## Proposed hypothesis as an explanation for CFS abnormalities


### ABSTRACT

**Chronic fatigue syndrome** (**CFS**) is a disorder characterized by extreme fatigue or tiredness that doesn't go away with rest and can't be explained by an underlying medical condition. **CFS** can also be referred to as myalgic encephalomyelitis (ME) or systemic exertion intolerance disease (SEID). Symptoms of CFS include fatigue/fatigue like symptoms, memory loss, unexplained muscle or joint pain, extreme exhaustion lasting more than 24 hours after physical or mental exercise (PEM) Patients with chronic fatigue syndrome showing signs of immune system involvement that play a major role in fatigue symptoms. CFS patients sharing similarities to that of autoimmune disease patients. Findings of symptom relief during pregnancy and the use of autoimmune drugs having major effect in CFS patients. HPA abnormalities found in CFS patients that is suggested to be the origin of the condition. Abnormalities that suggest hormonal depletion of cortisol and ACTH with ACTH autoantibodies found in a number of CFS patients. Hypothesized idea that the immune system is targeting the hormone molecules of CFS patients. Further hypothesizing the cause of post exertional malaise being dependent on the increase in stimulation between the immune system and autoantigen. Potential explanation for why patients with CFS symptoms get worse during stress. Synthetic hormone testing showing adverse reactions in CFS patients that supports the idea further.


### Introduction

Chronic fatigue syndrome is a complex disorder with a variety of unique aspects that are observed in diagnosed patients. Because of the vast differentiation between patients the idea that CFS does not represent one pathological illness is quite often presented by researchers. Unique symptoms such as PEM are key for further understanding the potential pathology of CFS. All hypothesis for CFS should touch up upon the explanation for PEM and why the hypothetical pathology would result in this symptom. Further more understanding and identifying similarities between CFS and other health conditions is key to progress forward in classifying the pathology of CFS. Researchers suggest that CFS is a gender bias condition with women significantly more likely to develop the illness [1]. More so, many researchers also believe there to be genetic disposition for developing CFS with a significantly higher probability of developing CFS if another family member has the condition [2]. Fatigue in CFS is one of the most prevalent symptoms experienced by patients and is suggested to have the biggest impact on the patient's ability to maintain their previous lifestyle. Fatigue can be observed as the lack of energy required to complete voluntary functions both physical and mental. This is a common symptom for a variety of different health conditions however, the exact mechanism of fatigue varies highly. Fatigue can occur as a result of a large variety of changes in normal bodily functioning, heart disease, autoimmunity, depression are all conditions that express the symptom of fatigue. For health conditions such as heart disease, kidney disease or Type 2 diabetes it is easy enough to interpret why fatigue symptoms would be experienced. However, conditions such as depression or any immune orientated illness the cause of fatigue remains unclear. Fatigue in general is an important mechanism of the body as it can be hugely beneficial in terms of survivability. The most important aspect of fatigue caused by sickness in my opinion would be that of the conservation of energy. The immune system just like any other system of

the body clearly requires energy in order to function properly. However, unlike the other bodily systems the immune system takes more of a vacant role in everyday activity. The amount of energy the immune system needs when the host is sick is going to be far greater to that of when the host is in a normalized state. So, where does this extra energy come from? My understanding is that all other systems of the body would become severely limited as to how much energy they can consume in order to prioritize the immune system. The inability to access the recourses needed for ordinarily body function is what I believe to be the mechanism of fatigue in immune orientated illnesses.

**CFS AS A MULTI SYSTEM DISORDERS**

**Involvement of the immune system in CFS**

The immune system being the root cause of CFS is one of the more common ideas presented by researchers and with good reason. The cause of fatigue in CFS is unexplained just as it is in any immune orientated illness. When dealing with an infection of some kind, fatigue is generally around as a primary symptom. Is it the virus that is causing the fatigue or is it the bodies response to the virus? If it was the virus that causes fatigue then what is the explanation for fatigue in autoimmunity [19, 20]. Taking a look deeper into autoimmunity [19] shows that quote" Fatigue is very prevalent among patients with Multiple Sclerosis (MS). Seventy to ninety percent of MS patients suffer from fatigue. It is often the most disabling symptom and often leads to early retirement." More so, from a survey done on RA patients. [20] More so from a survey showed that 98% of AD patients reported they suffer from fatigue. 90 % reported feeling depressed as a result of fatigue. 54% reported that fatigue negatively affected their sex life. Nine-in-10 (89 percent) say it is a "major issue" for them and six-in-10 (59 percent) say it is "probably the most debilitating symptom of having an AD. "More than two-thirds (68 percent) say their "fatigue is anything but normal. It is profound and prevents [them] from doing the simplest everyday tasks."While nearly nine-in-10 (87 percent) report they have discussed their fatigue with their doctor, six-in 10 (59 percent) say they have not been prescribed or suggested treatment by their doctors. Seven-in-10 (70 percent) believe others judge them negatively because of their fatigue. Three-quarters (75 percent) say their fatigue has impacted their ability to work; nearly four-in-10 (37 percent) say they are in financial distress because of it; one-in-five (21 percent) say it has caused them to lose their jobs; while the same number (21 percent) report they have filed for disability as a result of their fatigue. Fatigue impacts nearly every aspect of AD patients' lives including overall quality of life (89 percent), career/ability to work (78 percent), romantic (78 percent), family (74 percent) and professional relationships (65 percent) and their self esteem (69 percent), among others. Fatigue is clearly prevalent as a symptom in all AD patients but the exact reason for this fatigue is unclear. Researchers have suggested that the cause of fatigue is due to the body's response to the damage caused by the immune system. The idea that I am presenting is that fatigue is being applied by the immune system itself as a beneficial response in order to conserve energy. When we get sick from a viral illness, we stay home, we rest and then we recover. Why are we unable to carry on with daily activities whilst sick, if the body is responsible for purposely creating the mechanism of fatigue then there has to be reason.

