8+ T-cell
  - ↑ T-cell production

- NK cell
  - ↓ T-cell apoptosis
TA1 Effects

- TA1 significantly improved CD4 levels in mice with metastatic colorectal cancer with multiple liver metastasis.
- Only animals that were cured were ones that got triple treatment x two cycles (5FU/IL2/ZDX).
- Cure rate directly correlated with CD4 improvement.

TA1 Effects

T Helper Cells
TA1 increases Th1 subset

IL-2

Control  ZDX  IFN  ZDX + IFN

IL-4

Control  ZDX  IFN  ZDX + IFN

PBMCs from HCV patients

Th1 (IL-2, IFNγ)

Th2 (IL-4, IL-10)

CD4


TA1 Effects

Natural Killer Cells
TA1 increases activity

Immunorestorative Properties of TA1 in Lung Cancer Patients

- Double blind, randomized trial with 42 pts with localized, unresectable nonsmall cell lung cancer
- TA1 treatment given for up to 1 year following radiation therapy
- Statistically significant improvement in relapse-free survival (P=0.04) and overall survival (P=0.009) which correlated to T cell levels previously depleted by radiation

Bioidentical thymic protein was injected into mice starting at the age of 3.5 months prolonged mean life span by 28%, decreased rate of cancer 2.8 fold.
Thymosin Alpha-1 Dosing

- Ideal patient is CFS/FM/chronic Lyme disease or other chronic infection, Herpes family infection, hepatitis, low immunity, H-pylori, malignancy

- Dosing:
  - SQ: 300-2000 sq qd-q week
  - Titrate to symptoms and goal of TH1 improvement such as NK cell activity and number, CBC, CD counts, immune cell function, IgG subclass improvement and to markers of pathogen activation, including viral/bacterial titers, TMP (coag), ECP, VEGF
BPC-157

- Pentadecapeptide BPC 157, composed of 15 amino acids, is a partial sequence of body protection compound (BPC) that is discovered in and isolated from human gastric juice
- Accelerates the healing of many different wounds, including tendon, ligaments, muscles, nervous system and other organs
- BPC 157 increases growth hormone receptors
- BPC 157 also promotes the outgrowth of tendon fibroblasts, cell survival under stress, and the migration of tendon fibroblasts
- This peptide is also shown to decrease pain in damaged areas

BPC-157

- Protect and prevent gastric ulcers
- Improves digestive function
- Protects and heals inflamed intestinal epithelium (leaky gut)
- It has also been shown to help in Inflammatory bowel disease
- Protects liver from toxic insults (alcohol, antibiotics, etc) and promotes healing
- May protect against acute and chronic toxic effects of alcohol symptoms of alcohol withdrawal\(^2\)
  - May antagonize 5HT2 receptor (high numbers of 5HT2 receptors found in depression and suicidal patients)

“Stable gastric pentadecapeptide BPC 157 is an anti-ulcer peptidergic agent, safe in inflammatory bowel disease clinical trials and wound healing, stable in human gastric juice and has no reported toxicity. Particularly, it has a prominent effect on alcohol-lesions (i.e., acute, chronic) and NSAIDs-lesions (interestingly, BPC 157 both prevents and reverses arthritis)… and acts as a free radical scavenger and exhibits neuroprotective properties.”

BPC 157 Dosing

- Ideal patient is CFS/FM/chronic Lyme disease or other infection, systemic inflammation, autoimmune disease, GI inflammation, leaky gut, H-pylori, joint pain (via intraarticular injection), trigger points, post-surgical/injury

- Dosing:
  - Oral capsule: 500 mcg qd-q week or prn
  - SQ: 300-2000 sq qd-q week
  - Titrate to symptoms and inflammatory markers, such as C4a, ACE, HTGF-beta, CRP, ESR, soluble CD16 and TMP (coag)
Other peptides that can benefit Lyme patients:

- Thymosin B4
- Cerebrolysin
- GHRP/GHRP
- Follistatin (myostatin inhibitor)
- GH Frag 174-191
- PT 141
- Mechano growth factor (MGF-1)
- Epithalon
### Peptide Usage Overview

