Functional Medicine Meeting
Dr. Weitz

Kent Holtorf, MD
Medical Director/CEO, Holtorf Medical Group
Medical Director/CEO, Nonprofit National Academy of Hypothyroidism
Topics

- CFS/Fibromyalgia
- Thyroid dysfunction
  - Deidoninase
  - Thyroid transport
  - Alternative testing
    - SHBG
    - Thyroflex
    - Medical-legal
- Adrenal dysfunction
- Peptide therapy
- Stem cells
- Scheduled time: 6 hours
Cycle of Dysfunction
Figure 8: Patients Achieving Various Levels of Pain Relief – Fibromyalgia Study F1

- Pregabalin 800mg daily dose
- Pregabalin 450mg daily dose
- Pregabalin 300mg daily dose
- Placebo

Percent of Patients Improved vs. Percent Improvement in Pain from Baseline
Chronic Fatigue Syndrome and Fibromyalgia are very treatable Conditions!

When the multiple dysfunctions present are treated, significant improvement is seen, almost without exception.
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:

- 94 percent of patients having overall improvement by the 4th visit
- 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 center, the patients had seen an average of 7.2 different physicians for the treatment of CFS and/or FM without significant improvement.

Holtorf, K. Diagnosis and Treatment of Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysfunction in Patients with Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM). J of CFS 2008;14(3):1-14
Six Component Approach

- Component One: Stabilize the Patient
- Component Two: Mitochondrial Enhancement
- Component Three: Balance the Hormones
- Component Four: Treat the Infectious/Immune Components
- Component Five: Addressing Unique Etiologies
- Component Six: Maintenance
Integrated Approach to the Cycle of Dysfunction
Almost all CF/FM are low thyroid

- Discussed in previous lectures
- Usually normal or low TSH because of pituitary dysfunction and inflammatory suppression of the TSH
- Thyroid resistance is very common with CFS/FM

- Blood tests indicate how much thyroid is in the blood, not the effect
Why the TSH is Unreliable?
A study published in *The Lancet* performed thyroid biopsies in patients with chronic fatigue and found that 40% of these patients had lymphocytic thyroiditis.

Only 40% of those with lymphocytic thyroiditis were positive for TPO or antithyroglobulin antibodies or had an abnormal TSH.

Thus, the thyroid dysfunction would have gone undetected in the majority of patients if the biopsy had not been done.

This study also demonstrated that because the TSH is a poor indicator of thyroid function, it also does not predict whose symptoms will respond to thyroid replacement.

The authors state, "After treatment with thyroxine, clinical response was favorable, irrespective of baseline TSH concentration."

TRH testing of FM patients

Found that all of the patients with fibromyalgia were hypothyroid despite the fact that standard thyroid function tests, including TSH, T4 and T3, were in the normal range.

They found that these patients tended to have low normal TSH levels that averaged 0.86 vs 1.42 in normals with high normal free T4 and low normal T3 levels so doctors erroneously feel these patients are on the high side of normal because of the low normal TSH and high normal T4.

25 days of calorie restriction (dieting) significantly reduced D1, resulting in reduced T4 to T3 conversion with a 50% reduction in T3.

Associated with an increase in D2, so there was no increase in TSH but rather a decrease from an average of 1.20 ng/ml to 0.7 ng/ml.

Study by Leibel, et al found that individuals who significantly dieted in the past had, on average, 25% lower metabolism (equal to someone who weighed 60% less).

Additionally, the reduction was shown to be present years later.

This 25% percent reduction in metabolism equates to an approximate deficit of 500-600 kcal per day.

Obese rats fed a high-fat diet with one group going through caloric restriction and refeeding.

After two cycles of caloric restriction, weight loss occurred at half the rate and weight gain occurred at three times the rate compared to the control group.

“The data suggests that frequent dieting may make subsequent weight loss more difficult.”

Variable Bioactivity of TSH


Clin Endocrinol (Oxf) 1972; 1:115-25.
J Clin Endocrinol Metab 1973; 37; 595-601.
J Clin Endocrinol Metab 1974; 38:964-75.
Clin Endocrinol (Oxf) 1975: 4; 585-90.
Endocrinology 113:2145-2145-2154
Rec Prog Horm Res 41:577-606
Biochem J 287:665-679
Endocrinology, Vol 133, 1490-1503,
Thyroid. 8:941-946.
J Clin Endocrinol Metab. 48:989 -998

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**Fig. 3.** The TSH B/I in CH patients with secondary or tertiary defect (○, single cases; ●, mean ± sd) and in control subjects (mean ± sd; ♦, normal subjects;▲, primary hypothyroid patients). The dotted line indicates the lower limit of the normal range. Both groups of CH patients have B/I ratios significantly lower than those observed in normal or primary hypothyroid controls.
Because TT 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.

Results in cellular hypothyroidism despite having standard blood tests in the “normal” range.
Conditions associated with reduced mitochondrial function and impaired thyroid transport include: insulin resistance, diabetes and obesity; chronic and acute dieting; depression; anxiety; bipolar depression; neurodegenerative diseases; aging; chronic fatigue syndrome; fibromyalgia; migraines; chronic infections; physiologic stress and anxiety; cardiovascular disease; inflammation and chronic illness; and those with high cholesterol and triglyceride levels. Thus, standard blood tests can be very unreliable if any of these commonly occurring conditions are present.
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.
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
- The pituitary does not make RT3 (No D3)

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
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

Thyroid Hormone Transport (reverse T3)

Holtorf K. Thyroid Hormone Transport into Cellular Tissue. J AARM 2014;3:53-68
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.

Hi RT3 also indicates that T4 would not be optimal or appropriate therapy.
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.\(^{41,42,50}\)

Chronic and yo-yo dieting, frequently done by a large percentage of the population, is shown to be associated with reduced cellular T4 uptake of 25%-50%.\(^{3,49,112,114,115,116}\)

The dysfunction present with depression and bipolar depression includes reduced uptake of T4 into the cell.24-26,30,31,35,39-45

Thought to have “high normal” levels of thyroid—usually low normal TSH and high normal T4.

