Innovative "Alternative" Therapies for Chronic Lyme Disease

Kent Holtorf, M.D.
Holtorf Medical Group
National Academy of Hypothyroidism
Kholt@holtorfmed.com

AARM Regional Conference
Overcoming Diagnostic & Treatment Challenges of Lyme Disease, Infectious Diseases & CFS
Seattle, Washington, 2017

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?

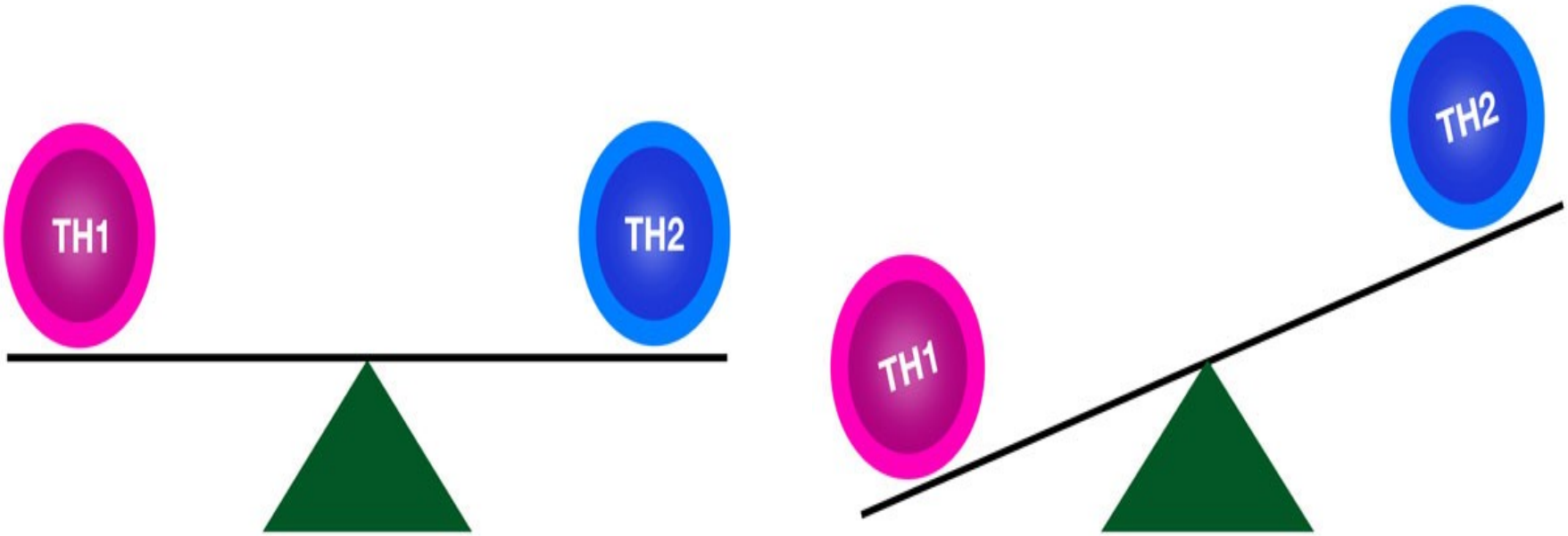
Multisystem Disease

- 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

Multisystem Disease

- 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)



Multisystem Disease

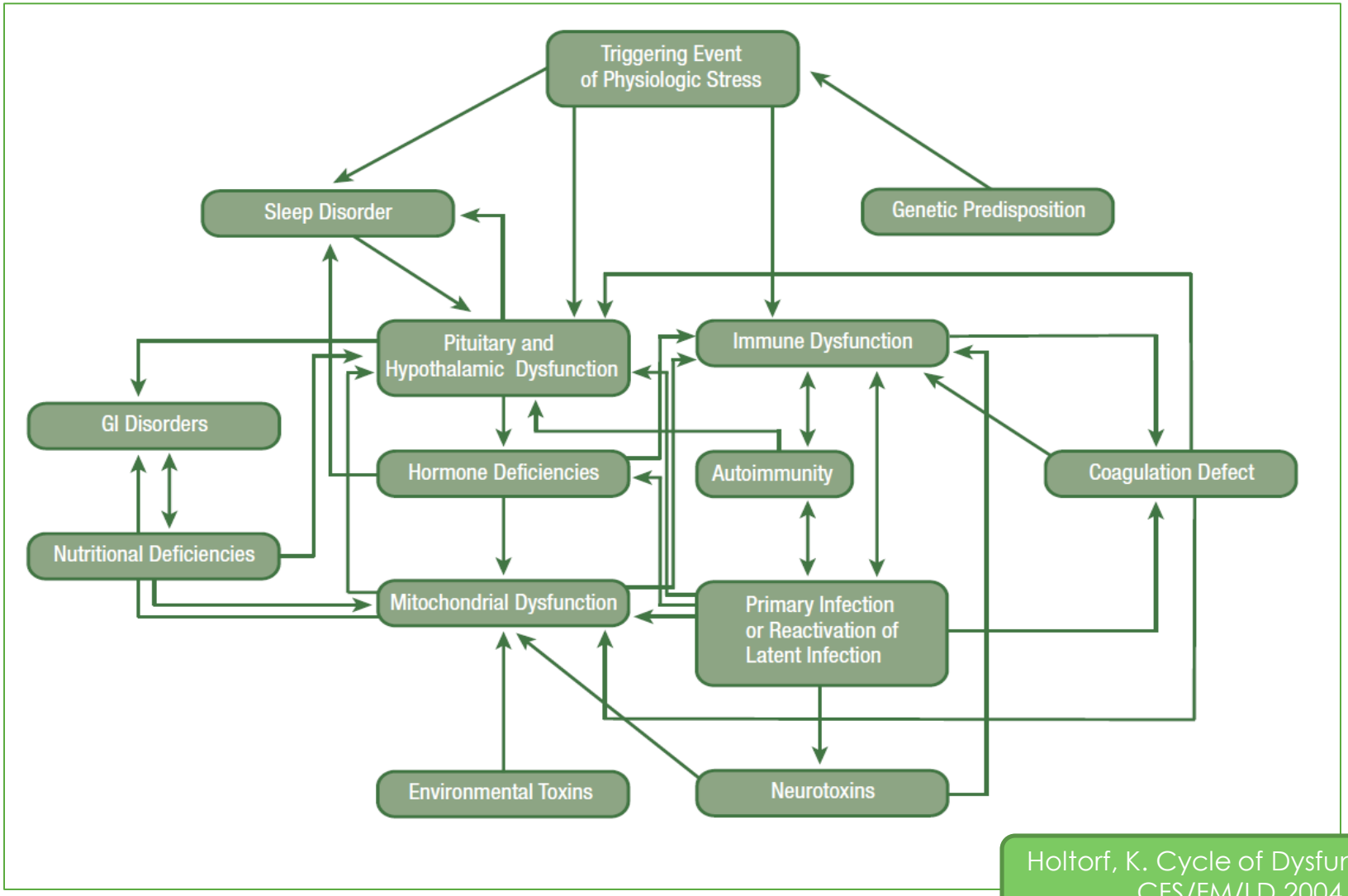
- Most patients with chronic (stage III) Lyme disease are generally asymptomatic for a variable time period (months, years)?
- Tests can be labeled as inaccurate because they are positive in "asymptomatic" patients?
- Do most people carry Borrelia? How about Babesia? Reason for epidemic of obesity, HTN and diabetes?
- Maybe a bigger problem than even **"WE"** believe?

Multisystem Disease

- An emotional or physiologic triggering event often occurs under the back-drop 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

Holtorf, K. A Confounding Condition: Treating chronic fatigue syndrome and fibromyalgia requires addressing the underlying problems. Healthy Aging 2008;Nov:1-7

Cycle of Dysfunction with LD



Holtorf, K. Cycle of Dysfunction of CFS/FM/LD 2004

Chronic Lyme Disease

- 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

Multisystem Disease

- 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

Immune Evasion

- Fast growing infections are generally most susceptible to antibiotics; borrelia has a very slow replication rate with stationary phase and production of persister cells[7]
- 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.**[67]

Immune Dysregulation

- 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

1. McManus M, Cincotta A. Advances in Integrative Medicine. Adv Integ Med 2015;2:81-89.

Immune Dysregulation

- 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.

1. McManus M, Cincotta A. Advances in Integrative Medicine. Adv Integ Med 2015;2:81-89.

Immune Dysregulation

- 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 Immunofluorescencent 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 immunofluorescencent 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 Immunofluorescencent 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

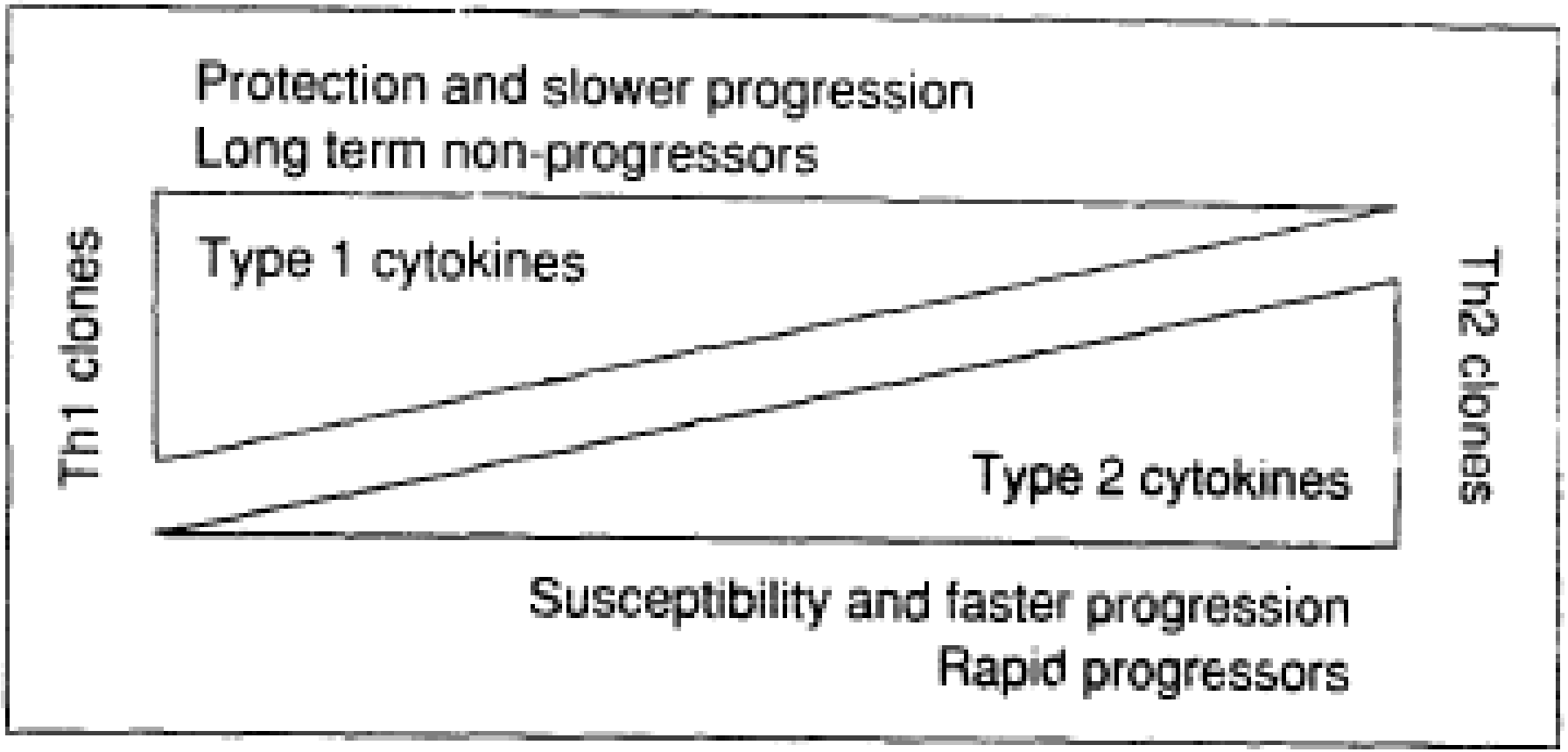
Multisystem Treatment (Component Four)