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Class</th>
<th>Immunity</th>
<th>Inflammation</th>
<th>Libido</th>
<th>Anti-aging</th>
<th>Weight Loss</th>
<th>Cognitive</th>
<th>Antioxidant</th>
<th>Sleep</th>
<th>Dose (i)</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOD</td>
<td>Truncated HGH</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>300-400 mg qd (oral)</td>
<td>Healing, body fat, rejuvenation</td>
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<tr>
<td>Cerebrolysin</td>
<td>Nootropic</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td></td>
<td>+</td>
<td>300-1000 mg qd</td>
<td>Cognitive dysfunction, memory, stroke, dementia, depression, TBI, ADHD</td>
</tr>
<tr>
<td>CJC 1295 + Imaporelin</td>
<td>GHRH/GHPR</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td>300/300-600/500 qd (pulse HRT)</td>
<td>Growth hormone stimulation</td>
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<tr>
<td>Follastatin</td>
<td>Myostatin Blocker</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>600 mg qd</td>
<td>Weight loss, muscle building</td>
</tr>
<tr>
<td>Melanotan II</td>
<td>MSH Analog</td>
<td>+</td>
<td></td>
<td></td>
<td>++</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td>300 mcg q 1-2 weeks</td>
<td>Tanning, weight loss, libido</td>
</tr>
<tr>
<td>PT 141/Bremelanotide</td>
<td>MSH Analog</td>
<td>++</td>
<td></td>
<td></td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td></td>
<td>+</td>
<td>1-2 mg q 1-3 days/week</td>
<td>Libido, weight loss, tanning</td>
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<tr>
<td>SARM</td>
<td>Selective Androgen Receptor</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td>300-400 mg qd</td>
<td>Testosterone agonist w/o estrogen and DHT formation</td>
</tr>
<tr>
<td>Thymosin Alpha 1</td>
<td>TH1 Stimulation</td>
<td>+++</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td>500-1000 mcg/d</td>
<td>Immune boosting for chronic infection, cancer</td>
</tr>
<tr>
<td>Thymosin Beta 4</td>
<td>TH1-TH2 Balance</td>
<td>++</td>
<td></td>
<td>+</td>
<td>++</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td>500 mcg up to 500,000 mcg qd</td>
<td>Immune modulation, cancer, rejuvenation, neuro-regulation</td>
</tr>
<tr>
<td>InflamaPep/BCP 157</td>
<td>Reduce TH2 (Inflammation)</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td>500 mcg qd or 200,000 mcg qd</td>
<td>Systemic or GI inflammation, healing, rejuvenation (GI)</td>
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<tr>
<td>Epithalon</td>
<td>Pineal Gland</td>
<td>+</td>
<td></td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td></td>
<td>+</td>
<td>300-500 mcg/day</td>
<td>Immunity, cancer, sleep, anti-aging, telomere lengthening, DNA repair</td>
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<tr>
<td>MGIF</td>
<td>Sarcopenic IGF-1</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td>300-500 mcg/day</td>
<td>Muscle pain, muscle building</td>
</tr>
</tbody>
</table>

*(i) Above dosing is based on the medical literature and what we have found safe and effective at Holtorf Medical Group; dosing given for SQ delivery (other options potentially available).

**Start low and titrate up in prudent manner.

BTW, peel off 5 days on 2 days off and 4 weeks on and one week off.

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### Go to Hormone

<table>
<thead>
<tr>
<th>Condition</th>
<th>Go to Hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF/EM/ME/Lyme/Chronic Infection</td>
<td>Thymosin Alpha-1/BPC 157 (titrate to normalize NK cell function/Immune cell ATP production/C4a/Human transforming growth factor-beta)</td>
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<tr>
<td>Cognitive Dysfunction/Neuro Damage</td>
<td>Cerebrolysin and Thymosin Beta4</td>
</tr>
<tr>
<td>Aging/Preventive Medicine</td>
<td>Epithalon/Thymosin Alpha/BPC 157</td>
</tr>
<tr>
<td>Sleep</td>
<td>Epithalon</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>Follastatin</td>
</tr>
<tr>
<td>Libido/ED</td>
<td>PT-141</td>
</tr>
</tbody>
</table>
Sargramostim/Filgrastim
(Leukine/Neupogen)

- Granulocyte macrophage colony stimulating factor
- Approved for neutropenia immune dysfunction secondary to cancer and chemotherapy
- Boost TH1 immunity
- Modulates abnormal TH1/TH2 ratio
- Counteracts immune suppression cause by chronic Lyme disease

Dose much lower than standard daily dose:
- Add 2 cc BS water to vial, then dose at 0.01-0.03 sq qd.
- Monitor CBC, chem panel and other immune markers.
- Titrate to response
When to expect Lyme