Lack of benefit from T4 used as proof that they are not hypothyroid.

T3 stimulates production of serotonin.

References: Thyroid Hormone Transport
Thyroid Hormone Transport into Cellular Tissue
Holtorf, K. Thyroid Hormone Transport into Cellular Tissue
J Restor Med 2014;3(1):53-68
Treated 159 bipolar patients with T3 who had failed to adequately respond to an average of 14 medications (average dose 90.4 mcg (range 13 mcg-188 mcg)).

The medication was found to be well tolerated and 84% experienced significant improvement and 33% had a full remission.

One patient who was switched to T4 for cost reasons experienced a return of symptoms, which resolved with the reintroduction of T3.

The authors concluded, “Augmentation with supraphysiologic doses of T3 should be considered in cases of treatment resistant bipolar depression...”

The authors thanked several doctors who encouraged them to go beyond the traditional 50 mcg of T3 because it has helped so many of their patients.

Depression

- With over 4000 patients, The Star*D Report is the largest trial comparing antidepressant effectiveness for depression.
- It found that 66% of patients fail to respond to antidepressants or have side-effects severe enough to discontinue use.
- Of those who do respond, over half will relapse within one year.
- The trial found that T3 was effective even when other medications -- such as citalopram (Celexa), bupropion (Wellbutrin), sertraline (Zoloft), venlafaxine (Effexor), or cognitive therapy – were not.
- It was shown to be 50% more effective, even with the less than optimal dose of 50 mcg, under direct comparison with significantly less side effects than commonly used therapeutic approaches with standard antidepressants.

Thyroid Hormone Transport

Associated serum thyroid levels with progressively decreasing tissue thyroid levels due to stress, illness, depression, calorie reduction or aging (Why standard blood tests lack sensitivity to detect low thyroid in the presence of such conditions).

Demonstrates why TSH levels lack the accuracy to detect cellular levels and the free T3/reverse T3 ratio is the most accurate method to determine cellular thyroid levels in the presence of physiologic stress, illness, depression or obesity.

Severe of illness/depression stress/calorie reduction: none > mild > moderate > severe

Normal aging: young > middle > older > elderly

Tissue hypothyroidism (diminished tissue T3 level): none/mild > mild/moderate > moderate/severe > severe

Inaccuracy of TSH and T4 levels: none > potentially significant > significant > substantial

Diminished utilization of T4: none/mild > mild/moderate > moderate/severe > severe

Holtorf K. National Academy of Hypothyroidism (NAHypothyroidism.org)
### ESTIMATION OF TISSUE HYPOTHYROIDISM

**TABLE 1.** Sensitivity and specificity of the 14 symptoms and signs of hypothyroidism and analysis of their positive and negative predictive values

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle reflex</td>
<td>77</td>
<td>93.5</td>
<td>92.2</td>
<td>80.3</td>
</tr>
<tr>
<td>Dry skin</td>
<td>76</td>
<td>63.8</td>
<td>67.7</td>
<td>72.7</td>
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<tr>
<td>Cold intolerance</td>
<td>64</td>
<td>65</td>
<td>64.6</td>
<td>64.4</td>
</tr>
<tr>
<td>Coarse skin</td>
<td>60</td>
<td>81.2</td>
<td>76.1</td>
<td>67</td>
</tr>
<tr>
<td>Puffiness</td>
<td>60</td>
<td>96.3</td>
<td>94.2</td>
<td>70.7</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>58</td>
<td>42.5</td>
<td>50.2</td>
<td>50.3</td>
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<tr>
<td>Sweating</td>
<td>54</td>
<td>86.2</td>
<td>79.6</td>
<td>65.2</td>
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<tr>
<td>Wt increase</td>
<td>54</td>
<td>77.5</td>
<td>70.6</td>
<td>62.8</td>
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<tr>
<td>Paraesthesia</td>
<td>52</td>
<td>82.5</td>
<td>74.8</td>
<td>63.2</td>
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<tr>
<td>Cold skin</td>
<td>50</td>
<td>80</td>
<td>71.4</td>
<td>61.5</td>
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<tr>
<td>Constipation</td>
<td>48</td>
<td>85</td>
<td>76.2</td>
<td>62</td>
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<tr>
<td>Slow movements</td>
<td>36</td>
<td>98.7</td>
<td>96.5</td>
<td>60.7</td>
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<tr>
<td>Hoarseness</td>
<td>34</td>
<td>87.5</td>
<td>73.1</td>
<td>57</td>
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<tr>
<td>Hearing</td>
<td>22</td>
<td>97.5</td>
<td>89.8</td>
<td>52.6</td>
</tr>
<tr>
<td>Do you have or feel the following symptoms?</td>
<td>No Symptom Never</td>
<td>Few or Sometimes</td>
<td>Moderate or regularly</td>
<td>Much or Often</td>
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<tr>
<td>--------------------------------------------</td>
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<tr>
<td>Sensitive to cold</td>
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<tr>
<td>Cold hands or feet</td>
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<tr>
<td>Generalized fatigue</td>
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<tr>
<td>Morning fatigue</td>
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<td>Fatigue unless exercising</td>
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<tr>
<td>Sleepy during day</td>
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<tr>
<td>Distracted easily</td>
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<tr>
<td>Poor motivation for required tasks</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Headaches</td>
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<tr>
<td>Water retention</td>
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<tr>
<td>Constant swollen eyelids</td>
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<tr>
<td>Swollen eyes in morning</td>
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<tr>
<td>Swollen calves/feet</td>
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<tr>
<td>Difficulty losing weight despite dieting</td>
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<tr>
<td>Constipation</td>
<td></td>
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<tr>
<td>Bedwetting as child</td>
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<tr>
<td>Slow heart palpitations</td>
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<tr>
<td>Muscle cramps</td>
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<tr>
<td>Carpal tunnel syndrome</td>
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<tr>
<td>Stiff joints in morning</td>
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<tr>
<td>Joint pain worsens with cold</td>
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<tr>
<td>Hoarse voice in morning</td>
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<tr>
<td>Dry skin (general/feet or elbows)</td>
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<tr>
<td>Slow growing or brittle nails</td>
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<tr>
<td>Diffuse hair loss</td>
<td></td>
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<tr>
<td>Muscle achiness or soreness</td>
<td></td>
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<tr>
<td>Low body temperature</td>
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<tr>
<td>Diminished sweating</td>
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<tr>
<td>Tingling or numbness in extremities</td>
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<tr>
<td>Hoarse voice (constant or in morning)</td>
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<tr>
<td>Decreased hearing</td>
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<tr>
<td>Course skin (rough skin)</td>
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</tbody>
</table>

Available at HoltorfMed.com
Diagnosis (laboratory)

Good news! Your test indicates that you're in the normal range!