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 provocated 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
  - Acupunture

TH1-TH2 Shift in HIV Determines Progression of Illness



70. Clerici M, Shearer, GM. The Th1-Th2 hypothesis of HIV infection: new insights. Immunology Today 1994;15(12):575-581

LDN

- 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, tachyphylxis and addiction

LDN

- Reversible competitive antagonism of LDN transiently blocks the opioid receptor
  - This stimulates a positive feedback mechanism to increase production of endogenous opioids (endorphins)

1. McManus M, Cincotta A. Advances in Integrative Medicine. Adv Integ Med 2015;2:81-89.

LDN

- LDN blocks the maladaptive neuro-inflamatory 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

LDN

- 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

LDN

- 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%

21. Younger J, Mackey S. Fibromyalgia Symptoms Are Reduced by Low-Dose Naltrexone: A Pilot Study. *Pain Med*. 2009 ; 10(4): 663–672.

LDN

- 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)

22. Younger J, Noor N, McCue R, Mackey S. Low-Dose Naltrexone for the Treatment of Fibromyalgia. Arthritis & Rheum 2013;65(2):529-538.

LDN

- 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)

Peptides

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

Peptide Therapy

- 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 Secretaogoues (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

10. Morozov, V.G. and V.K. Khavinson, *Natural and synthetic thymic peptides as therapeutics for immune dysfunction.* International. Journal of Immunopharmacology, 1997. **19**(9-10): p. 501-505.

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

10. Morozov, VG, Khavinson, K *Natural and synthetic thymic peptides as therapeutics for immune dysfunction.* International. Journal of Immunopharmacology, 1997. **19**(9-10): p. 501-505.

TA1 Applications

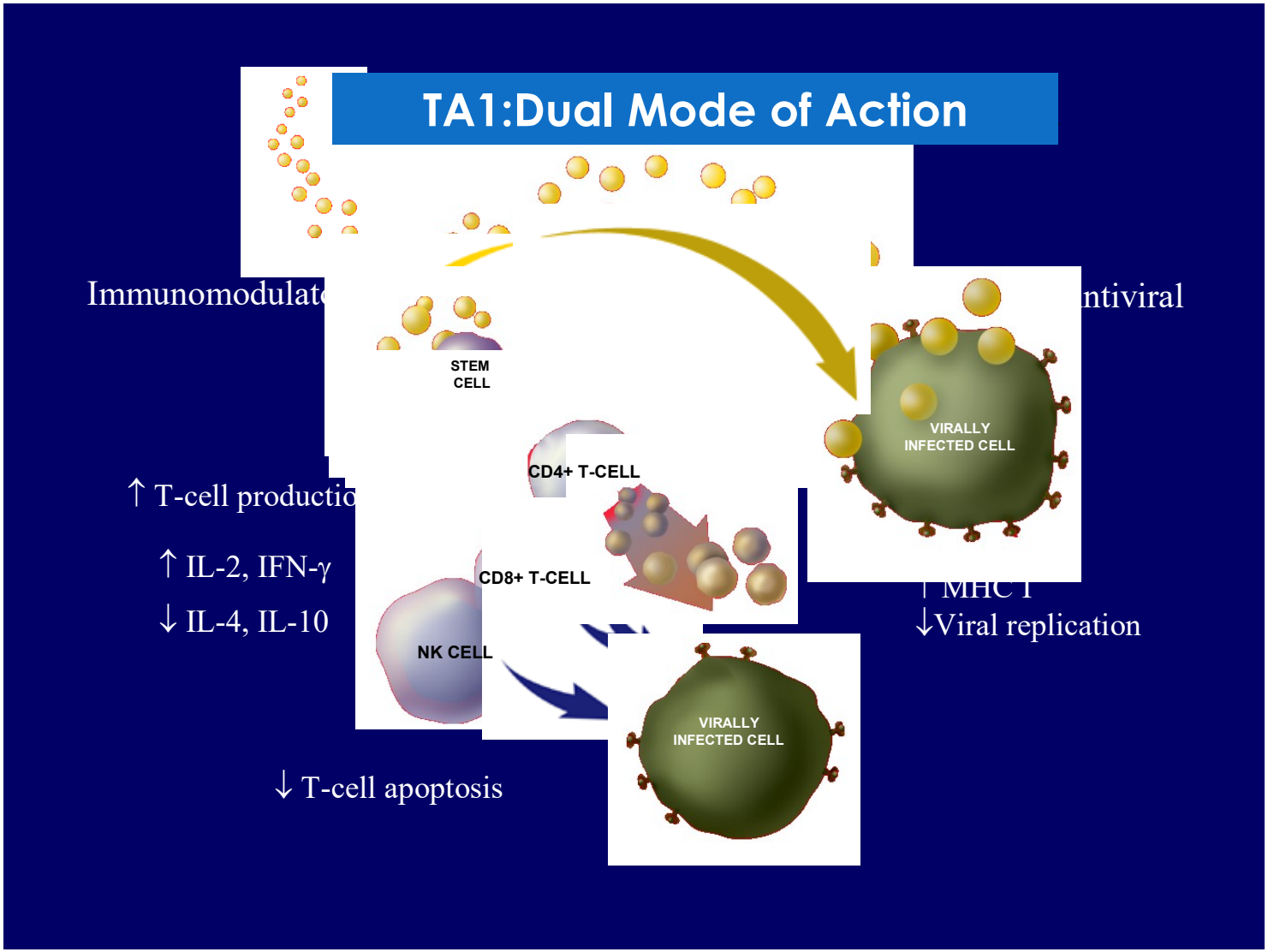
- Approved in over 30 countries
  - Vaccine adjunct[27]
  - Cancer treatment/chemotherapy adjunct[27-29]
  - Treatment of Hepatitis B and C[26,28]
  - Treatment of AIDS[26]
  - Very low incidence of adverse effects
  - FDA approved under Orphan Drug Program in US

TA1 Effects

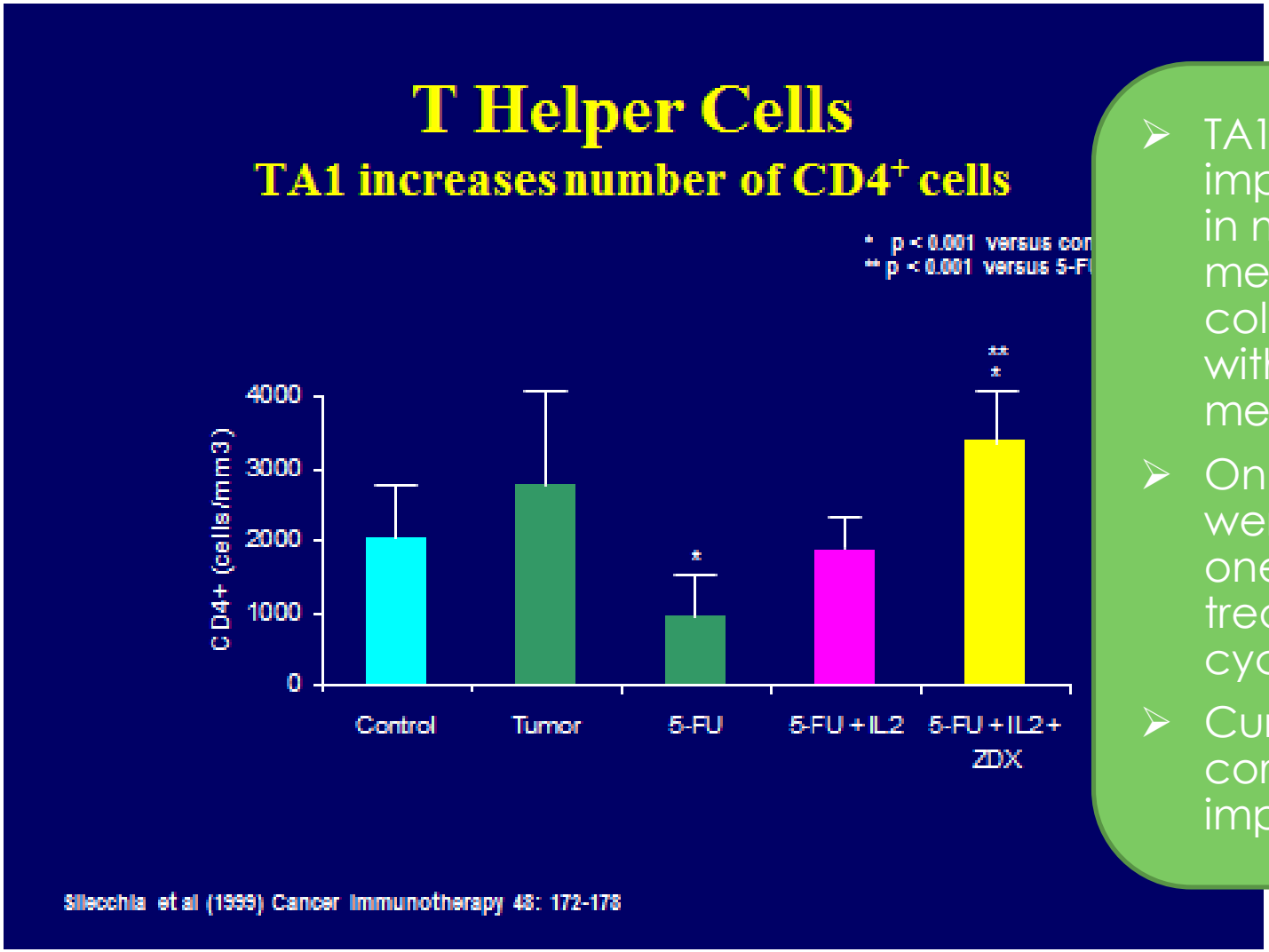
- Directly suppresses viral and tumor replication and also increases viral and tumor antigenic expression on cell surface, making them more susceptible to immune destruction
  - Possibly same with Lyme?
  - *"Not only activating immuno-effector cells or modulating cytokines expression, TA1 also directly 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."*[26]

26. Li J, Liu CH, Wang FS. Thymosin alpha 1: biological activities, applications and genetic engineering production. Peptides. 2010 Nov 30;31(11):2151-8.