Fatigue observed in a sub group of CFS has a clear correlation with an alteration of gene expressions. This is backed up by [3] where they conclude that (qutoe)"At least two subgroups of CFS patients can be identified by gene expression changes following exercise. The larger subgroup showed increases in mRNA for sensory and adrenergic receptors and a cytokine. The smaller subgroup contained most

of the CFS patients with orthostatic intolerance, showed no post-exercise increases in any gene, and was defined by decreases in mRNA for α-2A. FM only patients can be identified by baseline increases in 3 genes. Post-exercise increases for 4 genes meet published criteria as an objective biomarker for CFS, and could be useful in guiding treatment selection for different subgroups." If gene expression is equivalent to the bodies blue print then an alteration in gene expression should bring about changes in the body. More so, an alteration of gene expression in general can only come as a result of a function of the body. So, if fatigue in CFS patients correlates with exercise and exercise correlates with an alteration in gene expression then potentially gene expression could be somewhat responsible for the fatigue in CFS.

**Involvement of the neuroendocrine system in CFS**

Although fatigue during sickness may be a beneficial process of the body; it has some serious implications that go with it. From a survivability perspective during sickness such as a viral infection you would be in a fairly vulnerable state as you would be unable to protect yourself against any adverse events. For survival there must be some way to remove the symptoms of fatigue temporarily in order to focus on the life-threatening event. This is where the fight or flight response comes into play as the release of epinephrine and norepienphrine make changes around the body that counteract the changes that occur as a result of immune system functions. I theorized that the stimulation of the fight or flight response should potentially result in some serious relief in fatigue symptoms for immune orientated illnesses.

Imagine that fatigue is represented by a switch that is either off or on, by default the fatigue switch is set to off and this would be a normalized state for the individual to be in. However, after infection from a virus the immune system becomes activated and forms a response but in order to run the immune systems response the body has to make certain changes. The immune system will require a large amount of energy to function properly. in order to function, the immune system turns the fatigue switch in the body to **on**. This will then stop the individual from wasting crucial energy while the immune system works to destroy the viral threat. However, whilst the individual is in bed resting up the building suddenly catches fire and now the individual's life is in danger where if they do not act, they may die. This external stimulus triggers the fight or flight response into releasing the adrenal hormones that then turns the fatigue switch that was set to **on** back to **off.**

This response is so great that it is used for life threatening allergic reactions, EPI pens are given out to those with allergic reactions as they work the same as in the above example. The immune system makes changes throughout the body that are then overruled by the release of epinephrine throughout the bloodstream. If epinephrine is capable of alleviating the impact of the immune systems response in allergic reactions then the same could be true for any immune orientated illness. If fatigue is caused by the immune systems response like I am suggesting it is for some CFS patients then stimulating the fight or flight response could potentially result in some major decreases in fatigue like symptoms. [4] Further testing will be required to prove this idea an understanding right but for now it is just an idea to help grasp the mechanism of fatigue.