Brian Narelle
**Best Method of Diagnosis**

- Look at T3 to reverse T3 (T3/rT3) ratio (should be >2)
- Free T3 should be above 3.5
- Reverse T3 less than 16 LC/MS/MS or 150 on RIA
- TSH greater than 2.0 is significant
- Usually low normal free T3 and above average reverse T3
- Signs and symptoms (body temp, pulse, cold ext, etc.)
- SHBG < 70 for women; < 30 for men
- Relaxation phase ankle reflexes
- Basal metabolic rate
- Leptin > 12
- Any positives on TMP
- High C4a, ECP
T4 preparations are not optimal or adequate for patients who have CFS/FM/Lyme dz, depression, chronic illness, diabetes, weight gain, etc. because they have a high incidence of reduced T4 to T3 conversion, reduced uptake of T4 and thyroid resistance.
Measure tissue thyroid levels in hypothyroid animals receiving T4 replacement.

Plasma TSH, T4 and T3 levels and 10 different tissue levels of T4 and T3 were measured.

Demonstrated that all tissues, except the brain (pituitary), required supraphysiologic levels of plasma T4 to provide normal tissue levels of T3.

The pituitary was able to maintain normal levels of T3 despite the rest of the body being hypothyroid.

Consequently, the pituitary levels of T3 and subsequent level of TSH is a poor measurement of tissue thyroid levels.

Demonstrated that T4 only preparations such as Synthroid or Levoxyl, are unable to achieve normal levels of T3 in all tissues, except the brain and pituitary, unless supraphysiologic plasma levels of T4 and T3 are obtained and the TSH is suppressed.

Escobar-Morreale HF et al. Replacement therapy for hypothyroidism with thyroxine alone does not ensure euthyroidism in all tissues, as studied in thyroidectomized rats, J Clin Invest 96:2828-2838.
Normal T4 or T3 levels did not ensure tissue euthyroidism.

Supraphysiologic plasma T4 and T3 levels were required to obtain normal levels in some tissues.

At some amounts of T4 infused, the level of thyroid hormones in the pituitary was over twice that of other tissues, again demonstrating that pituitary levels and thus TSH secretion is not an accurate measure of tissue hypothyroidism.

T4/T3 combinations are required to normalize tissue levels of T4 and T3 or T3 to normalize tissue T3 levels.

Escobar-Morreale HF et al. Replacement therapy for hypothyroidism with thyroxine alone does not ensure euthyroidism in all tissues, as studied in thyroidectomized rats, J Clin Invest 96:2828-2838
The false positive rate that a suppressed TSH indicates hyperthyroidism in someone on thyroid replacement is 80%.

The positive predictive value of a suppressed TSH is demonstrating hyperthyroidism is equal to:

\[
\text{Positive predictive value (PPV)} = \frac{\text{sensitivity} \times \text{prevalence}}{(\text{100-specificity}) \times (\text{100-prevalence})} + (\text{sensitivity} \times \text{prevalence})
\]

\[
= \frac{59 \times 20}{(100-51) \times (100-20)} + (59 \times 20)
\]

\[
= \frac{1180}{49 \times 80 + 1180} = 23\%
\]

Comparison of Second and Third Generation Methods for Measurement of Serum Thyrotropin in Patients with Overt Hyperthyroidism, Patients Receiving Thyroxine Therapy, and Those with Nonthyroidal Illness*

J. A. FRANKLYN, E. G. BLACK, J. BETTERIDGE

Department of Medicine, University of Birmingham, Queen Elizabeth Edgbaston, Birmingham, United Kingdom B15 2TH

ABSTRACT

We compared serum TSH results determined in second and third generation assays in patients with thyroid disease and nonthyroidal illnesses (NTIs) to evaluate the usefulness of the more sensitive assay. We studied 19 subjects with untreated hyperthyroidism, 12 hyperthyroid subjects sampled at 4-week intervals after beginning carbimazole, 153 subjects receiving T4 replacement, and 300 hospital in-patients with a variety of NTIs. Serum TSH was measured, using a second generation immunometric method, together with free T4 and free T3. Samples with subnormal TSH (<0.5 mU/L) were reassayed, using a more sensitive chemiluminescent immunometric method.

Both assays revealed undetectable serum TSH levels in 18 of 19 overtly hyperthyroid patients. Undetectable TSH values (in both assays) were found in 30 of 33 patients with low serum TSH levels who were receiving treatment for hyperthyroidism, in association with normal thyroid hormone levels in 11. Undetectable TSH was evident in (P < 0.001) and in those receiving T3 with low TSH (r = -0.33; P < 0.05); no significant correlation was evident in subjects with low serum TSH levels associated with NTI.

An improvement in assay sensitivity led to a reduction in the number of patients being treated with T4 or with NTI in whom serum TSH was undetectable and, hence, an increase in those in whom overt hyperthyroidism could be excluded. Undetectable TSH results, even in a third generation assay, are not diagnostic of overt hyperthyroidism, but are also found in subjects with treated thyroid disease and NTI.

