

# **How pain and stress create fatigue; and how to repair it with a personalized medicine and lifestyle strategy.**

**Carolyn McMakin, MA, DC**

Most clinicians have seen patients diagnosed with fibromyalgia or muscle and nerve pain accompanied by fatigue. And most people have experienced the reductions in function and energy that happen when pain or stress levels rise and stay elevated for a long period. The mechanisms by which pain and stress lead to fatigue, hormonal changes and decreases in cognitive function are as complex as they are fascinating. If practitioners are going to help patients cope with or recover from pain, stress and fatigue, it helps to know the pathways and mechanisms that contribute to strategies for repair.

The nervous system and centers in the brain control hormone function directly by increasing or decreasing levels of releasing factors and regulatory hormones that modify the peripheral endocrine system - the ovaries, the testicles, the pancreas, the adrenals, the kidney and the thyroid. The hormonal regulating factors in the brain combined with the peripheral hormone secreting glands are described as the neuroendocrine system.

When the body is under stress, regardless of the cause, the sympathetic nervous system and the brain respond in a preprogrammed fashion. If you think of all the processes that would be useful if a tiger was chasing you through the woods, it makes it easier to understand how these processes create problems when the stress response lasts longer than the 20 minutes it would take for the tiger to catch and eat you.

## **The threshold sets the tone**

Pain and emotional distress can both act as stressors. Different patients have different thresholds at which pain or stress becomes bothersome or are perceived by the nervous system as “life threatening” or serious. These thresholds are set as the brain is developing, even in utero. Children of women who had high levels of stress hormones during pregnancy have heightened stress responses when they are adults. Children conceived through artificial insemination in which the blastocyst was frozen and then inserted into the womb, have higher blood pressures and stronger stress responses in childhood by the age of seven than children

conceived naturally. Children who were molested or abused, or who had surgeries or severe physical trauma such as accidents before the age of seven have a stronger adult stress response and are seen more commonly as adult pain patients.

It is presumed that this heightened stress response exists because at these vulnerable ages the stress was literally life threatening and the neuroendocrine system threshold levels were set to react to all subsequent stressors at the same threat level. Any pain is perceived as a threat to existence even when an objective assessment would never label it as life threatening. Any stressor can provoke what seems to an outside observer as unreasonable anxiety and an exaggerated stress response.

The real neuroendocrine problems start when the stress lasts longer than 24 to 48 hours.

The sympathetic nervous system responds immediately to stress by increasing your heart and respiratory rate and increasing cortisone output from your adrenals. CRH (corticotrophin releasing hormone) or CRF (corticotrophin releasing factor) becomes elevated in the brain when the stress response is very strong or when it lasts longer than 24-48 hours. CRF can begin to rise in as little as 20 minutes in susceptible patients. If you want to understand what CRF does, think about what would be useful if you are being chased or dragged through the jungle by a tiger.

### **Stress and Pain Change Cognitive function**

CRF in particular, and stress hormones in general, change the brain and cognitive function. CRF impairs short-term memory, attention to detail, sequencing and higher cognitive functions. With stress, there is no need for short-term memory because the only important short-term event is the tiger. Why would you need to remember details or lists when a tiger is dragging you through the woods?

Epinephrine and norepinephrine, the short-term stress hormones, directly inhibit memory for details. Most people experience this problem as the "test-anxiety" when well-known facts and details become inaccessible during a stressful test situation.

Long-term memory is not affected because you may need to remember how you got away from the tiger the last time. So chronic pain patients cannot remember what they did 2 hours

ago but they can tell you in great detail about every bad thing that has ever happened to them. The brain is biased to remember every difficulty it has survived and to forget the known immediate threat.

The multiple affected pathways explain why no single intervention is equally beneficial in every patient who experiences stress and fatigue. Not everyone has each pathway equally dominant or equally affected.

### **Stress Changes all Repair Functions**

Think about the things you would not need to do if you were going to be eaten by a tiger in the next 60 minutes.