- Meets criteria for CFS/FM/ME or MSIDS
- More severe forms of CFS/FM
- More neurologic/autonomic symptoms and brain fog
- The more “strange” symptoms the more likely Lyme disease
- The more immune dysfunction the more likely Lyme disease
Low NK cell function < 30 L.U. (TH1)
Low immune cell function (ATP production) (Quest)
low CD 57 (Labcorp, Armin Labs) (TH1)
Elevated C4a (Quest-Nat. Jewish) (TH2)
VEGF (increased with bartonella, suppressed by molds)
Eosinophil cationic protein (Babesia—may only increase after treatment)
ACE above 30
Soluble CD14 (Redlabs/Armin labs)
Immune activation of coagulation (D-dimer, soluble fibrin monomer, prothrombin fragment 1+2, thrombin antithrombin complex, PAI-1) (Lyme/Babesia)
Low Igg subclasses (Secondary to TH1-TH2 shift (low Ifgamma) (lack of TH1)
Leptin above 12
High Human transforming growth factor beta (TH2)
Any band on Quest WB, (even a 41 kd)
  • Provocate with antibiotics before doing indirect testing and/or be sure immune system is functioning before testing
  • Igenex/MDL-any one significant bands or multiple other bands
Low NK cell activity is an objective marker for severe disabling CFS/Lyme

A decrease in the CD57 is a marker for CFS/chronic Lyme disease and significant neurologic disease

30% of CFS/Lyme patients have a low NK cell number

70% have low NK cell function


ACE

Serum Angiotensin-Converting Enzyme as a Marker for the Chronic Fatigue-Immune Dysfunction Syndrome: A Comparison to Serum Angiotensin-Converting Enzyme in Sarcoidosis

Figure 1. Serum ACE levels in CFIDS patients, endemic controls, and non-endemic controls. CFIDS patients from Lyndonville, New York, and Charlotte, North Carolina, are combined as are the two groups of endemic controls.

Serum ACE levels were elevated in 80% of patients with CFIDS and 30% of endemic control subjects as compared with 9.4% of nonendemic California control subjects.
Immune Activation of Coagulation

- Studies have found that 60-90% of CFS/FM/GWS/LD patients have abnormal immune activation of the clotting system.

- 75% having a genetic predisposition for thrombophilia (4 fold increase over general population).

- * ISAC Panel by HEMEX Laboratories was significantly more sensitive than panel available through standard laboratories.

54. Blood Coagulation and Fibrinolysis, 1999
55. Blood Coagulation and Fibrinolysis, 2000
Soluble Fibrin Protofibrils are generated to isolate invading pathogens.

Berg D, The Role of Hypercoagulation and Biofilm in Chronic Illness. April, 2011
Consequences of FIBRIN Deposition?

Nutrients & Hormones Can’t Enter Tissues

Cellular Wastes cannot reenter the blood stream

2 Secs

5.3 Min

RBC

Berg D, The Role of Hypercoagulation and Biofilm in Chronic Illness. April, 2011
Thyroid hormones are large molecules and if there is fibrin coating the vessels they have poor penetration into the cell and have little effect.

“Thyroid in the blood is not doing anything”
Thrombotic Marker Panel

- D-dimer
- Soluble fibrin monomer
- Prothrombin Fragment 1+2
- Thrombin antithrombin complex
- PAI-1 number (activity degrades quickly)
- PAI-1 4G/5G genetic test (4G/4G (about 15% incidence) and 4G/5G have up to a 10 fold increase risk of thrombotic event and IAC)(also increased CA risk)
- Protein C/S activity
- Elevated fibrinogen
- Low PTT

- Low PTT, elevated fibrinogen, increased LP(a) and high homocystine make more likely
Treatment consists of vascular enzymes such as:

- Lumbrokinase (directly activates TPA, degrades fibrin and works intravascular and in intracellular space and reduces Lp(a))
- Natokinase (indirectly acts on TPA and degrades fibrin in intravascular space)
- Serropeptidase (breaks down inflammatory proteins)

- Heparin 1000 to 5000 iu bid.
- Response can be dramatic
- Treatments that previously had no effect become effective
- Biofilm buster
Hypercoagulability and Babesia (TAT)

Fig. 1. Concentration of thrombin-antithrombin III (TAT) complexes

Acta Veterinaria Hungarica 57, 2009
The SFM coating not only limits the oxygen and nutrient flow, but it also provides a place for the virus, yeast and bacterial to “hide” and escape destruction by the immune system.