Patients with CFS experiencing temporary remission during pregnancy. One of the more abnormal events that is experienced by patients with CFS. Furthermore, Warren Tate New Zealand biochemist with an interest in CFS research backs this up by stating that his daughter also experienced this temporary remission. More from [5] stated that (quote)"Although some pregnant women with chronic fatigue syndrome experience no change or a worsening of the severity or frequency of their symptoms, some experience relief. This relief has been linked to the mother's increase level of pregnancy hormones, as well as the suppression of the immune system that is associated with pregnancy. This suppression helps make sure that the mother's immune system does not recognize the developing fetus as a foreign substance and reject it. After delivery, however, most mothers with chronic fatigue syndrome experience a relapse of symptoms, which can be caused by the strain of delivery and exertion it takes to raise a newborn. At this time, support and healthy lifestyle choices are crucial to maintain the new mother's health." How and why would someone's illness be reduced significantly during pregnancy? What changes occur during pregnancy? [35] Human placental lactogen, Relaxin and Progesterone are hormones that are involved in the changes that occur during pregnancy. Hormones alter functions of the body so for symptom relief to occur as a result of hormone production then what does this mean for the pathology of CFS. Not to mention there are clear observable changes in immunity during pregnancy. [6]Qutoe" The findings of this study suggest that there are a number of immunological changes occurring in normal pregnancy. The main changes appear to be an increase in immunological potential of T and B lymphocytes without an increase in activity'.The fact that patients found some kind of remission during pregnancy is fairly important in further classifying the mechanism of CFS.

**CFS AS AN IMMUNE DISORDER OF THE NEUROENDOCRINE SYSTEM**

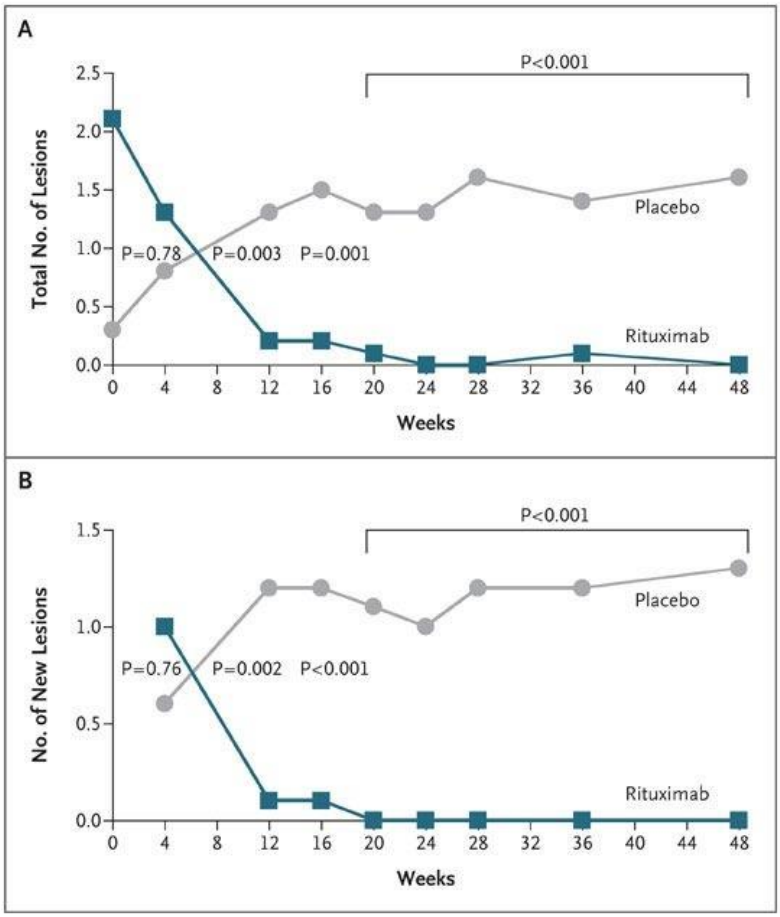
If the immune system is reacting to a threat and is then interrupted whilst entering the stage of pregnancy wouldn't there be some serious implications as a result of this. Does some unknown pathogen decide to take a break whilst the host enters pregnancy? This gives serious rise to the possibility of autoimmunity. Patients with various autoimmune conditions described significant relief during pregnancy similar to the relief that CFS patients have. [8] Summarized that quote" In some cases, pregnancy may have a profound effect upon the symptoms of autoimmune disease, such as in the case of RA and multiple sclerosis." [36]qutoe" I was diagnosed with MS in 2000. Before I became pregnant with Matthew in 2010, my walking was becoming more difficult. I used a stick for balance at the very least. I was not able to write or use the keyboard very well. But then, during pregnancy, lots of those things changed. It became easier to walk. I could write legibly again and type on a keyboard. The tremor on my hands almost disappeared. I also seemed to get stronger, carrying things was easier and, incredibly, I could even lift my baby son for about the first nine months, something I thought would be impossible." I am currently unaware of any other conditions that are affected in the same way CFS and autoimmune patients are whilst in pregnancy. This is quite serious as it really does show the possibility that there is a subgroup of CFS patients that have some kind of hidden autoimmune disease. Not all patients with CFS have had this experience but that is expected, the diagnosis of CFS does not represent one pathological illness so patients are always going to have varied responses to different tests. Autoimmunity is becoming a strong fit as the similarities between AD and CFS are quite significant. Autoimmune conditions are quite often progressive in onset and more common in women.[10] Some CFS patients report a progressive onset [9] and CFS in women is 4.1 for that in men

[1]. AD and CFS patients have both reported the unique experience on relief during pregnancy. Both CFS and AD quite often being associated as a hereditary illness [2, 11]. More so there is no real explanation for fatigue as a symptom in AD just as it is for in CFS patients.