(J Clin Endocrinol Metab 78: 1368-1371, 1994)
Document pulse, body temp

Need to use alternative means of diagnosis (thyroflex, BMR, SHBG)

Document used an alternative means of diagnosis and patient understands that this is not standard therapy (can prewrite with a check box)

Educate the patient

Give studies to patient and put studies in chart

Document more if suppress the TSH

Use T3SR (cardiac side-effects are mainly not from nuclear receptor (slow on/slow off) (variable levels don’t matter much) but rather from surface cell receptor-CA+ channels (variable levels matter)

Significant respectable minority rule

Symptom assessment each visit
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.

The majority of patients should be treated for adrenal dysfunction (especially if AM cortisol <10-12)

ACTH stimulation test is no better than flipping a coin in determining adrenal dysfunction in CFS/FM, as it is not a primary adrenal dysfunction

The data shows that such treatment is safer and more effective than commonly used treatments such as antidepressants.

While these conditions are similar, the abnormality in CFS is in the pituitary while the FM patients have abnormalities of the hypothalamus.
Diagnosis and Treatment of Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysfunction in Patients with Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM)

Kent Holtof M.D.
Medical Director, Holtof Medical Group, Inc. Torrance, CA

Abstract

There is controversy regarding the incidence and significance of hypothalamic-pituitary-adrenal (HPA) axis dysfunction in chronic fatigue syndrome (CFS) and fibromyalgia (FM). Studies that utilize central acting stimulation tests, including corticotropin-releasing hormone (CRH), insulin stress testing (IST), d-fenfluramine, ipsapirone, interleukin-6 (IL-6) and metyrapone testing, have demonstrated that HPA axis dysfunction of central origin is present in a majority of these patients. However, ACTH stimulation tests and baseline cortisol testing lack the sensitivity to detect this central dysfunction and have resulted in controversy and confusion regarding the incidence of HPA axis dysfunction in these conditions and the appropriateness of treatment. While both CFS and FM patients are shown to have central HPA dysfunction, the dysfunction in CFS is at the pituitary-hypothalamic level while the dysfunction in FM is more related to dysfunction at the hypothalamic and supra-hypothalamic levels. Because treatment with low physiologic doses of cortisol (<15 mg) has been shown to be safe and effective and routine dynamic ACTH testing does not have adequate diagnostic sensitivity, it is reasonable to give a therapeutic trial of physiologic doses of cortisol to the majority of patients with CFS and FM, especially to those who have symptoms that are consistent with adrenal dysfunction, have low blood pressure or have baseline cortisol levels in the low or low-normal range.

Key words: HPA axis dysfunction; hypothalamic-pituitary-adrenal axis; chronic fatigue syndrome; fibromyalgia; CFIDS; cortisol, hydrocortisone

Introduction
A study published in the Brazilian Journal of Infectious Disease demonstrates that in patients with chronic infections, cortisol level of less than 12 has a specificity of greater than 90% for adrenocortical dysfunction and a level less than 10 ug/dl has a specificity of 98% for adrenocortical dysfunction.

The most appropriate cutoff that optimizes specificity and sensitivity as found in this study as well as by others is 12 ug/dl.

In addition, a normal ACTH does not rule-out secondary hypoadrenalism, but an abnormally low or low normal ACTH level can be considered confirmatory.
Laboratory “normal” range 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
Infections/immune dysfunction

Treat the immune dysfunction and Infectious component

FROM IMBALANCE TO BALANCE
FROM INEFFECTIVE IMMUNITY TO EFFECTIVE IMMUNITY
High levels of type 2 cytokine-producing cells in chronic fatigue syndrome

A. SKOWERA*, A. CLEARE†, D. BLAIR†, L. BEVIS†, S. C. WESSELY† & M. PEAKMAN Departments of *Immunology and †Psychological Medicine, Guy's, King's & St Thomas's School of Medicine, King's College London, London, UK

(Accepted for publication 17 November 2003)

SUMMARY

The aetiology of chronic fatigue syndrome (CFS) is not known. However, it has been suggested that CFS may be associated with underlying immune activation resulting in a Th2-type response. We measured intracellular production of interferon (IFN)-γ and interleukin (IL)-4; type 1 cytokines), IL-4 (type 2) and IL-10 (regulatory) by both polyclonally stimulated and non-stimulated CD4 and CD8 lymphocytes from patients with CFS and control subjects by flow cytometry. After polyclonal activation we found evidence of a significant bias towards Th2- and Tc2-type immune responses in CFS compared to controls. In contrast, levels of IFN-γ, IL-2 and IL-10-producing cells were similar in both study groups. Non-stimulated cultures revealed significantly higher levels of T cells producing IFN-γ or IL-4 in CFS patients. Concluding, we show evidence for an effector memory cell bias towards type 2 responsiveness in patients with CFS, as well as ongoing type 0 immune activation in unstimulated cultures of peripheral blood cells.

Keywords chronic fatigue syndrome cytokines immune activation Th1/Th2 cytokines

Evidence for T-helper 2 shift and association with illness parameters in chronic fatigue syndrome (CFS)

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Abstract

Few immunological markers have been consistently reported in CFS. However, a shift to a T-helper 2 (Th2) type immune response has been hypothesized for individuals with CFS. The current study investigated whether individuals with CFS who exhibited a stronger shift towards a Th2 type of immune response were more severe symptoms, poorer neurocognitive functioning, and poor physical and psychosocial functioning. The current investigation measured the percentage of Th1-like and Th2-like memory cells using cell surface flow cytometry in 114 individuals with CFS. The associations between the ratio of Th1 and Th2 memory cells and various illness parameters were then examined, including symptom severity, psychiatric functioning, neurocognitive functioning, salivary cortisol levels, and chronic pain status. Results indicated that individuals who exhibited a more extreme shift towards a Th2 immune response also exhibited poorer sleep and high levels of basal salivary cortisol. The implications of these findings are discussed.