### **Adrenal hormones**

The adrenal glands sit on top of the kidney and produce cortisol, corticosterone, aldosterone, DHEA and platelet aggregating factor. All very useful when a tiger is chasing you and is going to be biting you. They raise heart rate, stop bleeding, dilate blood vessels in the muscles, constrict blood vessels in the fingers and toes, and make more blood sugar available to the muscles. But when these hormones are elevated long term, cortisol thins the gut wall and the other peripheral receptors get desensitized to adrenal hormones. Eventually the gland is exhausted and unable to produce enough for normal daily function. Cortisol cannot be tested in the blood because it is too short lived. Testing cortisol levels in saliva can be done by many laboratories and tells you whether the patient will benefit from cortisol replacement until the gland can recover.

**Thyroid hormone** regulates energy metabolism and tissue repair. TSH increases secretions of T4, the storage form of thyroid hormone. TSH is suppressed centrally by CRF during prolonged stress or pain. T4 is converted by an enzyme that takes off an iodine molecule to create the active hormone T3 that can bind to receptors. Epinephrine and norepinephrine, the immediate stress hormones, inhibit the conversion of T4 to T3. Decreasing TSH and decreasing T4 to T3 conversion makes sense from a survival standpoint. You have lots of sympathetic and adrenal flight or fight drive to keep your heart pumping fast, your muscles active and your blood sugar up so why do you need Thyroid? CRF reduces thyroid-stimulating hormone (TSH) directly by inhibiting its production in the brain even though peripheral levels of active thyroid (T3) are low. The patients are fatigued, tired, cold and constipated and have dry hair and brittle nails but their TSH levels are "normal".

**Growth hormone** (GH) is suppressed centrally by CRH. In an adult, growth hormone facilitates transport of amino acids across the membrane for tissue repair. 85% of growth hormone is released during stage 4 deep sleep in an adult. Patients with chronic stress, fibromyalgia or other chronic pain problems never get to deep sleep. The reticular activating system prevents deep sleep so you will be able to escape from the tiger if he might drop you in the night. Normal people get a spike of growth hormone one hour after vigorous exercise. If CRH is elevated that spike is inhibited inside the brain – why would you need to repair muscles if you are going to be tiger snacks in 60 minutes?

The patient is told to exercise to relieve stress and improve function. But if you exercise you need to be able to repair your muscles. If CRF is elevated in the brain and if you have trouble getting to stage-four sleep you don't get enough growth hormone to repair the muscles and the simplest exercise can make you sore for weeks.

### **Estrogen, Progesterone and Testosterone**

CRH suppresses FSH (follicle stimulating hormone) and LH (luteinizing hormone) centrally. The brain's logic says, "Why would you want to have a libido or be pregnant if a tiger is chasing you through the woods?" FSH and LH promote progesterone secretion from the follicle in the ovary in women and control secretion of testosterone in men. Testosterone is responsible for libido in both women and men.

Patients with chronic stress or chronic pain and fibromyalgia patients have estrogen dominance, progesterone and testosterone deficiency caused by inhibition of FSH and LH in the brain from CRF being elevated. Both women and men experience the fatigue, irritability and depression characteristic of premenstrual syndrome. The opiates prescribed for pain patients further reduce testosterone.

### **Stress, digestion fatigue and food allergies**

Chronic stress and the presence of CRF in the brain decrease digestive secretions from the stomach and pancreas. The brain's logic says, "Why would you digest your food if a tiger is chasing you through the woods? We can eat tomorrow, if there is a tomorrow but right now there is this tiger thing happening!" Stomach acid and digestive enzymes are reduced but bicarbonate is so crucial for survival that it remains constant to keep the body pH normal.

The gut pH becomes more alkaline due to reduced acid from the stomach and steady levels of bicarbonate. Reduced stomach acid means that the proteins in the stomach do not break down well. Digestive enzymes are reduced which means the food rots instead of digesting once it gets to the small bowel. The patient becomes relatively malnourished and fatigued because food doesn't digest well and nutrients are lost. The 8 pounds of bacterial flora in the gut are very Ph sensitive. The proper acid-loving digestive bacteria produce short chain fatty acids that repair the gut wall and maintain the tight junctions that make the intestines leak proof. Those bacteria die because the gut pH is too alkaline for their survival. Unhelpful bacteria, pathogenic bacteria and yeast such as candida that thrive on alkaline conditions proliferate in the gut.