**The use of rituximab in CFS patients.**

Researchers were stunned when several patients with a diagnosis of CFS went into remission following the infusion of rituximab. [12] quote" The 2011 results showed 'lasting improvements in self-reported fatigue' in 67% of ME/CFS patients on rituximab compared with 13% of patients on placebo during a follow-up phase lasting 12 months. Also, rituximab was also associated with significant improvements in some quality of life measurements, and no serious adverse events were reported." More so [13] discusses quote" The randomized and placebo-controlled phase-II trial (KTS-1-2008) using the anti-CD20 monoclonal antibody rituximab as a B-lymphocyte depleting intervention for ME/CFS, suggested clinical benefit on ME/CFS symptoms in a subgroup of patients. This was big news for the CFS community as it gave rise to hope for a potential treatment option, patients actually meet some form of remission following this infusion.

Rituximab is a monoclonal antibody that binds to the CD20 protein on the surface of B cells and causing depletion via a variety of different mechanisms. It is essentially a drug that is used to treat b cell mediated auto immune conditions and with a great deal of success for that matter. Examples coming from [14] showed that complete remission of systematic rheumatoid vasculitis was achieve in three-fourths of patients receiving rituximab daily. Shown by [15] the results of rituximab used in MS displayed by graph.




More so, they concluded that, quote" In conclusion, a single course of rituximab significantly reduced both MRI and clinical evidence of inflammatory activity for 48 weeks. The magnitude of this effect and the rapidity of its onset provide support for the theory of B-cell involvement in the immunopathologic process of multiple sclerosis, and they show that B-cell depletion has the potential to decrease disease activity in patients with the relapsing form of this disease."The Rituximab trials for CFS may have been deemed an overall failure but that does not discount the fact that some CFS patients clearly improved following the course treatment. Not only did these patients improve significantly they also got worse as the effects of the drug on B cell population started to weir off [16]. This is a clear indication that the depletion of B cells in CFS patients resulted in significant improvements in symptoms experienced. This means that the pathology of the illness for these particular patients has to incorporate the function of B cells in some way or another. This is a fine explanation of why some CFS patients have a progressive onset as B cell autoimmune condition are generally progressive that worsen over time [17]. Patients with RA symptoms may start off small and insignificant but then will progress further down the line, this is the same for types of multiple sclerosis where patients are likely to receive an extremely late diagnosis from when the symptoms first occurred. Rituximab clearly made significant improvements in a select group of patients with exact numbers varying between different trials. The patients with CFS recovery from Rituximab was reminiscent of the recovery made from autoimmune conditions such as rheumatoid arthritis with the delaying response following the infusion.[18] The majority of the drugs used to treat autoimmune condition can be used across the whole range of auto immune conditions, this is because

the drugs are generally made to block or impaired immune pathways resulting in a decrease in severity of the illness. The fact that a drug used to treat auto immune conditions works on an unexplained illness that I am theorizing to be an auto immune condition is fairly significant in terms of evidence.

**What is the auto antigen?**

If it is autoimmunity like I am suggesting that is behind CFS then there must of course be an identifiable antigen. There are no real distinct symptoms in CFS that can be observed as a result of the immune system attacking the body. For example, in rheumatoid arthritis where the immune system is targeting the synovial joints you have symptoms such as joint pain, joint swelling, joint stiffness and loss of joint mobility [22]. More so, in multiple sclerosis where the immune system is attacking the (CNS) you have visionary problems movement problems slurred speech and a whole lot more that I will not care to mention [23]. As if the immune system is attacking a function of the body then this should result in symptoms experience by the patient that represents this attack. For the cause of CFS to be autoimmune then the antigen has to meet a few conditions.

1. The antigen has to be short lived / disposable.

What was remarkable about the recovery seen in CFS patients from rituximab was that all the symptoms were diminished at the same time. This is completed different to various other AD conditions where symptoms of RA, MS are still noticeable after the full depletion on b cell population. Depleted b cells may stop damage from being inflicted but it does not remove the preexisting damage that has already occurred. Because there is no preexisting damage observed in CFS patients the idea that the antigen for CFS being short lived / disposable is a very logical possibility.

2. the antigen has to be more present during exertion to explain the symptom of PEM.