Keywords chronic fatigue syndrome; T-helper 2 shift; immunology; salivary cortisol; cognitive functioning
TH1-TH2 Shift in HIV Determines Progression of Illness

- Protection and slower progression
- Long term non-progressors

- Type 1 cytokines

- Type 2 cytokines

- Susceptibility and faster progression
- Rapid progressors

Important to diagnose and treat the immune dysfunction when treating the infectious component

You are probably using immune modulators in your practice

But novel immune modulators are a major breakthrough in the treatment of CLD

Biggest change in treatment strategy for CLD

Immune dysfunction and inflammation are major underlying causes of a wide-range of illnesses, including CLD, CFS, FM, depression, anxiety, CV disease, neurodegenerative diseases, aging (use for preventive medicine), metabolic illness, pain syndromes, autoimmune diseases, fertility issues, autism, diabetes, obesity, mitochondria dysfunction, inflammation, toxic exposure and addictions (many more)
Chronic Lyme Disease

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

- May never become symptomatic or continue to be misdiagnosed as other conditions, including CFS, FM, MS, autoimmune disease, migraines, depression, bipolar, pain syndromes, Parkinson’s, ALS, Alzheimer’s, CHF, obesity, OCD, ADHD, DM, lupus, Crohn’s, PCOS, PMS, IBS, IC, prostatitis, sleep disorder, etc.

- 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.
Increase TH1 and decrease TH2

Boosting NK cell and lowering inflammatory cytokines
- Peptides (Thymosin alpha-1/Thymosin B4/AMP (LL-37)/BPC 157/Nootropics)
- Stem Cells (Umbilical Cord)
- LDN (addendum)
- Heparin (addendum)
- Transfer factors (addendum)
- IVIG (low dose or high dose - give 10-20 iu pitocin IV with each treatment if possible)
- Ozone (MAH/Direct/High-dose/10-pass)
- UVBI
- LDA/LDI
- 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)
- Mushroom extracts
- Isoprinosine
- High dose B12
- GcMAF/Leukine/Neupogen
- Probiotics
- Silver
- Antioxidants/Glutathione (low glutathione decreases TH1 and increases TH2)
- Chelation (heavy metals stimulate TH2 and lower TH1)
- Bee Venom
A greater understanding of the underlying mechanisms of aging and chronic illness has shown that seemingly simple peptides are found to be involved with and regulate most every known process and system in the body in a tissue and cellular specific manner.

The body uses a vast array of highly specific signaling peptides to regulate different parts and functions of tissues throughout the body. Thus, peptide therapy offers the potential to achieve specific desired responses of select tissues rather than less precise and broad effects of hormone therapy or trying to achieve a desired effect by altering physiologic processes with synthetic medications.

Currently, peptides are available that are 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, weight loss and other metabolic activities, tissue healing and specific biological functioning of the brain, skin, eyes and urinary and reproductive systems.

Thus, increasing numbers of peptides are becoming clinically available that can safely improve, optimize or normalize specific functions of the body.
Peptides

- Thymic peptides
  - Thymosin Alpha 1 (TA1)
  - Thymosin Beta 4 (Tβ4)
  - Thymulin

- Pineal proteins
  - Epithalon (addendum)

- Nootropics
  - Semax
  - Selank
  - Cerebrolysin

- Antimicrobial peptides
  - LL-37

- Others
  - Follistatin
  - BPC-157
Peptides for CFS/Lyme

- **Thymic peptides:** Thymosin alpha-1 (boost TH1), thymosin beta-4/thymulin (TH1-TH2 modulation)
- **BPC-157**
  - Reduces inflammation and increases healing in most every tissue, including gut (probably best treatment for leaky gut), brain, skin, muscle, degenerative joints, cardiac (prevents and treats arrhythmia, & heart failure in Lyme myocarditis), neuropathic pain and protective against neuro and endotoxins.
- **Noortopics-Cerebrolysin/Semax/Selank**
  - Improves brain function, memory, depression and anxiety
- **GHRP/GHRP** - increases growth hormone
- **GH Frag 174-191** - fragment of growth hormone
- **PT 141** - libido for men and women & erectile dysfunction
- **Epithalon** (see Addendum Slides)
  - Pineal peptide-increases longevity with significant reduction in CVD and cancer
  - Increases telomere length
  - Can reverse infertility
- **Delta Sleep Inducing Peptide (DSIP)** - induces deep sleep and reduces pain
- **Follistatin** - weight loss, muscle gain
- **Antimicrobial peptides (LL-37)**
According to the U.S. Center for Disease Control (CDC), approximately 80% of aged individuals are afflicted with at least one chronic disease as a result of a declination of thymic-related immune function.\textsuperscript{73}

Obesity and calorie intake are strongly associated with thymic involution.

The majority of people have pineal gland calcification by age 30.


Thymic Peptides – Clinical Effects
(Thymosin alpha-1, thymosin beta-4, thymulin)

- Improved tissue repair and healing\(^{35,36,37,41}\)
- Improved host defense to infection\(^{26,27,28,29,30}\)
- Reverse immunosuppression of chronic infection (Lyme)\(^{24,26,27,28,29,33,34,37,}\)
- Increases antioxidant and glutathione production\(^{26,27,28,31,28,29,63,66}\)
- Boost NK function\(^{26,35}\)
- TH2-TH1 immune modulation (infections, cancer, herxheimer, autoimmune)\(^{26,27,28,30,31,33}\)
- Bind neuro/endotoxins\(^{111}\)
- Cardiac regeneration and protection post-MI, CHF, etc.\(^{39,65,98,99,100}\)
- Neurologic regeneration and protection post-stroke, TBI, Lyme, Alzheimer’s, neuropathy, Parkinson’s, etc.\(^{63,67,42}\)
- Stimulate stem cell activity and proliferation\(^{32,34,36,38,40,41,42}\)
- Increases longevity\(^{89,90,91}\)
- Almost non-existent side effects at 100-fold dose + excess\(^{103,104}\)
- Excellent safety profile with large therapeutic window (over 1000 fold)\(^{103,104}\)
Approved in over 30 countries

- Cancer treatment/chemotherapy adjunct\textsuperscript{29,30,31,33}
- Treatment of Hepatitis B and C\textsuperscript{28,30}
- Treatment of AIDS\textsuperscript{28}
- Approved in USA as orphan drug
- Vaccine adjunct\textsuperscript{29}
TA1 Effects

