III: Mechanism of Post-Covid-19 Syndrome: Oxidative Stress:

It has generally accepted by many scientists that serious organ dysfunction resulting from chronic disease is the result of overproduction of oxidants, which include Reactive Oxygen Species (ROS), Reactive Nitrogen Species (RNS), and other types of oxidative molecules and oxidative chemicals. However, usually, these chronic diseases, which are caused by an overproduction of harmful oxidants, are precipitated by an acute event such as an acute viral infection. We believe this is the case with COVID-19 virus.

Oxidative stress has been postulated to be the cause of chronic sequelae that occur after diseases such as Lyme disease, which is caused by the Borrelia bacterium. A common virus which has been implicated in the chronic fatigue syndrome is Epstein-Barr virus, which likewise can cause a severe oxidative stress reaction even after the virus has long been in remission. In fact, there are numerous types of viruses which have been shown to cause chronic fatigue syndromes, or at least have been implicated in them. And, again, oxidative stress is the usual mechanism that is postulated to be operative.

What happens is that once a patient has a bacterial or viral infection (it may not necessarily be an infection but can be a traumatic event, such as a concussion or head trauma), once the infection or event has transpired a cascade of events occur which perpetuate an oxidative stress cascade to occur.

How used overproduction of oxidants actually cause this oxidative stress which is harmful to various organs in the body. Oxidants may be necessary for the immune system to fight abnormal pathogens, such as bacterial and viruses, and to keep organs systems healthy and in balance. However, an overabundance of oxidants may lead to cell and organelle damage. The most important organelle of cell is the Mitochondria, which is the powerhouse of the cell that produces the ATP molecule, which is the energy molecule of the body. These organelles are extremely sensitive to damage from oxidants and are susceptible to adverse effects of oxidative stress. It is well known that the cardiovascular system and the nervous system have the highest numbers of mitochondria per cell and therefore are the most susceptible systems in the body to oxidative stress.

The parasympathetic and sympathetic nervous systems are branches of the autonomic nervous system and are extremely susceptible to oxidative stress as they are an important part of the body's nervous system. Once they are affected by oxidative stress, imbalance occurs, and this autonomic dysfunction disorder, or

dysautonomia, can accelerate cardiovascular disease and central nervous disease and even disease of other organ systems, such as the gastrointestinal tract, genitourinary tract, etc even before symptoms become manifested.

Oxidative stress when it induces dysfunction of the autonomic nervous system may cause a significant amount of adverse symptoms, such as brain fog, lightheadedness, fatigue, fluctuations in heart rate and blood pressure, fluctuations in blood sugars and hormone levels, chronic pain syndromes (including complex regional pain syndrome, also known as CRPS) and exercise intolerance. Cardiac symptoms due to orthostatic intolerance and the ability of blood to be timely transmitted from the legs to the heart and brain when one is upright can cause palpitations and shortness of breath and chest pain which can actually mimic organic or structural heart disease symptoms. Also, symptoms of depression and anxiety are often seen in dysautonomia states.

It is believed that COVID-19, by virtue of causing cytokine production and inflammatory messengers causes a overwhelming oxidative stress in various organ systems in susceptible individuals, which even after they have recovered from the virus can damage the autonomic nervous system chronically and cause these ongoing symptoms. This affects the quality of life in all individuals. They do not return back to their baseline level of functioning; these patients cannot work, cannot exercise and cannot think properly with no cognitive functioning as they had prior to the viral illness. When this extends beyond 12 months, some have described this as a chronic or "long" COVID-19 syndrome.

In our Post-Covid clinic setting, we actually test for autonomic system abnormalities on patients with many of the symptoms, as described above, in attempt to balance the autonomic nervous system. We use pharmacologic agents, which require prescriptions, and high dose supplements, which have antioxidant potential in various cocktails along with nitric oxide-producing substances, such as beetroot and amino acid, such as L-arginine and L-citrulline. We have found that alpha lipoic acid in very high concentrations, up to 1800 mg a day, has been effective in improving the balance and autonomic system dysfunction, and this oftentimes translates to improvement of quality of life and relief of the adverse symptoms that are experienced from dysautonomia.

We say in patients who have recovered from COVID-19 infection, we believe a basic model is one in which the COVID-19 virus has caused oxidative stress which is ongoing in many patients even after the virus has gone into remission or has been eradicated. In many of the patients who recover. It is the severity of this

oxidative stress which causes individuals to become debilitated and can affect up to 15%-20% of post-Covid cases with significant functional impairment. This oxidative stress damages cell membranes and DNA. The mitochondria is one of the organelles must susceptible. We have previously published a book "Autonomic Dysfunction and Mitochondrial Dysfunction" by Springer Publishers, which details the mechanism of how oxidants and oxidative stress impairs the autonomic nervous system (see reference below).