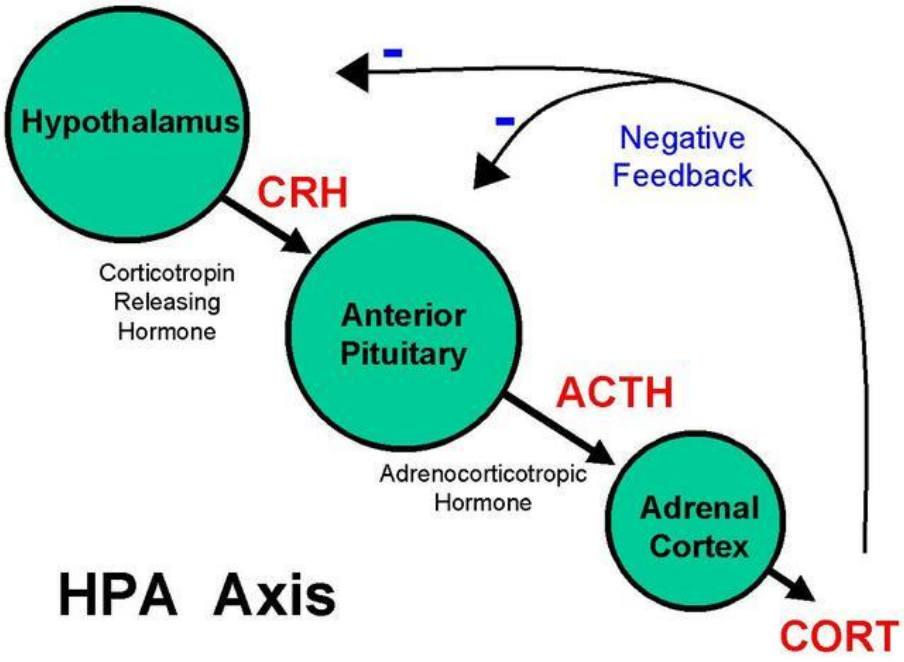
If the pathology of CFS is autoimmunity then why do patients have their symptoms elevated during exertion. The greater the amount of antigen would naturally result in a greater response from the immune system. The greater the stimulation between the immune system and the antigen would most likely bring about higher severity in fatigue symptoms. Prof? If I asked a person who was allergic to peanuts to choose between having to consume 1 peanut or 10 which would they choose? They would choose the less amount due this concept.

**HPA axis and it's relation to PEM**

Because of how prevalent PEM is in CFS patients understanding the symptom further would be key in order to identify the antigen. During research I have observed that the symptom of PEM which is a unique symptom which CFS patients experience seems to correlate highly with the HPA axis. The HPA axis can be viewed as the bodies stress response that is activated during a stress event, this event could be of minor stress such as making a cup of coffee to something more serious like playing high level sport or a job interview. The end result of this activation is the stress hormone cortisol released from the

adrenal gland that then goes on to make changes throughout the body to help deal with the stress event. When you think about stressors you can class them into three groups, physical stress, mental stress and phycological stress. Both physical stress and mental stress are fairly easy to interpret however, phycological stress is more of an abstract concept. An example of a phycological stressor would be perceiving doing something stressful such as thinking about going for a run or re running past stressful events in your head the likes of a failed joke you once told. The HPA axis is a chain of events that starts with brain signaling and ends in the release of cortisol from the adrenal glands. The brain is stimulated by a stress event resulting in the release of the corticotropin-releasing-hormone (CRH) for short from the hypothalamus, these hormones then travel down to the pituitary gland. The CRH hormone stimulates the pituitary gland to secrete the stress hormone adrenocorticotropic hormone or (ACTH) for short this hormone will then continue the chain going further down to the adrenal gland. Once again, the same process will occur here where the hormone ACTH will stimulate the adrenal gland to start secreting cortisol. The amount of cortisol is dependent on the amount of ACTH and the amount of ACTH is dependent on the amount of CRH and the amount of CRH is dependent on the stress event that is taking place. Because of the way in which this chain works the overall outcome will be the release of cortisol into the blood stream dependent on the severity of the stress event.

**Diagram of the HPA axis**




**Involvement of HPA hormones in CFS**

[24] States that patients with CFS are showing lower cortisol levels to that of healthy patients. More so, [25] quote" In this study we have demonstrated an impaired cortisol response to the naturalistic

stressor of awakening in a large sample of carefully characterized patients with CFS. More specifically, similar percentages of patients and controls showed a significant rise to awakening, suggesting that this is a valid challenge paradigm; however, the mean response in patients was significantly less than that in controls." CFS is labelled as the invisible illness due to the lack of biological evidence found by researchers. However, there are clear biological changes that have been found in CFS and these were differentiation in cortisol levels in relation to that of healthy patients. Furthermore, it has been recorded that a recovery of CFS is linked to the cortisol levels of CFS patients returning to normal. [26] Chronic Fatigue Syndrome has been referred to by many as stress intolerance and what changes in the body occur during stress? [26] States that the greater the symptom of PEM then the more significant this decrease in cortisol is likely to be. This drop-in cortisol levels are quite often overlooked by many CFS researchers but it is happening and it is significant.