T Helper Cells
TA1 increases Th1 subset

PBMCs from HCV patients

- IL-2
- Control, ZDX, FN, ZDX + FN
- * p < 0.05

- IL-4
- Control, ZDX, IFN, ZDX + IFN
- * p < 0.05

CD4
- Th1 (IL-2, IFNγ)
- Th2 (IL-4, IL-10)


* p < 0.001 versus control
** p < 0.001 versus 5-FU
TA1 Effects

Natural Killer Cells
TA1 increases activity

Thymosin β4 as a restorative/regenerative therapy for neurological injury and neurodegenerative diseases

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Thymosin β4 (Tβ4) promotes CNS and peripheral nervous system (PNS) plasticity and neurovascular remodeling leading to neurological recovery in a range of neurological diseases. Treatment of neural injury and neurodegenerative disease 24 h or more post-injury and disease onset with Tβ4 enhances angiogenesis, neurogenesis, neurite and axonal outgrowth, and oligodendrogenesis, and thereby, significantly improves functional and behavioral outcomes. We propose that oligodendrogenesis is a common link by which Tβ4 promotes recovery after neural injury and neurodegenerative disease. The ability to target many diverse restorative processes via multiple molecular pathways that drive oligodendrogenesis and neurovascular remodeling may be mediated by the ability of Tβ4 to alter cellular expression of microRNAs (miRNAs). However, further investigations on the essential role of miRNAs in regulating protein expression and the remarkable exosomal intercellular communication network via exosomes will likely provide insight into mechanisms of action and means to amplify the therapeutic effects of Tβ4.

Keywords: microRNA, oligodendrocyte progenitor cells, thymosin beta 4, tissue plasminogen activator, traumatic brain injury

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BPC (Body Protection Compound) Overview

- Protects and heals inflamed intestinal epithelium
  - Key treatment for leaky gut
- Significantly beneficial for inflammatory bowel disease, TBI, gastric ulcers, neurodegenerative diseases, pain syndromes as well as skin, muscle, tendon and ligament damage.
- Protects liver from toxic insults (alcohol, antibiotics, etc.) and promotes healing
- Protects against negative effects of acute and chronic stress, including increases cell survival under stress
- Prevents and reverses toxic damage from environmental, neuro and endotoxins (true of a number of peptides)
- Increases growth hormone receptors and effects of GH
- Prevents and inhibits arrhythmias

44. Boban-Blagaic A, Vladimir Blagaic, et al. The influence of gastric pentadecapeptide BPC 157 on acute and chronic ethanol
AMPs serve as endogenous antibiotics that are able to rapidly kill an unusually broad range of bacteria, fungi, parasites and viruses.\textsuperscript{76,80} Direct effects involve selective disruption of prokaryotic cell membrane\textsuperscript{106} In addition to their direct antimicrobial activity, also have multiple modes of action, including immune modulating effects\textsuperscript{106} LL-37 boosts mesenchymal stem cell migratory behavior and immunomodulatory effects.\textsuperscript{77} Significant anti-biofilm activity at low levels\textsuperscript{78,105} The MIC of LL-37 is much lower in vivo than in-vitro due to its immune modulating effects.\textsuperscript{78} AMPs are synergistic with antibiotics and reduce the development of drug resistance.\textsuperscript{79} Effective against free borrelia spirochetes and cystic forms\textsuperscript{76} Even low doses block the bioactivity of endotoxins and neurotoxins\textsuperscript{109,110} Well-tolerated, very safe with little side effects and a large therapeutic window Caution with autoimmune disease at high doses, as with any immune modulator.

\textsuperscript{78} Fuente-Nunez C, Hancock. Using anti-biofilm peptides to treat antibiotic-resistant bacterial Infections. Postdoc J 2015;3(2):1-8
AMP Mechanism of Action

Fig. 2. Association of amphipathic α-helical peptides (cylinders) with a lipid bilayer can occur in three general orientations: parallel to the membrane surface, at an oblique angle, or perpendicular to the membrane surface (i.e., along the bil

Fig. 8. Models of transmembrane channel formation. (A) Peptide α-helices (cylinders) initially associate parallel to the membrane surface, either superficially (left) or embedded just below the aqueous interface. (B) Peptides continue to accumulate at or near the bilayer surface, disrupting lipid packing and causing membrane thinning. This step may or may not involve peptide–peptide aggregation. Once a critical peptide/lipid ratio is reached, peptides either (C) insert into the membrane as a barrel-stave type pore, or (D) induce the localized formation of toroidal pores.

AMP-Rapid Onset of Effect (1 minute)

FIG. 3. Effects of SMAP29 or tobramycin treatment on the morphology of *P. aeruginosa* PAO1 evaluated by scanning electron microscopy. PAO1 was treated with media alone, tobramycin (5 μg/ml), or SMAP29 (0.5 μg/ml). At 1 min, 2 h, and 16 h the bacteria were processed for scanning electron microscopy. Within one minute, treatment with SMAP29 resulted in blebbing or blistering of the outer cell wall. The effects of tobramycin were much slower in their onset.

Nootropics

- Neurotrophic action similar to that of nerve growth factors \(^{72-74}\)
- Peripheral and central nervous system stimulation
- Neuroprotective effects
- Shields neurons from neurotoxins, inflammation and injury
- Protects from stress and depression
- Improves memory (even in healthy adults)
- Neurological regeneration
  - TBI \(^{69}\)
  - Alzheimer’s \(^{15,69-72}\)
  - Parkinson’s
  - Stroke \(^{69,73}\)
  - Toxin induced
- No significant side effects reported \(^{15,69,70,72,73}\)
Mesenchymal stem cell (MSC) treatment effects include:

- Direct replacement of the injured tissue with growth of the MSCs
- Paracrine action on injured cells and supporting tissue
- Activation of stem cells in and around the injured tissue
- Indirect effects on tissue support
- Stimulation of revascularization
- Protection of tissue from stress-induced apoptosis
- Protection of tissue and cells from neurotoxins
- Anti-inflammatory effects
- Immune modulatory effects
- Secretion of antimicrobial peptides

MSC paracrine effects are bidirectional, resulting in reprogramming of their exosomes and secretome to respond to specific need of the tissue.