The lack of repair and the inflammatory products produced by incomplete digestion damage the gut wall. The tight junctions are not repaired properly and the gut begins to leak small proteins and molecules to cause what is called "leaky gut". 85% of the immune system is clustered around the digestive system waiting for these foreign invaders. The immune system becomes activated and can develop food sensitivities and frank food allergies. The patient experiences this cycle as "irritable bowel".

Macrophages roam the body and gobble up IgG food antigen-antibody complexes until they burst. When they burst, the macrophages release histamine into circulation. Histamine from the macrophages stimulates class C pain fibers and produces widespread diffuse moderate pain that perpetuates the pain-stress-fatigue cycle indefinitely.

### **CRF and mood**

CRF interferes directly with dopamine and serotonin production. The brain's logic says, "Why would you worry about feeling good if you are trying to escape from a tiger?" Brain function during stress is all about stimulatory hormones and catecholamine hormones such as epinephrine and norepinephrine until they and their receptors become exhausted. By then the stress is prolonged, CRF is elevated and it suppresses dopamine and serotonin, centrally. If you reduce dopamine centrally you become lethargic and lose motivation and you also lose descending inhibition of motion that comes from dopamine's action in the brain. The patient complains of restless leg syndrome, lack of motivation and depression not knowing that reduction in dopamine is causing all of it.

Serotonin is reduced centrally and because estrogen dominance interferes with the serotonin production pathway when estrogen competes with B6 at two crucial steps. Tryptophan, the branched chain amino acid that forms the backbone of serotonin, is a large molecule with its own amino acid transport receptor in the gut. All of the branch chain amino acids use the same transport molecule. When the gut wall thins, as it does with stress, this branch chain amino acid transport molecule doesn't work well. Fibromyalgia patients are known to have reduced levels of all branch chain amino acids, including tryptophan. Reductions in serotonin create depression and fatigue and contribute to difficulties sleeping. As you recall difficulties with sleep interfere with growth hormone and tissue repair.

The thyroid hormone receptor has a pocket where the hormone binds to create its effect. This pocket is made up of 12 leucine amino acids lined up in a structure known as "the leucine zipper". If the branch chain amino acids, including leucine, are in short supply the zipper can be made improperly and can become less efficient at locking in the thyroid hormone molecule. Thyroid hormone contributes to positive mood, overall energy levels, body temperature and cognitive function.

### **Not one problem – not one solution**

In our simplistic clinical wishfulness we hope that every patient will have one condition that has a single remedy. If it is an infection we can give an antibiotic and it's a simple dramatic cure. If the joint is locked up, we can adjust the spine and everything returns to normal. If the meridian is blocked we can insert needles and return chi to its normal flow quickly. The happy ending comes quickly. The clinician is a hammer; the patient walks into the clinic with a nail and all ends well and quickly.

But with pain, fatigue and stress it is never, ever that simple. You can give a patient growth hormone but that doesn't fix the thyroid or digestive problems. They can take digestive enzymes but that doesn't help the short-term memory issue or depression. You can give them T3 but that doesn't return dopamine and serotonin levels to normal. You can support the exhausted adrenals but that doesn't help the digestion and memory issues and sometimes makes them worse.

To repair this complex situation takes a comprehensive view and multifactorial individualized treatment program.

## **Reduce the pain**

There are many ways to reduce the body pain that creates the stressor and it behooves us to use as many of them as possible simultaneously. Unfortunately using opiates to reduce pain doesn't help the other neuroendocrine issues because of the effects of opiates on the endocrine system. Finding some natural way of reducing pain is helpful. Any system that can reduce pain will let the nervous system know that the tiger has dropped you and the threat is gone.

If you use Frequency Specific Microcurrent you can reduce spinal cord inflammation and neuropathic body pain fairly quickly. It is useful for nerve pain, visceral adhesions, abdominal pain and myofascial pain from trigger points. If you use manual soft tissue therapies and gentle adjusting techniques to reduce mechanical body pain that will interrupt the cycle. Vigorous adjusting techniques used by some chiropractors are contraindicated because these patients don't have enough growth hormone to repair the tissues stretched by the forceful adjusting. Acupuncture to reduce pain helps break the cycle.