**HPA hormones as autoantigens in CFS**

What if CFS is an auto immune condition and revolves around the HPA axis. What if the antigen was a stress hormone? If the immune system is attacking a hormone like I am theorizing then the more hormones that are available to attack is going to result in a greater response from the immune system. (Potential explanation for PEM). Hormones are disposable and are constantly being synthesized so if the immune system was attacking these hormones like I am suggesting then not many changes would actually occur as a result of this. The attack would not accumulate and no visible damage would be observable, fitting the description for an invisible illness. Autoimmune conditions such as RA or MS you have a clear accumulation of damage that is done over time which can be seen by administering scans of the body. For CFS however, there will be no accumulation as although hormones are internal, they do not have the existing presence in the body that these other antigens do. More so, is it impossible for the immune system to start attacking a stress hormone of the body such as cortisol?

If the immune system was attacking hormones then there should be clear indication of hormone depletion found in CFS patients. [29, 30, 31, 32] Multiple studies have shown CFS patients producing less cortisol than healthy patients following an ACTH stimulation test. This is not just a few patients either, there is a multitude of patients who are showing abnormalities in cortisol readings following an ACTH stimulation test. When this test is performed there is a predicted range of what cortisol levels should be after stimulation which is dependent on what the starting levels of cortisol were pre synthetic ACTH. Multiple CFS patients are falling below this expected range which is another abnormality that CFS patients experience. A general assumption as to what this means would be that the adrenal gland is not producing cortisol to the same extent as a healthy patient would. The problem with this theory is that why would the adrenal gland be doing this and how would the pathology of CFS be orchestrating this change. I believe that the adrenal gland is producing the ideal amount of cortisol to that of healthy patients and that the low readings are a result of cortisol being destroyed. [29]Qutoe("Although this cortisol response to ACTH is clearly abnormal for all of the patients with CFS, the dose response curve varies. There is an initial exaggerated response followed by an abnormally blunted response, which is not the case for patients with primary or secondary adrenocortical insufficiency without a dysfunctional hypothalamus. Consequently, standard dynamic testing is not medically useful in these patients and

it is improper to use the defined normal cutoffs of response as is done with other conditions.") [29] quote" Numerous studies demonstrate that this lack of sensitivity likely explains the seemingly contradictory findings between studies using stimulation tests.[1,3,8,9,19,27,34-40] For instance, Scott et al in *Clinical Endocrinology* did 1ug ACTH stimulation tests on subjects with CFS and found a significant decrease in the delta cortisol value of patients with CFS vs. normals, but found that the reliance on this test and the arbitrary cutoffs that apply significantly impacts the sensitivity of stimulation tests in the patient population. They conclude, "*In conclusion, the amount of cortisol released following stimulation with 1ug ACTH, is lower in CFS patients than in healthy volunteers…We propose, as has been suggested from previous studies, that the abnormality of HPA regulation is more likely to be central in origin.*

Further observations of low peak cortisol levels.[31]

| **Study** | **Subjects** | **Illness duration** | **Comorbid psychiatric illness (method of assessment stated, if any)** | **Method** | **Cortisol findings in CFS patients** |
|---|---|---|---|---|---|
| Demitrack *et al.* (17) | 19 CFS (CDC) 18 healthy | 7.2 yr (mean) | Lifetime diagnoses: 7 major depression, 4 anxiety, 1 somatization disorder (DIS) | 3 samples at 2000 h | Low |
| Moorkens *et al.* (34) | 29 CFS (CDC) 9 healthy controls | 1.5 yr | Major psychiatric disorders excluded (no structured interview) | 5 samples between 2200 h and 0600 h | Low peak cortisol in CFS *vs.*controls |
| Hamilos *et al.* (35) | 7 CFS (CDC) 7 controls 7 depressed 7 allergy | Not given | 2/7 CFS had major depression, 1/7 CFS had panic disorder (DIS) | 7 samples over 24 h | Low peak cortisol in CFS *vs.*controls |
| MacHale *et al.* (37) | 30 CFS (CDC) 15 healthy | 5.2 yr | Depression excluded (SADS) | 2 samples at 0800+ 2200 h | No difference (but reduced diurnal variation in CFS) |

| | | | | | |
|---|---|---|---|---|---|
| Racciatti *et al.* (36) | 24 CFS (CDC) 5 depressed 16 healthy | Not given | No data | 6 samples over 24 h | No difference |
| Altemus *et al.* (33) | 19 CFS (CDC) 19 healthy | 3.7 yr | 3 CFS had current anxiety disorder, 11 CFS had somatoform pain disorder; depression excluded, but mean HRSD = 13.8 (DIS) | 5 samples at 0830–0930 h | No difference |