TA1 Effects

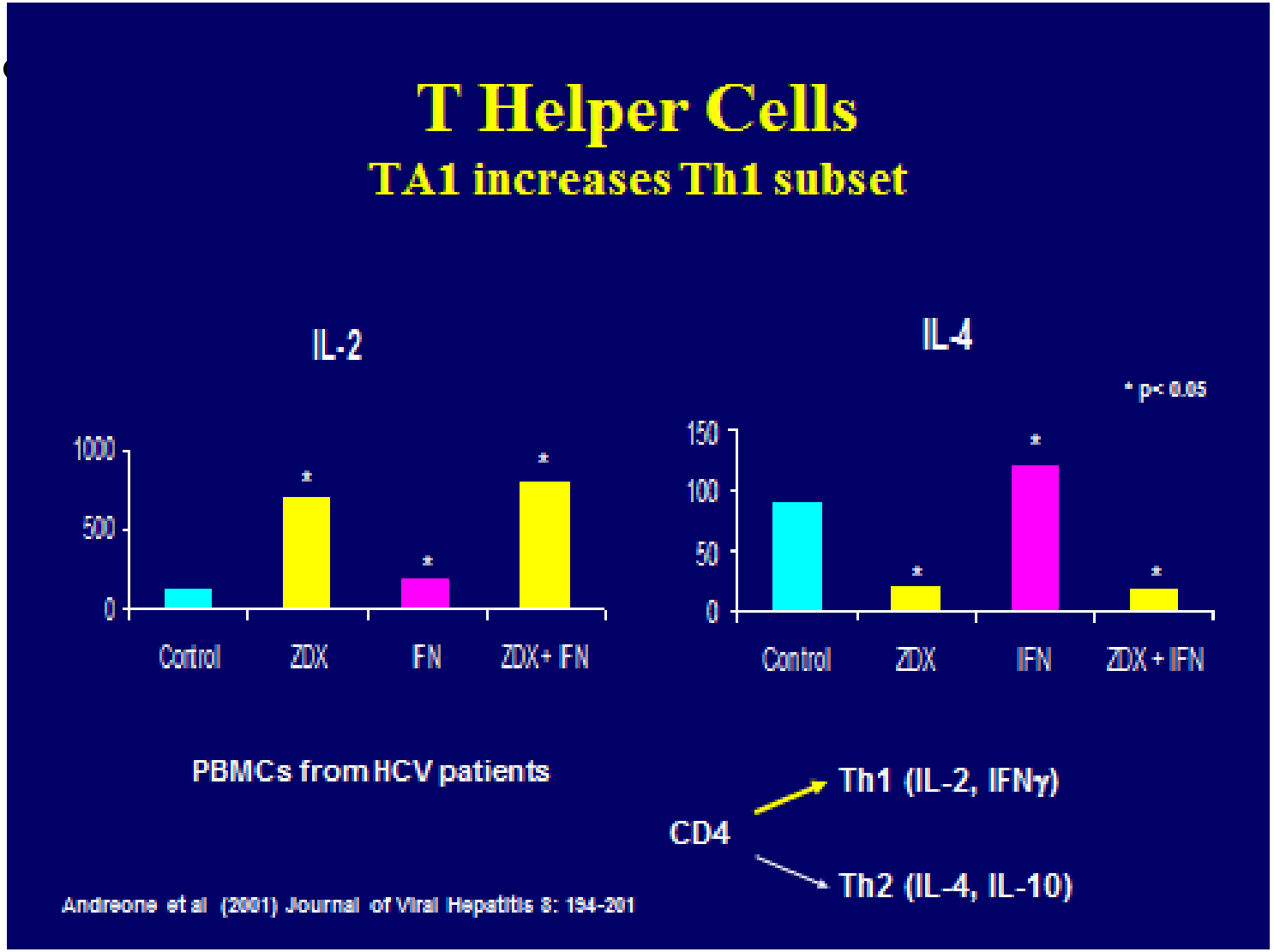

TA1:Dual Mode of Action
Immunomodulat
ntiviral
STEM CELL
CD4+ T-CELL
CD8+ T-CELL
NK CELL
VIRALLY INFECTED CELL
VIRALLY INFECTED CELL
↑ T-cell productio
↑ IL-2, IFN-γ
↓ IL-4, IL-10
↑ MHC I
↓Viral replication
↓ T-cell apoptosis

TA1 Effects

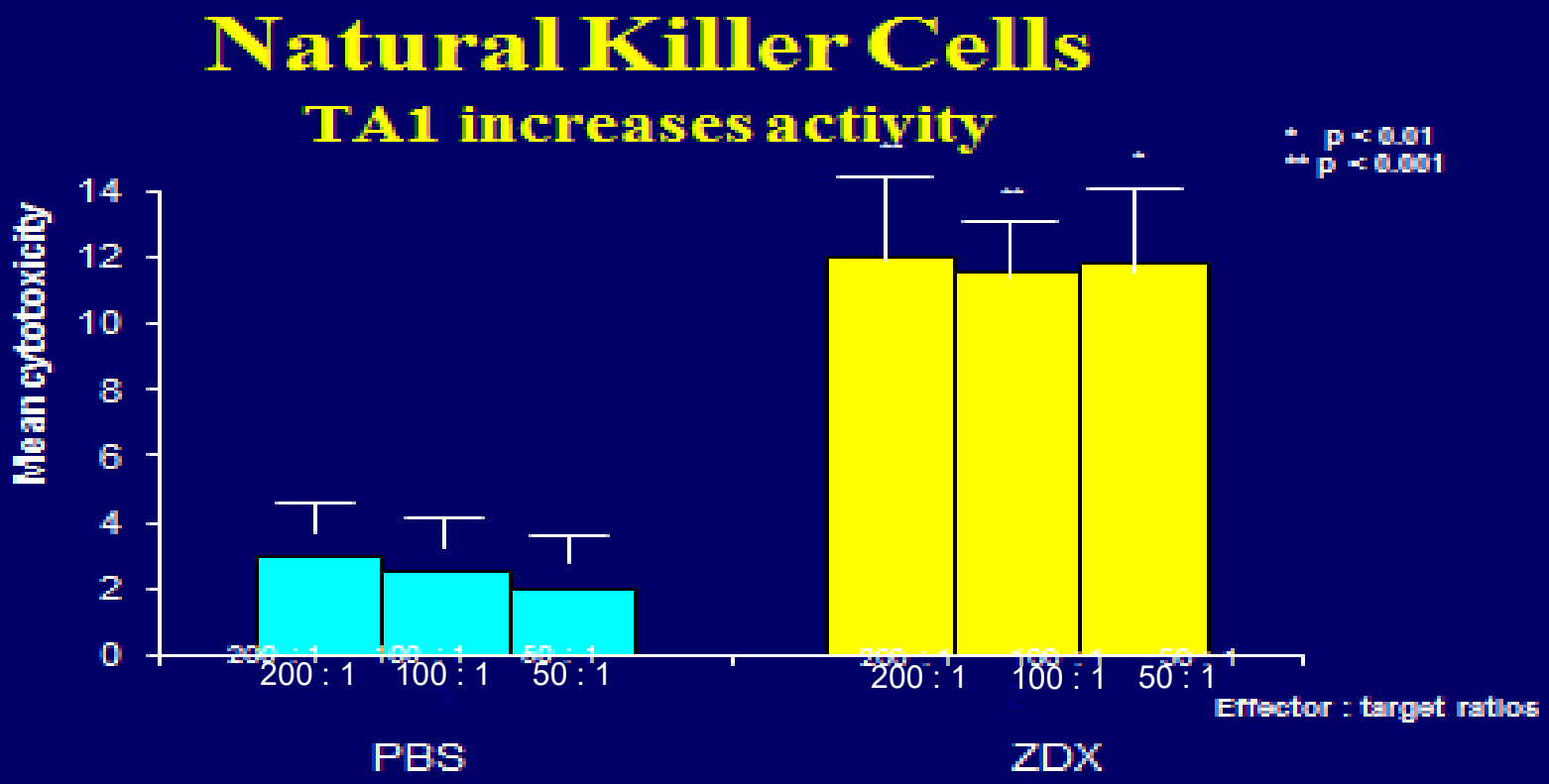


- TA1 significantly improved CD4 levels in mice with metastatic colorectal cancer with multiple liver metastasis
- Only animals that were cured were ones that got triple treatment x two cycles (5FU/IL2/ZDX)
- Cure rate directly correlated with CD4 improvement

TA1 Effects


T Helper Cells
TA1 increases Th1 subset
IL-2
1000
500
0
Control
ZDX
IFN
ZDX+ IFN
IL-4
* p< 0.05
150
100
50
0
Control
ZDX
IFN
ZDX + IFN
PBMCs from HCV patients
CD4
Th1 (IL-2, IFNγ)
Th2 (IL-4, IL-10)
Andreone et al (2001) Journal of Viral Hepatitis 8: 194-201

TA1 Effects



Shiau et al (1988) J Formosan Med Assoc 87: 34-42

Immunorestorative Properties of TA1 in Lung Cancer Patients

- Double blind, randomized trial with 42 pts with localized, unresectable nonsmall cell lung cancer
- TA1treatment 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**

31. Schulof, R.S. et al. 1985. A randomized trial to evaluate the immunorestorative properties of synthetic thymosin-alpha 1 in patients with lung cancer. J. Biol. Response Modif. 4: 147–158.