Can see herx when starting vascular enzymes or heparin
60 patients with CFS

78% were found to have abnormal activation of coagulation

Treated with heparin for 3-20 months (mean 8 months)

Average improvement: 8.5 (1-no improvement, 10-total resolution of symptoms)

Improvement correlated with improvement of coagulation abnormality

In order to have biological activity, the T4 and T3 must, however, cross the cellular membrane from the serum into the target cells.

This “free hormone” or “diffusion hypothesis” was formulated in 1960 and assumes the concentration of free hormones (free T4 and free T3) in the serum determines the rate and extent of uptake into the cell and thus intracellular thyroid hormone concentration.

Holtorf, K. Thyroid Hormone Transport into Cellular Tissue J Restor Med 2014;3(1):53-68
This hypothesis and mechanism of thyroid uptake into the cell has been shown to be totally incorrect.  \(^{1-43}\)

It has been shown that active thyroid hormone transport is the rate-limiting step in the determination of thyroid activity. \(^{5,20,41,44,45}\)

This transport has nothing to do with diffusion, but rather it is energy requiring active transport. \(^{1-43,45,46,47, 48-64,65,66,67}\)

The incorrect “diffusion hypothesis,” however, continues to be taught in medical school and is believed to be true by most physicians and endocrinologists.

Holtorf, K. Thyroid Hormone Transport into Cellular Tissue J Restor Med 2014;3(1):53-68
Because thyroid hormone transport into the cell is energy dependent, any condition associated with a reduced production of the cellular energy (mitochondrial dysfunction) will also be associated with reduced transport of thyroid into the cell, resulting in cellular hypothyroidism despite having standard blood tests in the “normal” range.
Muscle biopsies in CFS patients were examined by electron microscopy. 80% of CFS patients with infectious origin were found to have significant mitochondrial dysfunction.
A remarkable correlation is observed between the degree of mitochondrial dysfunction and the severity of the illness \((p<0.001)\). Only 1 out of 71 patients overlaps the normal region.
Treatment of Mitochondrial Dysfunction

- D-ribose
- Acetyl-L-carnitine
- Carnitine
- B vits
- ALA
- Resveratrol
- Malic Acid
- Ginseng
- CoQ10
- PQQ
- Pregnenolone
- Testosterone
- DHEA
- Serotonin/5HTP
- Growth hormone
- T3
- T2
- AMP
- NAD+
- IV (Myers)
- Ozone
- Estrogen
T2 and Mitochondria

- T3 determines the amount of mitochondrial replication. Thus T3 determines the number of mitochondria.
- T2 directly stimulates mitochondria and regulates mitochondrial activity.

T2 (Mitochondrial Effects)

- T2 thought to be an inactive metabolite of T3
- Does not work through usual T3 nuclear receptor
- Works directly on mitochondria
- If you block T3 to T2 breakdown, you don’t see an increase in metabolism
- Very little side effects, such as stimulation of pulse, jitteriness, insomnia, etc
- Results in increased metabolism, cellular energy, weight loss, increased body temp, cholesterol lowering, reduced insulin resistance

Vos RA et al. Impaired thyroxine and 3,5,3'-triiodothyronine handling by rat hepatocytes in the presence of serum of patients with nonthyroidal illness. J Clin Endocrinol Metab 1995;80:2364-2370

Specific and separate transporters for T4 and T3

The transporter for T4 is much more energy dependent than the transporter for T3\(^5,40,41,49,52,53,66\) (see figure 1)

Even slight reductions in cellular energy (mitochondrial function) results in dramatic declines in the uptake of T4 while the uptake of T3 is much less affected.\(^5,41,62,67\)

Pituitary has completely different transporters that are not energy dependent.

Holmef, K. Thyroid Hormone Transport into Cellular Tissue J Restor Med 2014;3(1):53-68
Cellular Uptake of Thyroid Hormones

Percent drop in cellular energy (above) and severity of stress, depression, cholesterol level, insulin resistance and dieting (below)

Testing Accuracy

- TSH
- T4
- T3
- Free T3/RT3 ratio

Stress, depression, cholesterol level, insulin resistance, dieting

NONE MILD MORE SEVERE VERY SEVERE

HIGH LOW HIGH LOW HIGH LOW HIGH LOW
Thyroid Hormone Transport (Reverse T3)

- How do you tell if you have reduced thyroid transport?
- RT3—The transporter for reverse T3 (rT3) has the same pharmacodynamics and kinetics as the T4.\(^6,41,45,62,66,67\)
- Main reason that rT3 goes up with stress, etc. is reduced transport.
- This property makes rT3 (and SHBG) a useful indicator of diminished transport of T4 into the cell.\(^45\)

References: Thyroid Hormone Transport
Thus, a high reverse T3 demonstrates that there is either increased T4 to reverse T3 formation or an inhibition of reverse T3 uptake into the cell (larger effect).