MSCs will secrete different products in presence of infection (maybe not if stem cells have been chronically exposed to insult or invader)
UC™MSC vs. Autologous MSCs

- Autologous stem cells derived from one’s bone marrow or fat tissue have served as the mainstay of rejuvenate stem cell therapy for the last decade.

- The aging of MSCs, as well as their microenvironment, dramatically affect the function, viability and rejuvenating potential of MSCs, especially over many years.

- The use of autologous MSCs of CFS/Lyme patients often have limited regenerative capacity due to age, chronic illness, inflammation, infections and cumulative negative effects of environmental toxins and endotoxins, unhealthy lifestyle and medications.

- Studies show that chronic use of seemingly safe, commonly used medications, such as NSAIDS, will dramatically reduce the body’s MSC function.

References:
Aged autologous MSCs from chronically ill patients, such as Lyme, often suffer from:

- Loss of ability to secrete numerous cytokine, peptide regulators, growth factors, and antimicrobial peptides
- Reduced anti-inflammatory effects
- Reduced immune modulatory capacity
- Reduced self-renewal and differentiation capacity
- Lower telomerase levels and shorter telomere length
- A reduction of chemokine receptors, limiting their effectiveness to home-in on the damaged target tissue.
- Overall loss of viability and increased apoptosis with stress (don’t survive the transplant)
- Reduced paracrine effects

Umbilical cord tissue MSCs do not suffer from the above limitations.

Systematic Review

Umbilical Cord Tissue Offers the Greatest Number of Harvestable Mesenchymal Stem Cells for Research and Clinical Application: A Literature Review of Different Harvest Sites

C. Thomas Vangsness Jr., M.D., Hal Sternberg, M.D., and Liam Harris, B.S.

Purpose: Recent years have seen dramatic increases in the techniques used to harvest and isolate human mesenchymal stem cells. As the potential therapeutic aspects of these cells further develop, informative data on the differences in yields between tissue harvest sites and methods will become increasingly valuable. We collected and compared data on cell yields from multiple tissue harvest sites to provide insight into the varying levels of mesenchymal stem cells by tissue and offer primary and alternative tissue types for harvest and clinical application. Methods: The PubMed and Medline databases were searched for articles relating to the harvest, isolation, and quantification of human mesenchymal stem cells. Selected articles were analyzed for relevant data, which were categorized according to tissue site and, if possible, standardized to facilitate comparison between sites. Results: Human mesenchymal stem cell levels in tissue varied widely according to tissue site and harvest method. Yields for adipose tissue ranged from 4,737 cells/mL of tissue to 1,550,000 cells/mL of tissue. Yields for bone marrow ranged from 1 to 30 cells/mL to 317,400 cells/mL. Yields for umbilical cord tissue ranged from 10,000 cells/mL to 4,700,000 cells/cm of umbilical cord. Secondary tissue harvest sites such as placental tissue and synovium yielded results ranging from 1,000 cells/mL to 30,000 cells/mL. Conclusions: Variations in allogeneic mesenchymal stem cell harvest levels from human tissues reflect the evolving nature of the field, patient demographic characteristics, and differences in harvest and isolation techniques. At present, Wharton's jelly tissue yields the highest concentration of allogeneic mesenchymal stem cells whereas adipose tissue yields the highest levels of autologous mesenchymal stem cells per milliliter of tissue. Clinical Relevance: This comparison of stem cell levels from the literature offers a primer and guide for harvesting mesenchymal stem cells. Larger mesenchymal stem cell yields are more desirable for research and clinical application.
Antimicrobial Effects of MSCs

Mesenchymal stem cells (MSCs) secrete LL-37. Younger MSCs secrete significantly more antimicrobial and immune modulating peptides as well as growth factors, cytokines and signaling molecules. MSCs shown to enhance bacterial clearance and increase survival in bacterial or LPS induced sepsis and cystic fibrosis, which is shown to be mediated by the antimicrobial and endotoxin binding of LL-37. Thymic peptides and LL-37 are shown to enhance the proliferation, differentiation and migration of MSCs into target tissues as well as increase their immune modulating effects. Thus, in addition to being used as stand-alone therapies, the peptides can multiply the already profound regenerative and healing effects of UC-TMSCs

Thymosin β4 Increases the Potency of Transplanted Mesenchymal Stem Cells for Myocardial Repair

Lei Ye, MD, PhD; Pengyuan Zhang, MD, PhD; Sue Duval, PhD; Liping Su, BSc; Qiang Xiong, PhD; Jianyi Zhang, MD, PhD

Background—Thymosin β4 (Tβ4) has been shown to enhance the survival of cultured cardiomyocytes. Here, we investigated whether the cytoprotective effects of Tβ4 can increase the effectiveness of transplanted swine mesenchymal stem cells (sMSCs) for cardiac repair in a rat model of myocardial infarction (MI).

Methods and Results—Under hypoxic conditions, cellular damage (lactate dehydrogenase leakage), apoptosis (terminal deoxynucleotidyl transferase dUTP nick end labeling cells), and caspase-8 activity were significantly lower, whereas B-cell lymphoma-extra large protein expression was significantly higher, in sMSCs cultured with Tβ4 (1 μg/mL) than in sMSCs cultured without Tβ4, and Tβ4 also increased sMSC proliferation. For in vivo experiments, animals were treated with basal medium (MI: n=6), a fibrin patch (Patch: n=6), a patch containing sMSCs (sMSC: n=9), or a patch containing sMSCs and Tβ4 (sMSC/Tβ4: n=11); Tβ4 was encapsulated in gelatin microspheres to extend Tβ4 delivery. Four weeks after treatment, echocardiographic assessments of left-ventricular ejection fraction and fractional shortening were significantly better (P<0.05) in sMSC/Tβ4 animals (left-ventricular ejection fraction=51.7±1.1%; fractional shortening=26.7±0.7%) than in animals from MI (39±3%; 19.5±1.7%) and Patch (43±1.4%; 21.6±0.9%) groups. Histological assessment of infarct wall thickness was significantly higher (P<0.05) in sMSC/Tβ4 animals (50%, [45%, 80%]) than in animals from MI (25%, [20%, 25%]) group. Measurements in sMSC (left-ventricular ejection fraction=45±2.6%; fractional shortening=22.9±1.6%; TH=43% [25%, 45%]), Patch, and MI animals were similar. Tβ4 administration also significantly increased vascular growth, the retention/survival of the transplanted sMSCs, and the recruitment of endogenous c-Kit+ progenitor cells to the infarcted region.