Antiaging Properties of Thymic Protein

- Bioidentical thymic protein was injected into mice staring at the age of 3.5 months **prolonged mean life span by 28%, decreased rate of cancer 2.8 fold**

24. Morozov VG, Khavinson KH. Natural and synthetic peptides and immune dysfunction. Int J Immunopharmac 1997;19(9/10):501-5

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

42. Sikiric P, Seiwerth S, Rucman R, et al. Stable gastric pentadecapeptide BPC 157: novel therapy in gastrointestinal tract. Curr Pharm Des 2011;17(16)1612-32
43. Boban-Blagaic A, Vladimir Blagaic, et al. The influence of gastric pentadecapeptide BPC 157 on acute and chronic ethanol administration in mice. The effect of NG -nitro-L-arginine methyl ester and L-arginine. Med Sci Monit, 2006; 12(1): BR36-45

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)

42. Sikiric P, Seiwerth S, Rucman R, et al. Stable gastric pentadecapeptide BPC 157: novel therapy in gastrointestinal tract. Curr Pharm Des 2011;17(16)1612-32
43. Boban-Blagaic A, Vladimir Blagaic, et al. The influence of gastric pentadecapeptide BPC 157 on acute and chronic ethanol administration in mice. The effect of NG -nitro-L-arginine methyl ester and L-arginine. Med Sci Monit, 2006; 12(1): BR36-45

BPC-157

"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."[42]

42. Sikiric P, Seiwerth S, Rucman R, et al. Stable gastric pentadecapeptide BPC 157: novel therapy in gastrointestinal tract. Curr Pharm Des 2011;17(16)1612-32

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)

Peptides

- 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 Overview

Peptide Usage Overview

Holtorf, Kent Innovative "Alternative" Therapies for Chronic Lyme Disease, ILADS, Philadelphia, PA 2016;
Holtorf, Kent. Introduction to Peptide Therapy for the Age-Management Physician, A4M, Las Vegas, NV 2016

	Class	Immunity	Inflammation	Libido	Anti-aging	Weight Loss	Cognitive	Antioxidant	Sleep	Dose (1)	Conditions
AOD	Truncated HGH		+		+	+	+		+	120-500 mcg qd (pulse)	Healing, body fat, rejuvination
Cerebrolysin	Nootropic	+	++		++		+++	++	+	200-1000 mcg qAM	Cognitive dysfunciton, memory, stroke, dementa, depression, TBI, ADHD
CJC 1295 + Ipamorelin	GHRH/GHRP	+			+	+	+		+	200/200-500/500 qd (pulse)(1b)	Growth hormone stimulation
Follastatin	Myostatin Blocker					+++				100-200mcg 1-2 x/week	Weight loss, muscle building
Melanotan II	MSH Analog			+		++				200 mcg q 1-2 weeks	Tanning, weight loss, libido
PT 141/Bremelanotide	MSH Analog			+++		+				1-2 mg q 1-3 days prn	Libido, weigh loss, tanning
SARM	Selective Androgen Receptor			+	+	+				200-400 mcg 2x/ week	Testosteorne agonist w/o estrogen and DHT formation
Thymosin Alpha 1	TH1 Stimulation	+++	+		+		+	+		300-1000 mcg qd	Immune boosting for chronic infection, cancer
Thymosin Beta 4	TH1-TH2 Balance	++	++		++		++	++	+	300-1000 mcg qd	Immune modulation, cancer, rejuvination, neurorejuvination
InflamaPep/BCP 157	Reduce TH2 (Inflamation)	+	+++		++		+	+		500 mcg qd to q week oral; 200-1000 mcg qd - q week	Systemic or GI inflamation , helaing, rejuvinaition (GI
Epithalon	Pineal Gland	+			+++		++	++	++	300-1000 mcg/ day	Immunity, cancer, sleep, anti-aging, telomere lengthening, DNA repair
MGF	Sarcopenic IGF-1				+	+	+			200-500 mcg/day	Muscle pain, muscle building

(1) 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).
**Dosing are suggested guidelines; clinical and labatory assessment is required
***Start low and titrate up in prudent manner
(1b) Pulsing suggested 5 days on 2 days off and 4 weeks on and one week off.

Condition	Go to Hormone
CFS/FM/ME/Lyme/Chronic Infection	Thymosin Alpha-1/BPC 157 (titrate to normalize NK cell function/Immune cell ATP production/C4a/Human transforming growth factor-beta)
Cognitive Dysfunction/Neuro Damage	Cerebrolysin and Thymosin Beta4
Aging/Preventive Medicine	Epithalon/Thymosin Alpha/BPC 157
Sleep	Epithalion
Weight Loss	Follistatin
Libido/ED	PT-141

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

Using Immune Dysfunction to Diagnose Lyme

- 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

Identification of Immune Dysfunction

- 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)
  - Provacate 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

NK Cell

- 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

51. Ojo-Amaize EA, Conley EJ, Peter JB. Decreased natural killer cell activity is associated with severity of chronic fatigue immune dysfunction syndrome. Clin Infect Dis. 1994 Jan;18 Suppl 1:S157-9.

52. Clin Infect Dis 1994
Stricker RB, Winger EE. Decreased CD57 lymphocyte subset in patients with chronic Lyme disease. Immunol Lett. 2001 Feb 1;76(1):43-8.

ACE

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

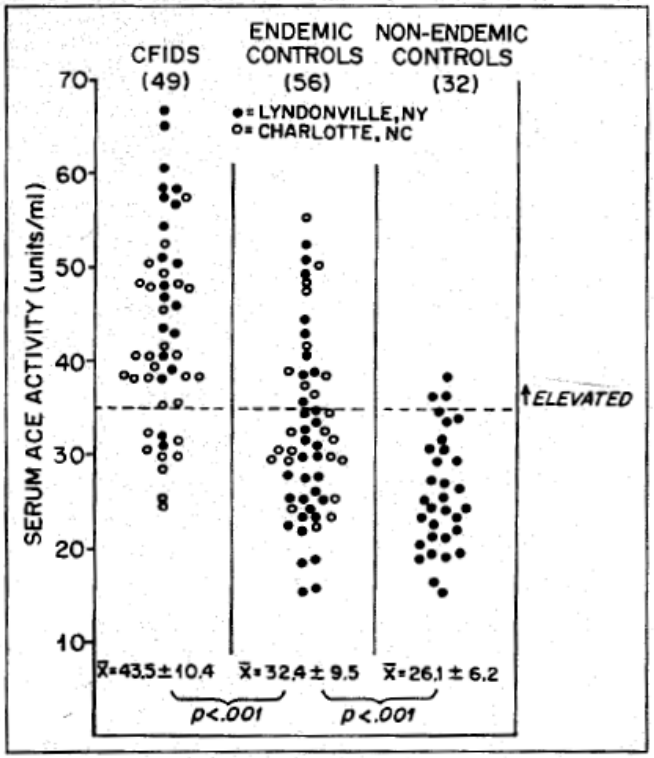


Figure 1. Serum ACE levels in CFIDS patients, endemic controls, and nonendemic controls. CFIDS patients from Lyndonville, New York, and Charlotte, North Carolina, are combined as are the two groups of endemic controls.

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

53. American Journal of Medicine, 1993

Immune Activation of Coagulation

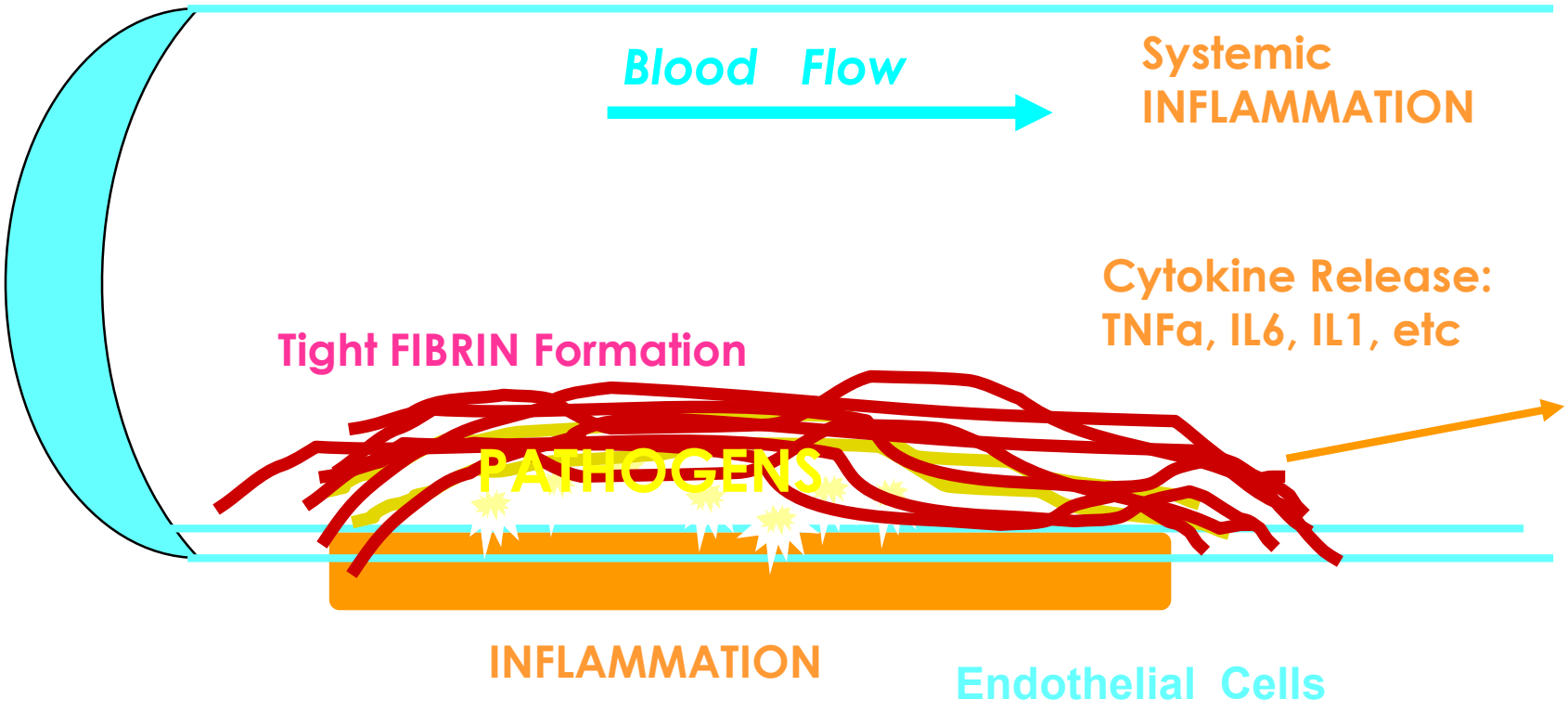
- Studies have found that 60-90% of CFS/FM/GWS/LD patients have abnormal immune activation of the clotting system
- 75% having a genetic predisposition for thrombophilia (4 fold increase over general population)
  - ISAC Panel by HEMEX Laboratories was significantly more sensitive than panel available through standard laboratories