If patients are on a statin drug that causes muscle pain and lowers cholesterol to a level that interferes with the production of the steroid hormones required for normal endocrine function none of the recommendations in this section will help. The patient must be allowed to take a statin holiday of three to four months and must be put on CoQ10 to help reverse the damage done by the statins to the energy systems in the body. In some cases the statin alone is the cause of the fatigue and pain and its elimination is sufficient for recovery.

If patients have the macrophage mediated, IgG histamine related full body pain the solution is to remove the most common allergens from the diet. IgG testing can be expensive and inaccurate. If the patient is motivated enough, they can be persuaded to remove the most common allergens: wheat, corn, soy, milk, eggs, citrus, peanuts, strawberries and in some cases nightshades. It is a very difficult diet but worthwhile. The first 7 days are the most difficult as withdrawal can cause symptoms and supporting the patient during this period is crucial to success. Once the overlying histamine mediated pain is down and the allergens are removed the gut can start to repair and the gut and body pain symptoms go away.

After 10 weeks of complete and absolute compliance the patient can do a two-day trial of exuberant re-exposure to allergenic foods. They most often feel so poorly on day three that the elimination diet is forever after seen as their friend and any tendency to stray is restrained by the memory of the painful consequences.

### **Repair the gut**

Once the patient has eliminated allergenic foods the gut inflammation will start to ease up. If you use Frequency Specific Microcurrent, it can help speed this process by treating for inflammation, allergy and chronic inflammation. FSM seems to shorten gut repair time by months in most patients. Digestive enzymes and stomach acid (betain hydrochloride) will help improve digestion and set the stage for the return of normal acid loving gut flora. Probiotics and non-colonizing yeast, such as saccromyces, that competes with candida help speed the process as the pH returns to normal levels.

### **Repair the brain and endocrine system**

The neuro-endocrine effects seen with increased pain and stress take about 12 to 18 months to develop and about four months to resolve when we reduce or eliminate the body pain. If the patients are on psychotropic drugs for depression, sleep and pain they often must reduce or eliminate these drugs, as tolerated, before they can return to normal. While on these drugs they may not feel as bad, but they don't feel anything emotionally and they certainly don't feel "normal". None of these agents have been studied for long-term use. All were approved for short-term use of 6-12 weeks. Medication management and withdrawal is the most time consuming part of the recovery process.

As CRF comes down in the brain and the adrenals begin to recover, patients begin to sleep better, get warm, digestion improves, menses regulate, PMS goes away, libido returns and exercise tolerance increases. Symptoms start to improve in about two to four weeks as CRH drops when the pain comes down and approach normal in 12 to 16 weeks.

Patients may need to be on low dose hydrocortisone replacement to bring their cortisol levels up to normal if they have adrenal exhaustion, as verified by salivary hormone testing. None of the other endocrine systems will work properly without adequate levels of cortisone. Hydrocortisone replacement is thought of as short-term strategy for endocrine recovery that may be useful for up to

two to three years. It gives the adrenal gland a rest while supplements can be used to support and restore gland health.

As the gut wall repairs itself, digestion improves, branch chain amino acid levels approach normal and become available to make serotonin, dopamine and thyroid hormone receptors. Energy levels and mood improve; restless leg symptoms go away. Medications that were helpful now produce side effects and have to be reduced as tolerated. Careful individualized titration as symptoms change is the key to success at this stage.

When CRF and stress hormones in the brain are reduced, the reticular activating system in the brain stem returns to normal alert levels and sleep is allowed to return to normal. The tiger is asleep in the neighbor's yard and is no longer a threat. As serotonin rises naturally, melatonin can increase and help promote deep sleep. The patient may need some instruction in "sleep hygiene" and may need some supplemental melatonin or 5-HTP and magnesium to support these changes. Once deep sleep returns to normal, growth hormone can increase. Once growth hormone improves, tissue repair and exercise tolerance improves.

Watching this picture normalize has become so regular over the last 16 years in fibromyalgia patients treated with FSM and functional medicine that the progression becomes predictable. Recovery is expected. The recovery strategies including nutrition, exercise, diet and pharmaceuticals must be personalized to fit the particular profile of dysfunction characteristic of each patient.

Recovery is possible with these strategies but it takes patience, creativity and determination from the patient and the physician. There is a sign in a doctor's office that says it all: "Be realistic, expect a miracle. But be patient, the impossible takes longer than the difficult."