



Oxidative Stress: Burning Down the House

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People with CFS show signs of significant oxidative stress in their bodies. Here's an overview of what oxidative stress is and ways it could be putting people with CFS in the hot seat.

AT-A-GLANCE ►

- Oxidative stress is caused when unstable oxygen molecules, called “free radicals,” rob electrons from surrounding tissues.
- Studies show that oxidative stress affects people with CFS and could account for some of its symptoms.
- Measures for preventing damage from oxidative stress include antioxidant supplementation and lipid replacement therapy.

We think of oxygen fondly, and we should. Although it makes up only about 20% of the air we breathe, it's what our bodies are really after. Oxygen is the core of life support on this planet, helping to power our cells, our bodies and the world around us.

But the oxygen molecule is a little “off.” Unpaired electrons in its outer atomic shell make it an unbalanced molecule—what's called a “radical.” As such, oxygen molecules seek electrons with which to bind. For example, as electrons stream down the electron transport chain in our mitochondria—the energy factories of our cells—oxygen scoops them up, then unites with hydrogen to make water and disappears quietly and harmlessly into the body.

But needing that extra electron makes oxygen extremely reactive. It may last in its unbalanced state for only a 1000th of a second, but if it isn't quickly rebalanced it will literally rip another electron out of the closest substance. This process, called oxidation, is where the trouble starts.

During oxidation the oxygen molecule, in its free radical state (called superoxide), will steal an electron from the nearest available source. In the absence of adequate antioxidants as defense, this electron may be torn from healthy tissue such as DNA, your cellular membranes or a host of other tissues better left intact.

All too often the tissue damaged belongs to a cellular membrane. This is because the fatty acids that make up the bulk of our cellular membranes have trouble holding onto their electrons. To make things worse, when fatty acids are compromised by superoxide they release substances that turn into more powerful free radicals. These radicals flail about, ripping apart more

and more fatty acids, creating a dizzying array of oxidative products that can turn a small brush fire into a raging free radical wildfire.

The damage free radicals cause depends on where in the body this wildfire has broken out. Free radical damage, called oxidative stress, can interfere with fundamental processes such as oxygen transportation, energy production, detoxification, immune function and more. The damage can be severe. Oxidative stress plays a role in many chronic disorders including arthritis, atherosclerosis, diabetes, heart failure, sleep apnea and many neurological disorders. One theory posits that even aging is simply the result of our cells gradually succumbing to the never ending onslaught of free radical attacks.

The body has developed a sophisticated antioxidant system to keep free radical production from flaring out of control; however, despite needing this special handling, free radicals serve a purpose in our bodies in moderation. They can help drive the inflammatory process, they play an important role in our bodies' signaling networks, and are a critical part of our immune defense.

There's little doubt, though, that the antioxidant/oxidant balance is out of kilter in CFS patients. Every CFS study that has looked for evidence of oxidative stress has found it. Increased levels of oxidative stress can seemingly be found everywhere: the red blood cells, the plasma, the serum, the urine, the muscles and, some studies suggest, even the brains of CFS patients.

In fact, oxidative stress has become a fruitful area of CFS study. For example, in 2003 Italian researchers implicated oxidative stress in impaired muscle functioning. In 2005 a research team from the United Kingdom found increased levels of two powerful oxidants in CFS patients' blood. In 2007 Australian researchers uncovered oxidative stress-induced damage to red blood cells.

Already this year, Belgian researcher Dr. Maes has proposed in a theory paper published in *Current Opinions of Psychiatry* that oxidative stress and inflammation cause most of the symptoms found in CFS. Even in just the last six months Canadian and American studies have suggested it contributed to abnormal exercise and brain imaging results.

Even with all this investigation it's still too early to understand precisely what effect this increased free radical activity is having in people with CFS. Some possibilities do stand out, however.