Conclusions—Extended-release Tβ4 administration improves the retention, survival, and regenerative potency of transplanted sMSCs after myocardial injury. (Circulation. 2013;128[suppl 1]:S32-S41.)

Key Words: angiogenesis ■ microsphere ■ myocardial infarction ■ stem cell ■ tissue engineering
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 LD
Identification of Immune Dysfunction

- Low NK cell function < 30 LU
- Low immune cell function (ATP production) (Quest)
- Low CD 57 (Labcorp)
- Elevated C4a (Quest-Nat. Jewish on dry ice)
- VEGF (increase with bartonella, suppressed by molds)
- Eosinophil cationic protein (Babesia—may only increase after treatment)
- ACE above 30
- 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 IF gamma))
- Leptin above 12
- Elevated human transforming growth factor beta (HTGFB)
- Most any band on Quest WB, (even a 41 kd—selection bias on my part)
  - Provoke with antibiotics before doing indirect testing and/or treat the immune system before testing
  - Will know with a high probability who will or should test positive on further Lyme testing
Markers of Immune Dysfunction

- Low or low normal NK cell function <30 (Quest)
- Elevated C4a (Quest)
- Elevated HTGF-beta
- ECP-Eosinophil cationic protein (high sensitivity for Babesia with provoked test)
- Immune activation of coagulation (D-dimer, soluble fibrin monomer, prothrombin fragment 1+2, thrombin antithrombin complex, PAI-1 often with Babesia)
- Low immune cell function (ATP production) (Quest)
- Low CD 57 (Labcorp)
- Elevated VEGF with bartonella (if zero, not a valid test)
- Low IgG subclasses
- ACE above 30

Importance is based on combination of sensitivity, specificity and logistics (ability to get useful results due to difficult processing, complex processing needed or send out required and based on over 10 years of clinical practice (mostly with Quest for the standard tests).

Do not include specialty tests or specialty laboratories which can be extremely useful.
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<td>Conditions</td>
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- Healing, body fat
- Cognitive dysfunction, memory, stroke, depression, TBI, anxiety
- Growth hormone
- Weight loss, muscle relaxation
- Tanning, weight loss
- Libido, weight loss
- Immune boosting, infection, cancer
- Immune modulation, rejuvenation, muscle pain
- Systemic or GI infection, rejuvenation
- Sleep
Thank You

Questions?

(can email kholt@holtorfmed.com or office phone # 310-375-2705)
Conclusions

Summary:

- Lyme disease is a multisystem disease with a key component being immune dysfunction.
- The immune dysfunction (TH1-TH2 shift) is a key component for understanding the ability for effective diagnosis and treatment of LD.
- Failure to address these immune abnormalities are a common cause of treatment failure.
- Treatments that address these abnormalities, including peptide therapies and umbilical cord stem cells can be very effective and may be replacing the standard of long-term antibiotics.
Markers of CFS

- Low NK cell function < 30 LU (low TH1)
- Low CD 57 (Labcorp)(low TH1)
- Elevated C4a (high TH2)
- Elevated HTG FB (High TH2)
- ECP (provocated)
- Immune activation of coagulation (D-dimer, soluble fibrin monomer, prothrombin fragment 1+2, thrombin antithrombin complex, PAI-1)(high TH2)
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 was 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
Immune Modulating Therapies

- Increase TH1 and decrease TH2
- Boosting NK cell and lowering inflammatory cytokines
  - Peptides (Thymosin alpha-1/BPC 157/Epithalon)
  - LDN
  - IVIG (low dose or high dose—give 10-20 iu pitocin IV with each treatment if possible)
  - Ozone (MAH/Direct/High-dose/10-pass)
  - UVBI
  - LDA/LDI
  - 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
  - GcMAF/Leukine/Neupogen
  - Probiotics
  - Silver
  - Heparin
  - Antioxidants/Glutathione (low glutathione decreases TH1 and increases TH2)
  - Chelation (heavy metals stimulate TH2 and lower TH1)
  - Bee venom
  - Acupuncture
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\textsuperscript{1,19,12,14,66}
- 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
- Anti-tumor effects
TA1 Effects

Natural Killer Cells

TA1 increases activity

Mean cytotoxicity

PBS

ZDX

Effector : target ratios

Murine model of herpes simplex virus

Identification of immune dysfunction

- Elevated CRP, ESR
- Low testosterone/estrogen dominance
- Adrenal dysfunction (cortisol/DHEA)
- Low NK cell function < 30 LU
- Low immune cell function (ATP production) (Quest)
- Low CD 57 (Labcorp)
- Elevated C4a (Quest-Nat. Jewish)
- Low IgG subclasses (Secondary to TH1-TH2 shift (low IFN-gamma))
- Leptin above 12
- Elevated human transforming growth factor-B (TGF-B)
- Any condition on slide 9
Initial Labs CFS/FM

- 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)

- NK cell activity (Quest)
- Thrombotic Marker panel
  - D-dimer
  - Prothrombin fragment 1+2
  - Thrombin-antithrombin complex
  - SFM
- Natural killer cell # (CD57) (Labcorp)
- ACE
- HTFG Beta -1
- Eosinophilic cationic protein (ECP)
- VEGF (prone to error)
- Lymphocyte subpanel #1
- IgG subclasses

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
Initial Labs CFS/FM

(Sicker the patient)

- **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
Thank You

Questions?