Christ, Berg et al. Does Borreliosis Activate the Coagulation System and is Coag Regulatory Protein Defect predispostional? IDSA, Oct 2003
54. Blood Coagulation and Fibrinolysis, 1999
55. Blood Coagulation and Fibrinolysis, 2000
56. American Association of Clinical Chemistry, 2003

Immune Activation of Coagulation

HOST DEFENSE MECHANISMS

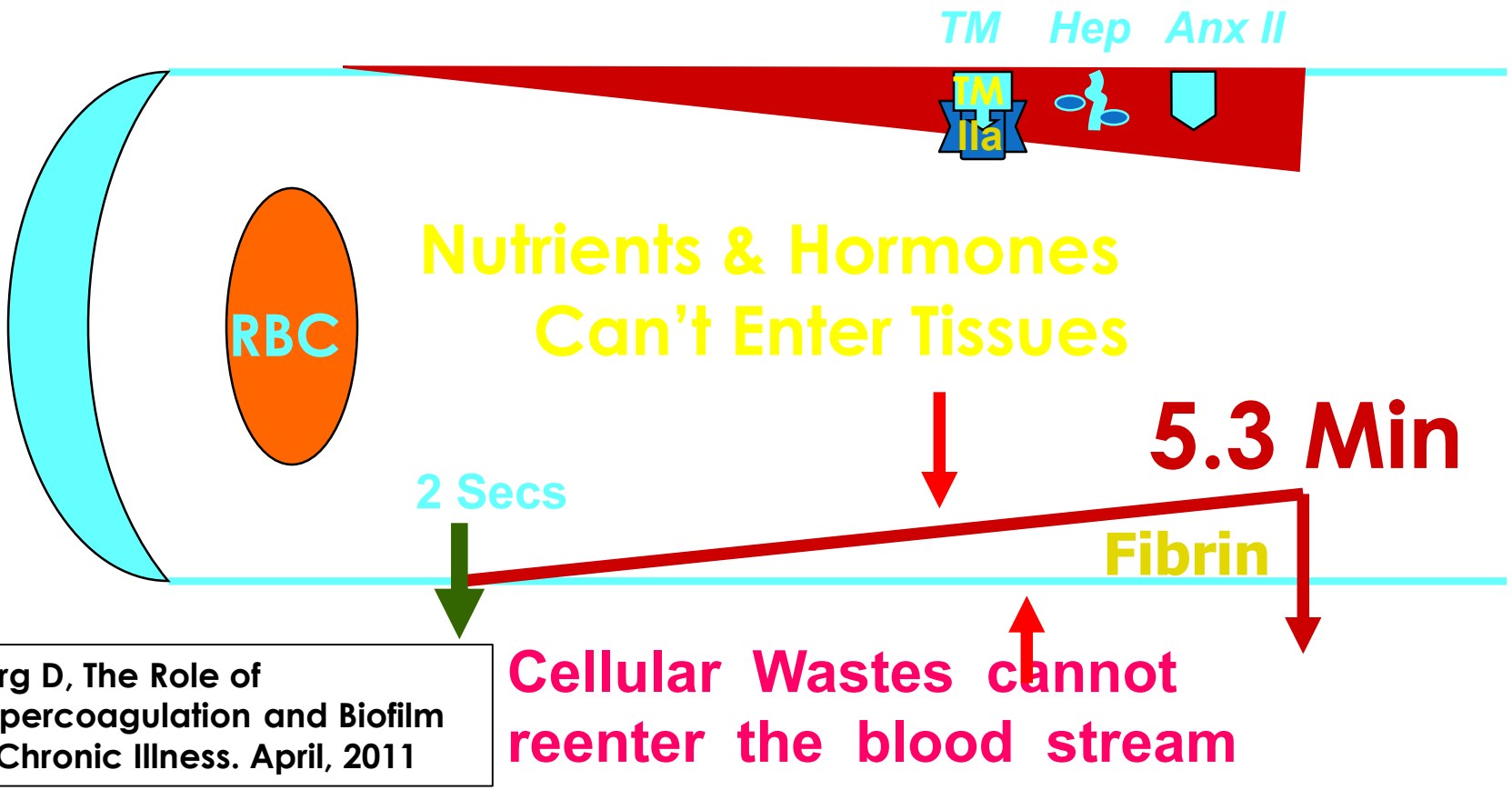
Berg D, The Role of Hypercoagulation and Biofilm in Chronic Illness. April, 2011



Soluble Fibrin Protofibrils are generated to isolate invading pathogens.

Immune Activation of Coagulation

Consequences of FIBRIN Deposition?



Berg D, The Role of Hypercoagulation and Biofilm in Chronic Illness. April, 2011

Immune Activation of Coagulation

- 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"

Immune Activation of Coagulation

- 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

Immune Activation of Coagulation

- 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 inflamatory 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)

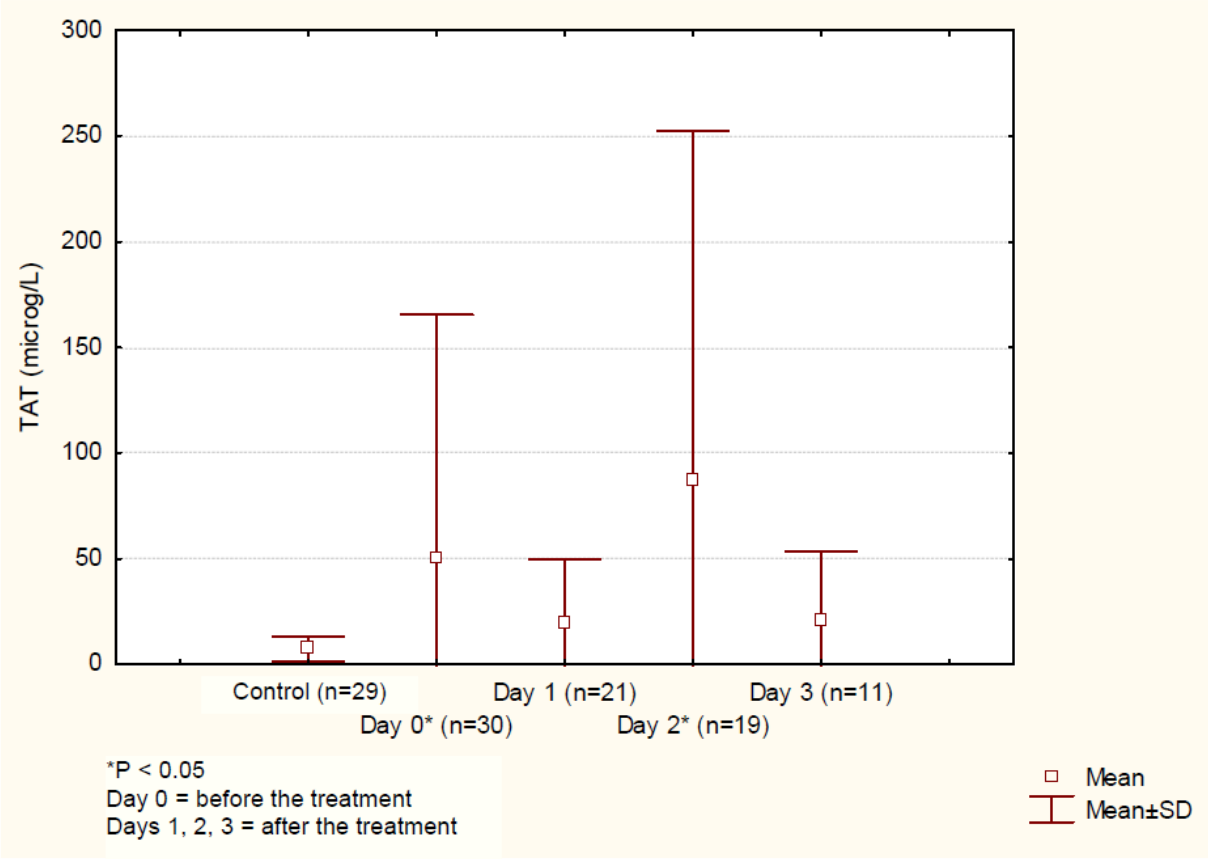


Fig. 1. Concentration of thrombin-antithrombin III (TAT) complexes

Acta Veterinaria Hungarica 57, 2009

Immune Activation of Coagulation

- 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

Immune Activation of Coagulation

- 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

56. American Association of Clinical Chemistry, 2003

Thyroid Hormone Transport

- 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

Thyroid Hormone Transport

- 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

Thyroid Hormone Transport

- 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.

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

Mitochondrial Dysfunction in CFS

Mitochondrial abnormalities in the postviral fatigue syndrome*

W. M. H. Behan[1], I. A. R. More[1], and P. O. Behan[2]

Departments of [1]Pathology, and [2]Neurology, University of Glasgow, Scotland

Received February 1, 1991/Revised April 24, 1991/Revised, accepted August 5, 1991

Summary. We have examined the muscle biopsies of 50 patients who had postviral fatigue syndrome (PFS) for from 1 to 17 years. We found mild to severe atrophy of type II fibres in 39 biopsies, with a mild to moderate excess of lipid. On ultrastructural examination, 35 of these specimens showed branching and fusion of mitochondrial cristae. Mitochondrial degeneration was obvious in 40 of the biopsies with swelling, vacuolation, myelin figures and secondary lysosomes. These abnormalities were in obvious contrast to control biopsies, where even mild changes were rarely detected. The findings described here provide the first evidence that PFS may be due to a mitochondrial disorder precipitated by a virus infection.