Areas of damage

Circulatory problems: Sometimes it's not the free radicals but the substances they leave behind that are problematic. Injured fatty acids turn into substances called F2 isoprostanes which can cause our blood vessels to narrow and impede blood flow to the tissues. Increased F2 isoprostane levels in CFS patients suggest oxidative stress could play a role in the orthostatic intolerance, low blood volume and low blood flow found in many people with CFS.

Muscles: Free radical production peaks, interestingly enough, in the very activity CFS patients have the most trouble with: exercise. In fact, free radical output during exercise is so high that even the antioxidant systems of healthy people are temporarily overwhelmed when they start a new exercise program. A study published in the *Neuromuscular Disorders Journal* found that exercise not only quickly depletes muscular antioxidant stores in CFS patients and increases their free radical levels, but it also leaves their muscles in an unusual state of excita-

tion. Another study recently published in *Clinical and Investigative Medicine* indicated that levels of an important antioxidative agent fell after exercise in CFS patients. So it would seem that oxidative stress could play a role in both the muscle pain and postexertional fatigue associated with CFS.

The brain: Given the high energy production in the brain, it's not surprising that many neurological disorders are associated with increased levels of oxidative stress. Could free radicals contribute to the cognitive and neurological problems in CFS? There's no hard data on this yet, but it's intriguing that the brain volume depletion in CFS occurs in the most oxidatively active—and therefore most vulnerable—part of the brain: the grey matter. The CFIDS Association is currently funding a study examining the role oxidative stress may play in the brains of people with CFS (see profile on page 24).

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The point of origin

Unfortunately the fact that CFS patients are suffering from oxidative stress tells us little about where it comes from. Two general possibilities exist: The first is that CFS patients' antioxidant systems might not be up to the job of protecting them from oxidative stress. The other is that a free-radical-generating process might have been ignited.

Most studies suggest the antioxidant systems of CFS patients are operating normally. University of Washington researcher and author, Martin Pall, PhD, however, has suggested that once a free radical wildfire is touched off, CFS (or fibromyalgia or MCS) patients have trouble putting it out. He believes each patient's distinctive CFS symptom signature depends on where the oxidative fires have been stoked, so to speak. While his theory has yet to be verified, it has raised some discussion in the CFS community.

However, if the antioxidant systems of people with CFS are operating normally, then an overabundance of free radicals could be generated by any number of processes. Here are a few possibilities:

Mitochondrial dysfunction: The idea that CFS is a mitochondrial disorder is controversial, but mounting evidence suggests mitochondria abnormalities may play some role in this disease.

Free radicals are produced in such large amounts during aerobic energy that difficulties controlling them could result in mitochondrial abnormalities and ultimately poor energy production and fatigue. In a 2005 review paper published in *Pathology Oncology Research*, Garth Nicholson, PhD, proposed that mitochondrial dysfunction and oxidative stress play a key role not just in CFS but in cancer and other fatiguing disorders.

Immune activation: The body uses free radicals' destructive capabilities to destroy pathogens when it comes under attack. Free radicals are never easy to control, however, and collateral damage can result when the heavy guns of the immune system open fire. An ongoing chronic infection could, therefore, easily cause increased levels of oxidative stress. Furthermore, recent findings by the Centers for Disease Control and Prevention (CDC) of

abnormal activity in two important modulators of the immune system, the HPA axis and autonomic nervous system, suggest that an infection need not be present for CFS patients to have chronic immune activation and increased free radical production.

Toxins: Since many free radicals are formed as the body breaks down toxins, CFS patients with high toxin levels could have high levels of oxidative stress.

Containing the blaze

Oxidative stress is common in chronic illness, and few would suggest that it's either the cause of CFS or that removing it will make CFS patients well. But studies indicate that CFS patients with high levels of oxidative stress tend to have more severe symptoms, which further suggests that reducing free radical damage could be beneficial.