*[32]* copy&paste ( Demitrack *et al.* (17) undertook a careful dose-response study of 12 CFS and 10 healthy controls in which 4 doses of ACTH (Cortrosyn at 0.003, 0.01, 0.1, and 1.0 μg/kg) or placebo were administered on 5 separate days at 1800 h. Once again, there was a high rate of comorbid depression. Dose-response curves were significantly different in patients and controls: at low doses of ACTH, only CFS subjects showed cortisol rises above placebo, suggesting a hypersensitivity of the adrenal cortex to ACTH. However, at higher doses of ACTH, cortisol responses were significantly lower than controls, suggesting an overall reduced maximal secretory capacity of the adrenal cortex. A second study (24) used only one dose of ACTH (Synacthen), the standard 1-μg low-dose challenge (58, 59), administered at 1400 h. They demonstrated an inverse relationship between the baseline cortisol and the incremental cortisol rise in response to ACTH, again suggesting hypersensitivity of the adrenal cortex to ACTH in CFS subjects with impaired HPA activity. They also found significantly attenuated cortisol responses overall, which they interpret as reflecting a diminished adrenocortical reserve secondary to reduced stimulation from an impaired pituitary output of ACTH. However, Hudson and Cleare (60) repeated the1-μg Synacthen challenge in 20 nondepressed, medication-free CFS subjects, this time administered at 1200 h. There was no difference in cortisol response in comparison to a matched control group, although in males there was a trend toward a blunted response. This blunted response from ACTH testing is a clear indication of cortisol destruction. I believe there is no problem with the adrenal gland in CFS and that the low peak levels are due to hormone depletion and not the inability of the adrenal gland to produce cortisol.

**Further evidence to prove my hypothesis**

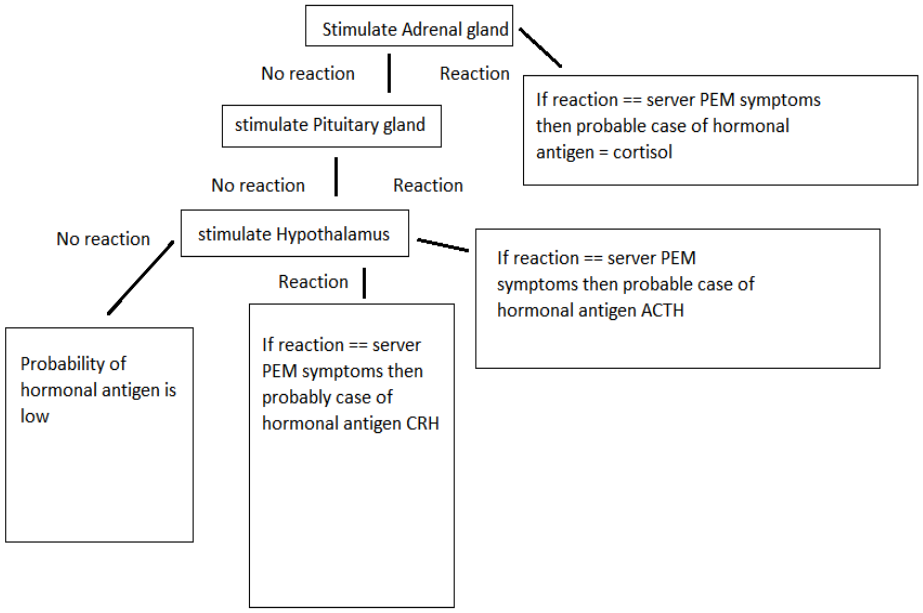
For rituximab to work on CFS patients the way it did and for my hypothesis to be correct then finding autoantibodies for a stress hormone would be an essential task. ACTH autoantibodies found in CFS patients [33, 34] Quote" Significant levels of chronic ACTH autoantibodies are a common pathological factor in CFS, AN and MD. These antibodies interfere with ACTH's ability to stimulate the production and secretion of cortisol, causing HPA dysregulation. As a result, patients suffer from the symptoms of adrenocortical insufficiency and the side effects of overactive cortisol-stimulating mechanisms utilized to compensate for this interference." The patients that had autoantibodies for the stress hormone ACTH had

a blunted response of ACTH production similar to blunted response of cortisol in other CFS patients. Quote "ACTH, it would explain why CRH stimulation in depressed patients provokes b-endorphin secretion similar to normal subjects but an apparently blunted ACTH response" [34] Quote "It is unlikely that isolated ACTH deficiency is a specific disorder. Most cases may be better characterized as adrenocortical insufficiency due to chronic ACTH autoantibodies" [34] Validating my belief that the immune system is destroying cortisol in a subgroup of CFS patients. If there are autoantibodies targeting the ACTH hormone in CFS patients then surely this would result in fatigue? Practically every other autoimmune condition expresses fatigue like symptoms.