Key words: Postviral fatigue syndrome – Branching and fusion of mitochondria – compartmentalization – Mitochondrial vacuolation

laboratory ha
tion and a
patterns (in p
The lack
very difficult
has not beer
Attempts hav
diagnosis, wit
nately, the te
selected and
since fatigue
medical and
"postviral fati
the basis that th
the time of a viral
since then. The fatigue appears to have a central nervous system component because there is no lack of power on testing but the patient has to make a determined effort to carry out simple routine tasks. It is also invariably accompanied by depression, a reduced ability to concen-

Muscle biopsies in CFS patients were examined by electron microscopy. 80% of CFS patients with infectious origin were found to have significant mitochondrial dysfunction

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

Mitochondrial Dysfunction in CFS

Int J Clin Exp Med (2009) 2, 1-16
www.ijcem.com/IJCEM812001

Original Article

Chronic fatigue syndrome and mitochondrial dysfunction

Sarah Myhill[1], Norman E. Booth[2], John McLaren-Howard[3]

[1]*Sarah Myhill Limited, Llangunllo, Knighton, Powys, Wales LD7 1SL*
College, University of Oxford, Oxford OX1 3RH, UK; [3]*Acumen, PO Bo*

Received December 2, 2008; accepted January 12, 2009; available

Abstract: This study aims to improve the health of patients suffe
interventions based on the biochemistry of the illness, specifically
(adenosine triphosphate), the energy currency for all body function
to replenish the ATP supply as needed. Patients attending a priva
diagnosed using the Centers for Disease Control criteria. In consult
Ability Scale was assigned, and a blood sample was taken for the
fatigue conditions. Each test produced 5 numerical factors which de
the fraction complexed with magnesium, the efficiency of oxidative phosphorylation, and the transfer efficiencies
of ADP into the mitochondria and ATP into the cytosol where the energy is used. With the consent of each of 71
patients and 53 normal, healthy controls the 5 factors have been collated and compared with the Bell Ability
Scale. The individual numerical factors show that patients have different combinations of biochemical lesions.
When the factors are combined, a remarkable correlation is observed between the degree of mitochondrial
dysfunction and the severity of illness ($P<0.001$). Only 1 of the 71 patients overlaps the normal region. The "ATP
profile" test is a powerful diagnostic tool and can differentiate patients who have fatigue and other symptoms as
a result of energy wastage by stress and psychological factors from those who have insufficient energy due to
cellular respiration dysfunction. The individual factors indicate which remedial actions, in the form of dietary
supplements, drugs and detoxification, are most likely to be of benefit, and what further tests should be carried
out.

"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

Goglia F, et al. Action of thyroid hormones at te cellular level: the mitochondrial target. FEBS Letters 1999;452:115-20

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

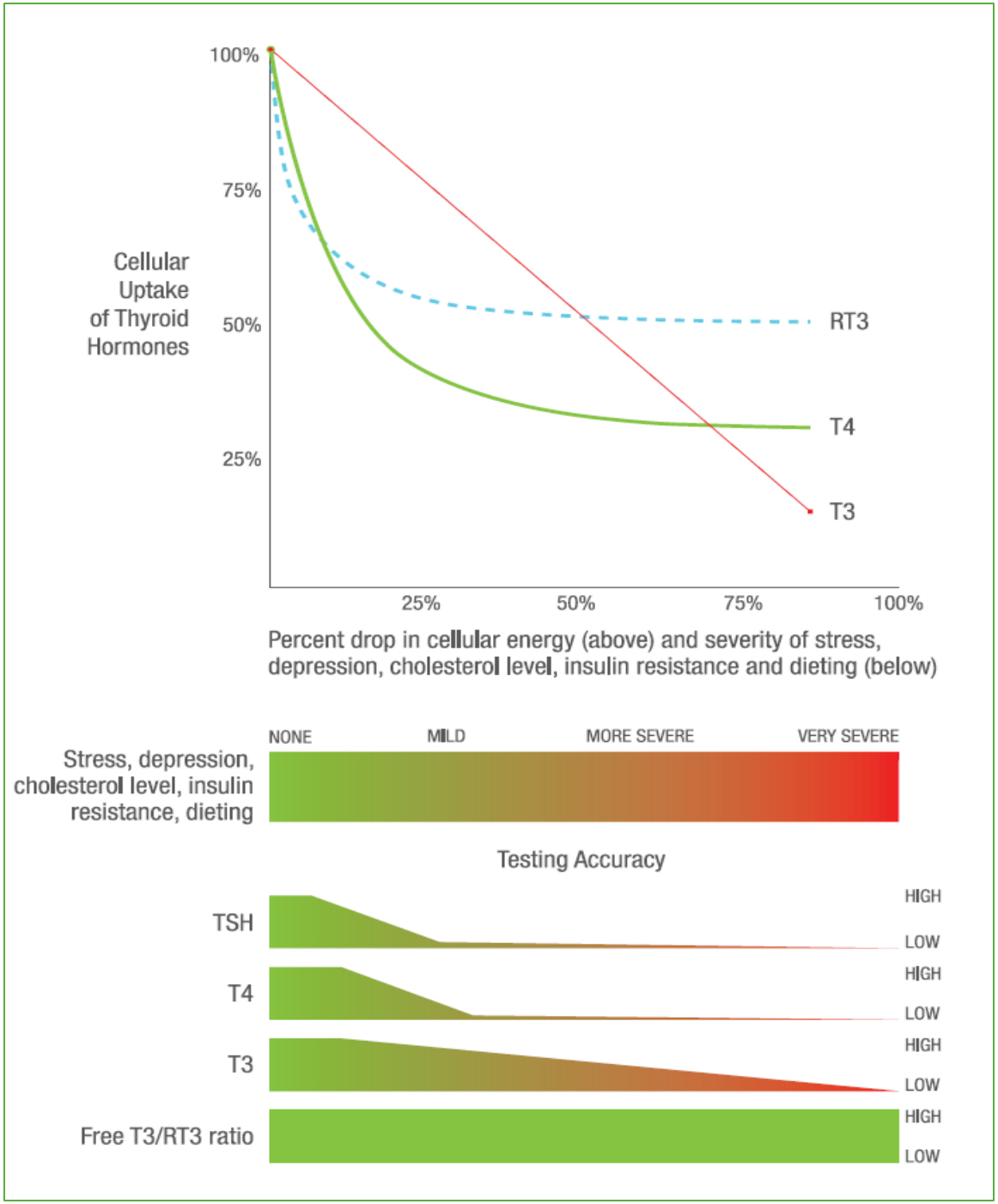
Vos RA et al. Impaired thyroxine and 3,5,3'-triiodothyronine handling by rat hepatocytes in the presence of serum of patients with nonthyroidal illness. J Clin Endocrinol Metab 1995;80:2364-2370

Antonelli A, et al. 3,5-diiodo-l-Thyroxine Increases resting metabolic rate and reduces body weight withut udesirable side effects. J Bio Regulators & Homeostatic Agents. 20011;25(4):655-653

Thyroid Hormone Transport

- 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.

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


100%
75%
50%
25%
Cellular Uptake of Thyroid Hormones
RT3
T4
T3
25%
50%
75%
100%
Percent drop in cellular energy (above) and severity of stress, depression, cholesterol level, insulin resistance and dieting (below)
NONE
MILD
MORE SEVERE
VERY SEVERE
Stress, depression, cholesterol level, insulin resistance, dieting
Testing Accuracy
TSH
T4
T3
Free T3/RT3 ratio
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

Thyroid Hormone Transport (reverse T3)

- 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

Thyroid Hormone Transport (free T3/reverse T3)

- 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.

References: Thyroid Hormone Transport

Thyroid Hormone Transport (pituitary)

- 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)

Placenta (1999), 20, 65–70

Uptake of Reverse T_3 in the Human Choriocarcinoma Cell Line, JAr

A. M. Mitchell[a,d], S. W. Manley[b], K. A. Rowan[a] and R. H. Mortimer[a,c]

[a] Conjoint Endocrine Laboratory, Royal Brisbane Hospital, Brisbane, Queensland, 4029, Australia
Departments of [b] Physiology and Pharmacology, and [c] Obstetrics and Gynaecology, The University of Queensland, Australia

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 ± , $n=15$) 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 e ective as inhibitors of ^{125}I-rT_3 uptake than rT_3. Unlabelled T_3 and thyroxine (T_4) (10 µ) reduced cellular uptake of ^{125}I-rT_3 by around 82 and 74 per cent, respectively. The calculated inhibition constants K_i 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 K_i 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 di usion.

Reverse T3 blocked cellular uptake of T3 by 34% and T4 by 23%.

Thyroid Hormone Transport (physiological stress)

- 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.[41,42,50]

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

Thyroid Hormone Transport (stress)

- 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

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.

CFS/FM

- 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

CFS/FM

© Med Sci Manit, 2006; 12(7): CR282-289
PMID: 16810133

www.MEDSCIMONIT.COM
Clinical Research

Received: 2006.02.28
Accepted: 2006.03.22
Published: 2006.07.01

Female fibromyalgia patients: Lower resting metabolic rates than matched healthy controls

John C. Lower.m:rn, Jackie Yellin!Elil, Gina Honeyman-Lowelllll

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

Source of support: General public to non-profit foundation

Authors' Contribution:
1J Study Design
lJ Data Collection
I i Statistical Analysis
1iJ Data Interpretation
D Manuscript Preparation
D Literature Search
[IJ Funds Collection

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 patientare hypometabolic compared to matched controls.

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

Results: Patients had a lower mRMR (4,306.31±1077.66 kj vs 5,411.59±695.95 kj, p=0.0028) and lower percentages ofpRMRs (SP: –28.42±15.82% vs -6.83±12.55%, p<0.0001. 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 T_3 (FT.) accounted for 30% of the variance in pressure-pain threshold.