The cells that utilize the most energy in the body are the neurons, such as the nerves in the cardiovascular system, are these are the most susceptible to oxidative stress. This is why many of the symptoms in post-COVID-19 syndromes involve abnormalities of the central and autonomic nervous system and cardiovascular systems, the latter of which also has significant content of mitochondrial and heart muscle cells. In addition, the cardiovascular system is richly innervated by the autonomic nervous system. In addition, the pulmonary system, gastrointestinal system, urological system, and virtually any other system in the body can be affected chronically and not just acutely by the COVID-19 virus infection.

Mitochondrial dysfunction in the parasympathetic and sympathetic autonomic nervous system may cause symptoms 3-6 months after the initial pathology occurs and it may not be readily apparent that this was sequelae of the COVID-19 affliction. Many individuals do not realize the association of autonomic dysfunction and COVID-19 when there is this delayed gap.

We have found that the most common symptom is persistent fatigue, which is refractory to treatment by standard therapies. We have also found chest pain, shortness of breath, racing heart, especially when standing, lightheadedness, and inability to concentrate, especially when in the upright position are also common complaints. Severe exercise intolerance is also a common problem.

Both oxidative stress and the autonomic dysfunction are identifiable and treatable, and simple noninvasive testing such as heart rate variability in the outpatient center can give us clues and direction of where to start with diagnosis and treatment. We are also testing for small fiber inflammation and damage with sudomotor testing, which we have found to be useful.

It is well known that rebalancing oxidation in the peripheral nervous system leads to improved outcomes including quality of life, such as relieving fatigue and improved functional activity in patients who respond to treatments. Our goal is to individualize treatment to patients that had been inflicted with this post-COVID

syndrome, which involved autonomic dysfunction, so that they can return back to a good functional state of health.

We can report that malfunctioning brain perfusion and cardiac perfusion are often the result of oxidative stress which is mediated by dysfunction of the autonomic nervous system. Both the parasympathetic nervous system (the brakes of the body, for which the vagus nerve is the longest nerve in the body and a major component) and the sympathetics (the accelerator of the body) can be affected. If dysfunction of both of these branches is not treated, they can result in further progression of disability and dysfunction in the body as each amplifies the other resulting in the adverse symptoms that patients experience. Fortunately, we have many antioxidants that are known to help and treat autonomic dysfunction as well as oxidative stress, and this is one of the many tenets of our approach to dealing with patients with chronic fatigue syndromes post-COVID by reliving oxidative stress and balancing the autonomic nervous system, and it is hoped that this will relieve the lightheadedness, dizziness, fatigue, sleep difficulties, GI difficulties, anxiety, depression, difficulties controlling blood pressure and blood glucose or hormone levels, headaches or migraines, brain fog, cognitive or memory problems and exercise intolerance that we commonly see in post-COVID-19 syndromes associated with autonomic dysfunction.

In summary, symptoms of oxidative stress may include:

1. Lightheadedness.
2. Fluctuation of blood pressure, blood glucose, hormone levels and weight.
3. Temperature dysregulation (to heat and/or cold and sweat responses).
4. Symptoms of depression and anxiety.
5. Attention deficit
6. Difficulties to describe pain, including complex regional pain syndrome. Some people describe the pain as "I hurt all over).
7. Exercise intolerance.
8. Sexual dysfunction.
9. Sleep dysfunction.
10. GI disturbances which can vary.
11. Cognitive dysfunction or brain fog.
12. Palpitations.
13. Seizures.
14. Frequent headaches or migraines.
15. Severe fatigue.
16. Chest pain.

17. Shortness of breath.

Of course, it is important to rule out structural abnormalities of disease entities that may be causing these symptoms and therefore a differential diagnosis and workup needs to be embarked upon and oftentimes objective laboratory testing is utilized. Also, oxidative stress can be measured with various blood and urine testing modalities. While this is considered experimental for the most part, it can be confirmatory and used to follow select patients.

Reference: Clinical Autonomic and Mitochondrial Disorders: Diagnosis, Prevention, and Treatment for Mind- Body Wellness, DePace N.L., Colombo J., 1st ed.2019, Springer Publishers, New York.