These two effects occur together in a wide range of physiologic conditions.

High RT3 also indicates that T4 would not be optimal or appropriate therapy.

Holtorf, K. Thyroid Hormone Transport into Cellular Tissue J Restor Med 2014;3(1):53-68
A high reverse T3 can be associated with hyperthyroidism as the body tries to reduce cellular thyroid levels.

Hyperthyroid patients with high RT3 have significantly less symptoms.

This can be differentiated by symptoms and by utilizing the free T3/reverse T3 ratio.

High T3 and reverse T3 can result in symptoms of both high and low.
The pituitary is different than every cell in the body
1,17,43,50,52,55,59,60,61

- Different deiodinases
- Different high affinity thyroid receptors
- Different thyroid transporters that are not energy dependent

Pituitary will maintain or increase the uptake of T4 and T3 in low energy states, while the rest of the body will have significantly reduced transport of T4 and T3 causing intracellular hypothyroidism
1,17,22,43,50,52,55,59,60,61

Holtorf, K. Thyroid Hormone Transport into Cellular Tissue J Restor Med 2014;3(1):53-68
Reverse T3
(blocks cellular uptake of T4 and T3)

Uptake of Reverse T$_3$ in the Human Choriocarcinoma Cell Line, JAR

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Paper accepted 13 July 1998

The uptake and e$^+$ ux of reverse triiodothyronine (rT$_3$) in JAR cells were investigated. Uptake of $^{125}$I-rT$_3$ was time dependent and reversible with a saturable component of around 70 per cent of total uptake after 30 min of incubation. E$^+$ ux was not saturable. Kinetic analysis of the initial specific uptake rates revealed an uptake process with a Michaelis constant of 3.04 ± 0.53 µ (mean ± SD, n=15) and a corresponding maximum velocity of 9.65 ± 2.49 pmol/min/mg protein (n=15). Uptake of rT$_3$ was stereospecific, but not specific for rT$_3$, as unlabelled stereoisomers of thyroid hormone analogues were more effective as inhibitors of $^{125}$I-rT$_3$ uptake than rT$_3$. Unlabelled T$_3$ and thyroxine (T$_4$) (10 µ mol) reduced cellular uptake of $^{125}$I-rT$_3$ by around 82 and 74 per cent, respectively. The calculated inhibition constants Ki were 1.23 ± 0.29 µ (n=4) and 0.66 ± 0.19 µ (n=4) for T$_3$ and T$_4$, respectively. Similarly, rT$_3$ reduced cellular uptake of $^{125}$I-T$_3$ and $^{125}$I-T$_4$ by 34 and 23 per cent, respectively. The calculated inhibition constants Ki were 1.75 ± 0.55 µ (n=8) and 1.08 ± 0.36 µ (n=8) for the inhibition of $^{125}$I-T$_3$ and $^{125}$I-T$_4$ uptake, respectively. Reverse T$_3$ inhibited e$^+$ ux of $^{125}$I-T$_3$ from the cells by around 20 per cent, but did not inhibit e$^+$ ux of $^{125}$I-T$_4$. These results suggest that uptake of rT$_3$ in JAR cells may occur via a single, saturable membrane carrier, which also interacts with T$_3$ and T$_4$, while e$^+$ ux of rT$_3$ may occur by passive diffusion.

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Placenta (1999), 20, 65-70
When cell cultures are incubated with the serum from physiologically stressed or dieting individuals; there is shown to be a dramatic reduction of the uptake of T4 by the cells that correlates with the degree of stress.\textsuperscript{41,42,50}
Serum from non-stressed individuals had no effect on T4 cellular uptake, while those with significant physiologic stress had up to a 44% reduction in T4 uptake into the cell.

It was shown that the free T3/reverse T3 ratio was the most accurate marker for reduced cellular uptake of T4.