Conclusions: Patients had lower mRMR and percentages ofpRMRs. The lower RMRs were not due to calorie restriction or low FFW. Patients' normal FFW argues against low physical activity as the mechanism TSH, FTr and FT_3 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 reliabl 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"

Clinical Bulletin of Myofacial pain 2(2/3):91-124

HPA Axis Dysfunction in CFS/FM/Chronic Infections

- 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

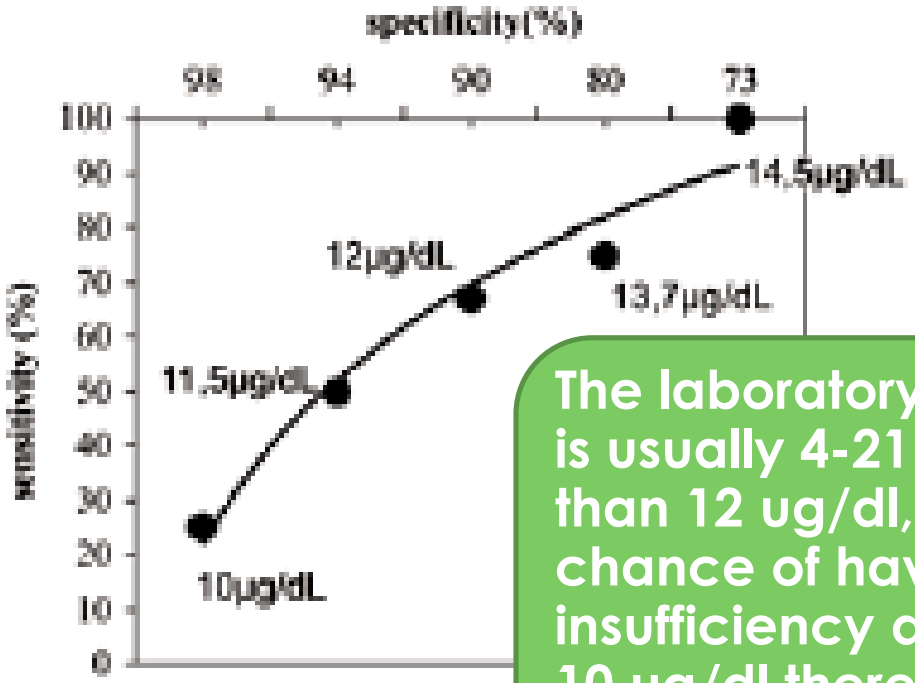
HPA axis dysfunction in CFS/FM/Chronic Infections

- 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

HPA axis dysfunction in CFS/FM/Chronic infections

Figure 2. ROC curve showing the relation of sensitivity and specificity of the basal cortisol level to detect adrenocortical dysfunction



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

(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

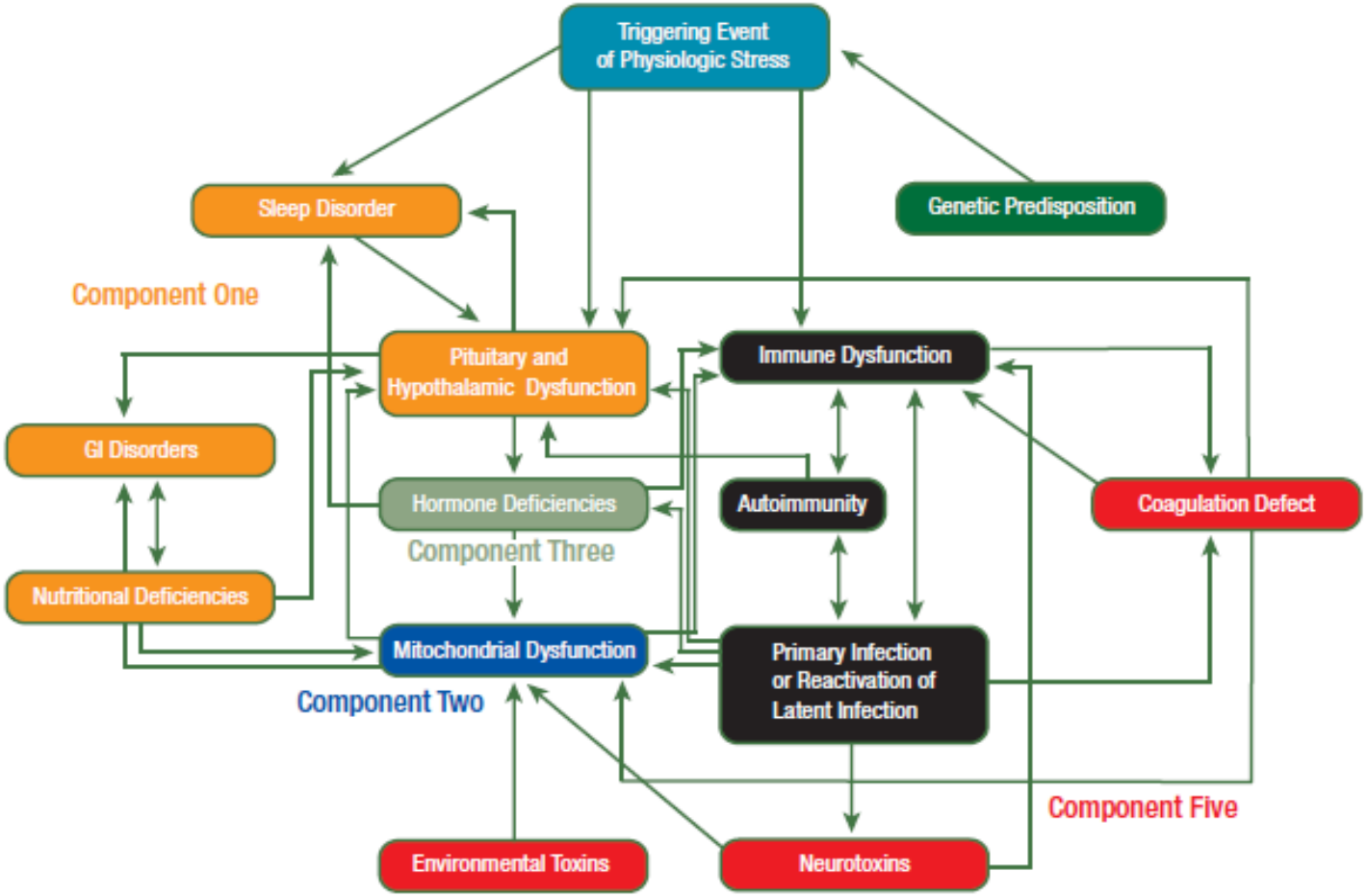
Ozone (overview)

- 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)

Multisystem treatment of CFS/FM/Lyme



Holtorf, K. Cycle of Dysfunction of CFS/FM/LD 2004

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

Holtorf K. J Chronic Fatigue Syndrome 2008;14:3:1-14

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)

(Sicker the patient)

- **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)

Review of Key Labs:

- 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?

Kent Holtorf, MD
Medical Director/CEO, Holtorf Medical Group Affiliate Centers
Medical Director/CEO, National Academy of Hypothyroidism
Kholtorf@HoltorfMed.com

References

1. McManus M, Cincotta A. Advances in Integrative Medicine. Adv Integ Med 2015;2:81-89.
2. Ribeiro JM, Weis JJ, Telford 3rd SR. Saliva of the tick Ixodes dammini inhibits neutrophil function. Exp Parasitol 1990;70(May (4)):382–8.
3. Hovius JW, van Dam AP, Fikrig E. Tick–host–pathogen interactions in Lyme borreliosis. Trends Parasitol 2007;23(September (9)):434–8.
4. Sapi E, Bastian SL, Mpoy CM, Scott S, Rattelle A, Pabbati N, et al. Characterization of biofilm formation by Borrelia burgdorferi in vitro. PLoS One 2012;7(10):e48277 Jutras BL, Chenail AM, Stevenson B. Changes in bacterial growth rate govern expression of the Borrelia burgdorferi OspC and Erp infection-associated surface proteins. J Bacteriol 2013;195(4):757–64.
5. Bunikis I, Kutschan-Bunikis S, Bonde M, Bergstro¨m S. Multiplex PCR as a tool for validating plasmid content of Borrelia burgdorferi. J Microbiol Methods 2011;86(2):243–7.
6. Rupprecht TA, Koedel U, Fingerle V, Pfister HW. The pathogenesis of Lyme neuroborreliosis: from infection to inflammation. Mol Med 2008;14(3/4):205–12.
7. Jutras BL, Chenail AM, Stevenson B. Changes in bacterial growth rate govern expression of the Borrelia burgdorferi OspC and Erp infection-associated surface proteins. J Bacteriol 2013;195(4):757–64.
8. Scott S, Rattelle A, Pabbati N, et al. Characterization of biofilm formation by Borrelia burgdorferi in vitro. PLoS One 2012;7(10):e48277.
9. Stevenson B, Babb K. Lux-S mediated quorum sensing in Borrelia burgdorferi Lyme disease spirochete. Infect Immun 2002;70:4099–105.
10. Beermann C, Wunderli-Allenspach H, Groscurth P, Filgueira L. Lipoproteins from Borrelia burgdorferi applied in liposomes and presented by dendritic cells induce CD8(+) T-lymphocytes in vitro. Cell Immunol 2000;201(2):124–31
11. Results of Palatin Technologies' PT-141 phase 2b study in men with erectile dysfunction, May 10, 2004. www.palatin.com.
12. Wessells H, Gralnek D, Dorr R, Hruby VJ, Hadley ME, Levine N. Effect of an alpha-melanocyte stimulating hormone analog on penile erection and sexual desire in men with organic erectile dysfunction. Urology. 2000 Oct 31;56(4):641-6.
13. Ionescu M, Frohman LA. Pulsatile secretion of growth hormone (GH) persists during continuous stimulation by CJC-1295, a long-acting GH-releasing hormone analog. The Journal of Clinical Endocrinology & Metabolism. 2006 Dec;91(12):4792-7.

References

14. Alba M, Fintini D, Sagazio A, Lawrence B, Castaigne JP, Frohman LA, Salvatori R. Once-daily administration of CJC-1295, a long-acting growth hormone-releasing hormone (GHRH) analog, normalizes growth in the GHRH knockout mouse. American Journal of Physiology-Endocrinology and Metabolism. 2006 Dec 1;291(6):E1290-4.

15. Jette, L., Léger, R., Thibaudeau, K., Benquet, C., Robitaille, M., Pellerin, I., Paradis, V., van Wyk, P., Pham, K. and Bridon, D.P., 2005. Human growth hormone-releasing factor (hGRF) 1–29-albumin bioconjugates activate the GRF receptor on the anterior pituitary in rats: Identification of CJC-1295 as a long-lasting GRF analog.*Endocrinology*, *146*(7), pp.3052-3058.

16. Sackmann-Sala L, Ding J, Frohman LA, Kopchick JJ. Activation of the GH/IGF-1 axis by CJC-1295, a long-acting GHRH analog, results in serum protein profile changes in normal adult subjects. Growth Hormone & IGF Research. 2009 Dec 31;19(6):471-7.

17. Dickinson GS, Alugupalli KR. Deciphering the role of Toll Like receptors to Borreliae. Front Biosci 2012;4:699–712.

18. Kean IR, Irvine KL. Lyme disease aetiopathogenesis factors for disease development and control. Inflammopharmacology 2013;21:101–11.

19. Holtorf, K. Unpublished data

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

21. Younger J, Mackey S. Fibromyalgia Symptoms Are Reduced by Low-Dose Naltrexone: A Pilot Study. Pain Med. 2009 ; 10(4): 663–672.

22. Younger J, Noor N, McCue R, Mackey S. Low-Dose Naltrexone for the Treatment of Fibromyalgia. Arthritis & Rheum 2013;65(2):529-538.