Ultimately the best way to reduce oxidative stress and free radical damage is to address it at its source. Until that source is clear, CFS patients must do what they've always done: treat the symptoms and hope for the best.

The two general approaches to combating oxidative stress include boosting the body's antioxidant levels and building cells that are less susceptible to attack.

Increasing antioxidant levels: Most of the focus on treating oxidative stress in disease has been on building up the antioxidant system. Tinkering with the antioxidant system, however, has not always met with success.

Antioxidants were once believed to be a sure bet in heart disease, cancer and other diseases, but decades of research found little or no benefit (or even negative effects) from taking very simple antioxidant protocols like Vitamin C, E or A. Some researchers now believe that throwing a few antioxidants into such a complex system isn't likely to provide much help.

The antioxidant protocols suggested by CFS physicians are much more sophisticated. Alan Logan, MD, suggests CFS patients try antioxidants such as alpha lipoic acid, N-acetylcysteine (NAC), seleniumoligomeric proanthocyanidins (OPCs), Ginkgo biloba and Vaccinium myrtillus

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(bilberry). Paul Cheney, MD, PhD, suggests increasing uric acid intake through the use of D-Ribose, a mitochondrial energy enhancer. Grace Ziem, MD, in collaboration with Pall has gone a step further and developed an extensive protocol based almost chiefly on antioxidants. But that's not to say that all of these supplements should be administered together or without the supervision of a health care professional or nutritional specialist. There's no need to take every antioxidant on the market when you can find the one or two you best tolerate and take them in properly recommended doses.

Unfortunately no studies have examined the efficacy of antioxidant supplementation in treating CFS. So, as with any nutritional supplement, it's best to start small and monitor closely for any adverse reactions while determining the proper course of action.

Lipid replacement therapy

(LRT): Free radicals are attracted to the fatty acids in our cellular membranes, but there's more to it than that. It turns out that they're especially attracted to omega 6 fatty acids, but less so to omega 3 fatty acids. Damaged omega 6 fatty acids exacerbate matters by releasing high levels of inflammatory products and free radicals. This suggests that increasing omega 3 fatty acid levels (and decreasing omega 6 levels) could result in less inflammation and free radical activity (see "The ABCs of EFAs" in the summer 2008 *CFIDS Chronicle*). Researchers are investigating whether high omega 6 fatty acid levels and the inflammation they promote plays a role in chronic disease.

Several studies suggest that paying attention to the kinds of fats CFS patients ingest may be a good idea. For example, researchers in Belgium found that CFS patients have low omega 3 and high omega 6 fatty acid levels. Another study found that CFS patients have increased levels of the 'bad' low density lipoproteins (LDLs) and reduced levels of 'good' high density lipoproteins (HDLs). LDLs transport cholesterol to the tissues while HDLs transport them away.

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These findings suggest that the cellular membranes of CFS patients are awash in the kind of fatty acids that are more likely to set off a free radical wildfire. Some patients may even have a lipid profile that increases their risk for a cardiovascular event. So turning down the inflammatory "heat" in CFS could be a good thing not only for patients' everyday symptoms but for their cardiovascular health over time as well.

Preliminary research suggests that using LRT may help with that. Three CFS researchers recently published papers promoting LRT therapy in CFS—all for different reasons. One sought to increase energy production, another to reduce inflammation and oxidative stress and the third to normalize serotonin levels in the brain.

Several small studies suggest that omega 3 supplementation (with little or no omega 6)—such as taking fish oil or flaxseed—may be helpful in increasing energy and improving concentration and mood in CFS. Since western diets are typically high in omega 6 fatty acids and weight gain increases oxidative stress levels, people with CFS may

indeed wish to examine their dietary choices.

An ounce of prevention

Small free radical fires appear to be kindled in the bodies of CFS patients. How they were lit or how important a role they play awaits a better understanding of this disease. In the meantime, the oxidant/antioxidant system may be one that CFS patients can, with some work, help nudge back towards health. ■

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