Almost all CFS/FM are low thyroid

Combination of secondary/tertiary/reduced T4 to T3 conversion/increased rT3/reduced thyroid transport and thyroid hormone resistance

Holtorf, K. Understanding Local Control of Thyroid Hormones: (Deiodinases Function and Activity. J Restor Med 2014;3(1):1-52
Female fibromyalgia patients: Lower resting metabolic rates than matched healthy controls

John C. Lower, Mrn, Jackie Yellin-Ell, Gina Honeyman-Lowell

Fibromyalgia Research Foundation, Boulder, Colorado, U.S.A.

Source of support: General public to non-profit foundation

Summary

Background: Many features of fibromyalgia and hypothyroidism are virtually the same, and thyroid hormone treatment trials have reduced or eliminated fibromyalgia symptoms. These findings led the authors to test the hypothesis that fibromyalgia patients are hypometabolic compared to matched controls.

Material/Methods: Resting metabolic rate (RMR) was measured by indirect calorimetry and body composition by bioelectrical impedance for 15 fibromyalgia patients and 15 healthy matched controls. Measured resting metabolic rate (mRMR) was compared to percentiles of predicted RMR (pRMR) by free fatty weight (FFW) (Segal-Passmore SP) and by sex, age, height, and weight (Harris-Benedict HB).

Results: Patients had a lower mRMR (4,306.3±1077.66 kJ vs 5,411.50±695.95 kJ, p=0.0028) and lower percentiles of pRMRs (SP: -28.42±15.82% vs -6.83±12.55%, p=0.0000; HB: -29.20±17.43% vs -9.13±9.51%, p=0.0008), whereas FFW, age, weight, and body mass index (BMI) best accounted for variability in controls' RMR, age and fat weight (FW) did for patient. In the patient group, TSH level accounted for 28% of the variance in pain distribution, and free T3 (FT) accounted for 30% of the variance in pressure-pain threshold.

Conclusions: Patients had lower mRMR and percentiles of pRMRs. The lower RMRs were not due to caloric restriction or low FFW. Patients' normal FFW argues against low physical activity as the mechanism. TSH, FT3 and FT, levels did not correlate with RMRs in either group. This does not rule out inadequate thyroid hormone regulation because studies show these laboratory values do not reliably predict RMR.

30% reduction in RMR in FM patients
T3 SR for Fibromyalgia

➢ Summary quote of study on T3 therapy for “euthyroid” FM patients

➢ “It is highly probable, that improvement in fibromyalgia was functionally related to their use of supraphysiologic dosages of T3. These dosages were shown to be safe at a 4 month follow-up.”

➢ No patient met the diagnostic criteria for fibromyalgia by the end of the study”
Analysis of the data in over 150 studies that assessed adrenal function in CFS and FM patients demonstrates that the majority of CFS and FM patients have abnormal adrenal function due to hypothalamic-pituitary dysfunction.

It was also shown that the majority of patients should be treated for this adrenal dysfunction since many of the standard tests do not pick up this particular type of adrenal dysfunction.

(Review) Holtorf K. Diagnosis and Treatment of Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysfunction in Patients with Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM). J Chronic Fatigue Syndrome 2008;14:3:1-14
The data shows that treatment with physiologic doses of cortisol is safer and more effective than commonly used treatments such as antidepressants, pain medications and anticonvulsants.

While these conditions are similar, the abnormality in CFS is in the pituitary while the FM patients have abnormalities of the hypothalamus.

(Review) Holtorf K. Diagnosis and Treatment of Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysfunction in Patients with Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM). J Chronic Fatigue Syndrome 2008;14:3:1-14
The laboratory “normal” range is usually 4-21 ug/dl but if less than 12 ug/dl, there is a 90% chance of having adrenal insufficiency and with less than 10 ug/dl there is a 98% chance of having HPA axis dysfunction.
Ozone (overview)

- Stimulates the production of white blood cells
- Interferon levels are significantly increased
- Stimulates the production of Tumor Necrosis Factor
- Modulates TH1/Th2
- Kills most bacteria at low concentrations
- Effective against all types of fungi
- Fights viruses in a variety of ways
- Antineoplastic
- Increases the flexibility and elasticity of red blood cells
- Makes the anti-oxidant enzyme system more efficient
- Helps with heavy metal detoxification
- Degrades petrochemicals
- Breaks up biofilms
- Oxygenates tissues
Ozone (overview)

- Methods include MAH (indirect), DIV (direct), rozone (rectally), nasally and auricularly (ear) for sinuses and high dose (10-pass)

- Ozone does not work well if low T3 (probably secondary to T2)
Outcomes with Multisystem Treatment

- 500 consecutive patients on computerized outcome assessment demonstrated that a multi-system treatment protocol that addresses the known physiologic abnormalities in CFS and fibromyalgia resulted in:
  - 75 percent noting significant overall improvement
  - 62 percent reported substantial overall improvement.
  - The average energy level and sense of well-being for patients doubled by the fourth visit.