23. Horowitz open labeled study HVHAC (2009-2016)

24. Morozov VG, Khavinson KH. Natural and synthetic peptides and immune dysfunction. Int J Immunopharmac 1997;19(9/10):501-5

25. Tuthill C, Rios I, McBeath R. Thymosin alpha 1: past clinical experience and future promise. Annals of the New York Academy of Sciences. 2010 May 1;1194(1):130-5.

26. Li J, Liu CH, Wang FS. Thymosin alpha 1: biological activities, applications and genetic engineering production. Peptides. 2010 Nov 30;31(11):2151-8.

References

27. Ershler WB, Gravenstein S, Geloo ZS. Thymosin alpha 1 as an adjunct to influenza vaccination in the elderly. Annals of the New York Academy of Sciences. 2007 Sep 1;1112(1):375-84.

28. Garaci E, Favalli C, Pica F, SINIBALDI VALLEBONA PA, TERESA PALAMARA AN, Matteucci C, Pierimarchi P, Serafino A, Mastino A, Bistoni F, Romani L. Thymosin alpha 1. Annals of the New York Academy of Sciences. 2007 Sep 1;1112(1):225-34.

29. Qin Y, Chen FD, Zhou L, Gong XG, Han QF. Proliferative and anti-proliferative effects of thymosin a1 on cells are associated with manipulation of cellular ROS levels. Chemico-biological interactions. 2009 Aug 14;180(3):383-8.

30. Matteucci C, Minutolo A, Sinibaldi-Vallebona P, Palamara AT, Rasi G, Mastino A, Garaci E. Transcription profile of human lymphocytes following in vitro treatment with thymosin alpha-1. Annals of the New York Academy of Sciences. 2010 May 1;1194(1):6-19.

31. Schulof, R.S. et al. 1985. A randomized trial to evaluate the immunorestorative properties of synthetic thymosin-alpha 1 in patients with lung cancer. J. Biol. Response Modif. 4: 147–158.

32. Freeman KW, Bowman BR, Zetter BR. Regenerative protein thymosin β-4 is a novel regulator of purinergic signaling. The FASEB Journal. 2011 Mar 1;25(3):907-15.

33. Lee HR, Yoon SY, Song SB, Park Y, Kim TS, Kim S, Hur DY, Song HK, Park H, Cho D. Interleukin-18-mediated interferon-gamma secretion is regulated by thymosin beta 4 in human NK cells. Immunobiology. 2011 Oct 31;216(10):1155-62.

34. Kim S, Kwon J. Effect of thymosin beta 4 in the presence of up-regulation of the insulin-like growth factor-1 signaling pathway on high-glucose-exposed vascular endothelial cells. Molecular and cellular endocrinology. 2015 Feb 5;401:238-47.

35. Philp D, Kleinman HK. Animal studies with thymosin β4, a multifunctional tissue repair and regeneration peptide. Annals of the New York Academy of Sciences. 2010 May 1;1194(1):81-6.

36. Jeon BJ, Yang Y, Shim SK, Yang HM, Cho D, Bang SI. Thymosin beta-4 promotes mesenchymal stem cell proliferation via an interleukin-8-dependent mechanism. Experimental cell research. 2013 Oct 15;319(17):2526-34.

37. Stark C, Taimen P, Tarkia M, Pärkkä J, Saraste A, Alastalo TP, Savunen T, Koskenvuo J. Therapeutic potential of thymosin β4 in myocardial infarct and heart failure. Annals of the New York Academy of Sciences. 2012 Oct 1;1269(1):117-24.

References

38. Ershler N. Smart, C.A. Risebro, A.A. Melville, K. Moses, R.J. Schwartz, K.R. Chien, P.R. Riley, et al., Thymosin beta4 induces adult epicardial progenitor mobilization and neovascularization, Nature 445 (2007) 177–182.

39. A.L. Goldstein, E. Hannappel, H.K. Kleinman, et al., Thymosin beta4: actin-sequestering protein moonlights to repair injured tissues, Trends Molecul. Med. 11 (2005) 421–429.

40. D. Philp, A.L. Goldstein, H.K. Kleinman, et al., Thymosin beta4 promotes angiogenesis, wound healing, and hair follicle development, Mech. Ageing Dev. 125 (2004) 113–115.

41. Gondo H, Kudo J, White JW, Barr C, Selvanayagam P, Saunders GF. Differential expression of the human thymosin-beta 4 gene in lymphocytes, macrophages, and granulocytes. The Journal of Immunology. 1987; 139(11): 3840-8.

42. Sikiric P, Seiwerth S, Rucman R, et al. Stable gastric pentadecapeptide BPC 157: novel therapy in gastrointestinal tract. Curr Pharm Des 2011;17(16)1612-32

43. Boban-Blagaic A, Vladimir Blagaic, et al. The influence of gastric pentadecapeptide BPC 157 on acute and chronic ethanol administration in mice. The effect of NG -nitro-L-arginine methyl ester and L-arginine. Med Sci Monit, 2006; 12(1): BR36-45

44. Wong GK, Zhu XL, Poon WS. Beneficial effect of cerebrolysin on moderate and severe head injury patients: result of a cohort study. InIntracranial Pressure and Brain Monitoring XII 2005 (pp. 59-60). Springer Vienna.

45. Ruether E, Husmann R, Kinzler E, Diabl E, Klingler D, Spatt J, Ritter R, Schmidt R, Taneri Z, Winterer W, Koper D. A 28-week, double-blind, placebo-controlled study with Cerebrolysin in patients with mild to moderate Alzheimer's disease. International clinical psychopharmacology. 2001 Sep 1;16(5):253-63.

46. Rockenstein E, Torrance M, Mante M, Adame A, Paulino A, Rose JB, Crews L, Moessler H, Masliah E. Cerebrolysin decreases amyloid-β production by regulating amyloid protein precursor maturation in a transgenic model of Alzheimer's disease. Journal of neuroscience research. 2006 May 15;83(7):1252-61.

47. Alvarez XA, Cacabelos R, Laredo M, Couceiro V, Sampedro C, Varela M, Corzo L, Fernandez-Novoa L, Vargas M, Aleixandre M, Linares C. A 24-week, double-blind, placebo-controlled study of three dosages of Cerebrolysin in patients with mild to moderate Alzheimer's disease. European journal of neurology. 2006 Jan 1;13(1):43-54.

References

48. Ladurner G, Kalvach P, Moessler H. Neuroprotective treatment with cerebrolysin in patients with acute stroke: a randomised controlled trial. Journal of neural transmission. 2005 Mar 1;112(3):415-28.

49. Masliah E, Armasolo F, Veinbergs I, Mallory M, Samuel W. Cerebrolysin ameliorates performance deficits, and neuronal damage in apolipoprotein E-deficient mice. Pharmacology Biochemistry and Behavior. 1999 Feb 28;62(2):239-45.

50. Panisset M, Gauthier S, Moessler H, Windisch M, Cerebrolysin Study Group. Cerebrolysin in Alzheimer's disease: a randomized, double-blind, placebo-controlled trial with a neurotrophic agent. Journal of neural transmission. 2002; 109(7-8): 1089-104.

51. Ojo-Amaize EA, Conley EJ, Peter JB. Decreased natural killer cell activity is associated with severity of chronic fatigue immune dysfunction syndrome. Clin Infect Dis. 1994 Jan;18 Suppl 1:S157-9.

52. *Clin Infect Dis 1994* Stricker RB, Winger EE. Decreased CD57 lymphocyte subset in patients with chronic Lyme disease. Immunol Lett. 2001 Feb 1;76(1):43-8.

53. American Journal of Medicine, 1993

54. Blood Coagulation and Fibrinolysis, 1999

55. Blood Coagulation and Fibrinolysis, 2000

56. American Association of Clinical Chemistry, 2003

57. Annals of Internal Medicine 1992

58. Berende A, Oosting M, Kullberg BJ, Netea MG, Joosten LA. Activation of innate host defense mechanisms by Borrelia. Eur Cytokine Netw 2010;21(March(1)):7–18. http://dx.doi.org/10.1684/ecn.2009.00179 [Review].

59. Cadavid D, London˜o D. Understanding tropismand immunopathological mechanisms of relapsing fever spirochaetes. Clin Microbiol Infect 2009;15(May(5)):415–21. http://dx.doi.org/10.1111/j.1469-0691.2009.02785.x.

60. Kraiczy P, Hartman K, Hellwage J, Skerka C, Kirschwink M, Brade V, et al. Immunological characteristics of the complement regulation factor H binds CRASP and Erp proteins of Borrelia burgdorferi. Int J Med Microbiol 2004;293:152–7.

References

61. de Taeye SW, Kreuk L, van Dam AP, Hovius JW, Schuijt TJ. Complement evasion by Borrelia burgdorferi: it takes 3 to tango. Trends Parasitol 2010;117:1–10.

62. Kennedy M, Lenhart TR, Akins DR. The role of Borrelia burgdorferi outer surface proteins. Immunol Med Microbiol 2012;66:1–26.

63. Rui L, Yu N, Hong L, Feng H, Chunyong H, Jian M, Zhe Z, Shengshou H. Extending the time window of mammalian heart regeneration by thymosin beta 4. Journal of cellular and molecular medicine. 2014 Dec 1;18(12):2417-24.

64. Wei C, Kumar S, Kim IK, Gupta S. Thymosin beta 4 protects cardiomyocytes from oxidative stress by targeting anti-oxidative enzymes and anti-apoptotic genes. PloS one. 2012 Aug 3;7(8):e42586.

65. Xiong Y, Zhang Y, Mahmood A, Meng Y, Zhang ZG, Morris DC, Chopp M. Neuroprotective and neurorestorative effects of thymosin beta4 treatment initiated 6 hours post injury following traumatic brain injury in rats. Journal of neurosurgery. 2012 May;116(5):1081.

66. Matarese G, Moschos S, Mantzoros CS. Leptin in Immunology. J of Immunology 2005;174(6):3137-3142

67. Grier TM. The Complexities of Lyme Disease: A microbiology tutorial: Part 1. Lyme Disease Survival manual. LymeNet Europe

68. McDonald AB. Borrelia Burdoferi group spirochetes detected in blood and cerebrospinal fluid in seronegative patients. Current Research Discoveries May 2016, London, England

69. Christ, Berg et al. Does Borreliosis Activate the Coagulation System and is Coag Regulatory Protein Defect predispostional? IDSA, Oct 2003

70. Clerici M, Shearer, GM. The Th1-Th2 hypothesis of HIV infection: new insights. Immunology Today 1994;15(12):575-581