**Testing hypothesis**

If the fatigue in autoimmunity is dependent on the stimulating between the antigen and the autoantibodies then the greater the stimulation should result in greater fatigue experienced by the patient. If my theory on fatigue in autoimmunity is correct, fatigue symptoms should be elevated by stimulating the HPA axis to produce a greater amount of the hormonal antigen.

Below is a diagram of how the test would play out.




First off, I would start by stimulating the adrenal gland of CFS patients and then depending on how they respond will determine the next step that I will take. If there is a serious reaction that is in accordance with the symptoms they experience from PEM then the possibility that the immune system is attacking the hormone cortisol is probable. If no server PEM was experienced, I would then move on to stimulating the pituitary gland. Once again, server PEM symptoms = high probability of ACTH being an antigen. NO PEM symptoms = next step.

**Evidence of reactions occurring in CFS patients following ACTH stimulation tests.**

[28]

Hello I'm a 26 year old male diagnosed with CFS by Dr Montoya for 10 years. I had an ACTH injection test, to test my adrenal glands, the results were within normal range. However the next day my CFS symptoms increased X10 and have stayed that way since 3 years ago. My muscle fatigue/ pain is much worse, my sleep is way worse I can't fall asleep and wake up even more unrefreshed. The doctors say this test is just supposed to simulate a regular stress response, but this never happened to me since having CFS so I'm thinking my stress response is being blocked on purpose to prevent my disease from worsening. I've taken prednisone(cortisol) before and nothing happened at all, yet ACTH did this to me I'm so confused, how was that possible? Has anyone had this test or this type of reaction before to ACTH test before?

[27] quote" So this morning I had he ACTH Stim test. My starting cortisol was 8.0 at 8am . Range is 4-24. Then they injected the stimulation and in an hour it raised to 31.0. She said my adrenals were able to react to stress. My question is when you have a chronic illness and your body is stressed everyday how are the adrenals able to keep up? They inject this stuff and you get a one time dose of stimulation. I even felt like the walking dead a few hours later. Was that from my adrenals being drained or just because I have CFS.I am so upset right now because I feel that a morning level of 8 is on the low side and my former endo wanted it 15-20 in the morning and had me on 5mg Cortef in the morning. Maybe I am just overreacting because I was certain the levels would not double … Anybody have this test before and what was your starting level. I am not sure if I should get another opinion or just accept it"

[28] quote"I also had the same test and was considered "normal". I was passing out during the test and the nurses and office staff kept telling me how much i must need coffee in the am because i was falling asleep. I think i crashed later that day too. I can't remember now. every time i try to tell the Drs that that happened they shrug it off saying i was expecting the results to be different. I kept asking if it was possible to have an autoimmune reaction to cortisol and the Drs keep saying no. Garbage. I wish they would just open their eyes for a minute and see that the reaction was a problem."

Patients with CFS experiencing reactions during synthetic testing that were so significant that they felt the need to express their concern on what had occurred. So, when CFS patients post on a forum that they felt like the walking dead post stimulation of the adrenal glands then what am I to make of my hypothesis.

**Conclusion**

There is clear immune involvement in CFS which is demonstrated by various tests researchers have conducted. The idea of autoimmunity is a strong fit for the potential pathology of the illness given the relief during pregnancy and the response to Rituximab. The similarities between CFS and various AD are quite extensive. Progressive onset is a common trait for AD and CFS, also women significantly more likely to receive a diagnosis. Clear signs of correlation between the HPA axis and fatigue symptoms for CFS patients found by various researchers. Abnormalities in cortisol readings with lower levels of cortisol

associated with the greater the symptom of PEM. ACTH stimulation in CFS patients showed more abnormalities with patients showing a blunted response of cortisol released into the bloodstream suggesting potential cortisol depletion. Cortisol levels also were shown to peak lower in CFS patients to that of health patients with various researchers suggesting the HPA axis is the central origin in CFS. My hypothesis was that CFS for a subgroup of patients was caused by the immune system targeting stress hormones of the body. Autoantibodies for the ACTH hormone was founded to be a common pathological factor in CFS. Patients with the autoantibodies showed abnormal CRH stimulation readings with a drop in overall ACTH to that of healthy patients. Patients also had a blunted response similar to the response that other patients had during the ACTH stimulation test. I theorize that fatigue in autoimmunity was somewhat dependent on the stimulation between the immune system and the antigen. Given this understanding fatigue symptoms should be elevated under stress where the antigen is going to be more present. The symptom of PEM that correlates highly with stress is evidence to suggest this possibility. Furthermore, this idea is backed up by CFS patients having a strong negative response to ACTH stimulation testing. Although my hypothesis is a strong fit for explaining the abnormal condition of CFS further larger scale testing will be needed for confirmation.

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