- The effectiveness of this multi-system treatment was further confirmed through the analysis of the cumulative findings of over 40 independent physicians and over 5,000 patients.

- Prior to treatment at the Holtorf Medical Group, the patients had seen an average of 7.2 different physicians for the treatment of CFS and/or FM without significant improvement.

- Lyme patients can certainly be more difficult the of immune modulating therapies has certainly improved outcomes immune system.
Quickly Assess the Risk of Having LD/CFS/FM and Likely Severity

- TSH
- T4, Free
- T3, Free
- Reverse T3
- SHBG
- Cortisol
- ACTH
- DHEA-S
- Pregnenolone
- Vit D (25-OH)
- CBC
- Testosterone F&T
- IGF-1
- IGFBP-3
- Leptin
- Thyroid Peroxidase AB
- Anti-thyroglobulin AB
- Comp Metabolic Panel
- CRP
- Lipid Panel
- Homocysteine
- Hemoglobin A1c
- Insulin
- C4(a) (National Jewish-Quest)
- NK cell activity (Quest)
- Thrombotic Marker panel
  - D-dimer
  - Prothrombin fragment 1+2
  - Thrombin-antithrombin complex
  - SFM
- Natural killer cell # (CD57) (Labcorp)
- ACE
- TFG Beta -1
- Eosinophilic cationic protein (ECP)
- VEGF
- Leptin
- HTGF-beta

Consider:
- RBC Folate
- B12
- Heavy Metals Panel
- RBC Magnesium
- Protein C/S Activity
- Estradiol
- IGG mold panel
- IGG foods
- FSH
- LH
- Progesterone
- CTX/NTX
- DHT
- Chlamydia Pneum
- Mycoplasma
- Candida
- Ehrlichia
- Babesia
- WAI-1 Babesia
- Fibrinogen
 Quickly Assess Risk of Having LD with Likely Severity

- TSH (low)
- T4, Free (high)
- T3, Free (low)
- Reverse T3 (high)
- SHBG (low)
- Cortisol (low)
- ACTH (low)
- DHEA-S (low)
- Pregnenolone (low)
- Vit D (25-OH) (low)
- CBC (low wbc low or high mcv)
- Testosterone F&T (low)
- IGF-1 (low)
- IGFBP-3 (low)
- Leptin (high)

- C4(a) (National Jewish-Quest) (high)
- NK cell activity (Quest) (low)
- Immune cell ATP (Quest) (low)
- Thrombotic Marker panel
  - D-dimer (high)
  - Prothrombin fragment 1+2 (high)
  - Thrombin-antithrombin (high)
  - SFM (high) (+)
- Natural killer cell # (CD57) (Low) (Labcorp)
- ACE (> 35)
- ECP (> 8) stimulate with anti-malarial/anti-parasitics
- VEGF (high) stimulate with antibartonella meds/herbs
- HTGF-beta (high)
Markers of Immune Dysfunction

- Low NK cell function <30
- Low immune cell function (ATP production)
- Low CD 57 (Labcorp)
- Elevated C4a
- VEGF
- Eosinophil cationic protein
- ACE above 30
- Immune activation of coagulation (D-dimer, soluble fibrin monomer, prothrombin fragment 1+2, thrombin antithrombin complex, PAI-1)
- Low IgG subclasses
- Elevated HTGF-beta
Summary

- Lyme disease/CFS/FM are multisystem diseases with a key component being immune dysfunction.

- Being able to identify and treat the immune dysfunction (TH1-TH2 shift) that is consistently seen with these illnesses can improve diagnostic accuracy, result in significant symptomatic improvement and significantly increase the likelihood of successful long-term success.

- Multisystem treatments that address the underlying multisystem abnormalities, including LDN, peptide therapies, T3, cortisol, sargramostim/filgrastim, ozone and low dose heparin can be very effective for non-responsive patients.
Thank You

Questions?

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