A METABOLIC POINT OF VIEW ON PARKINSON'S DISEASE

In my newsletter series on inflammation, insulin resistance, and neurologic illness that I concluded in August of last year, while many neurodegenerative ailments were addressed, certainly the primary focus was Alzheimer’s disease. Others, such as Parkinson’s disease, were addressed, but not in nearly as much detail. In particular, given the incidence of Parkinson’s disease in the US, I feel it warrants more attention. Therefore, I was pleased to find a paper that addresses this ailment from a metabolic, allostatic load point of view, the recently published paper (February 2018) “Aging and Parkinson’s disease: Inflammaging, neuroinflammation and biological remodeling as key factors in pathogenesis” by Calabrese et al (1). The first quote I would like to feature from this paper discusses the significant frequency of Parkinson’s disease (PD):

“Age is a major risk factor for PD, the second most frequent common neurodegenerative disease, affecting approximately 1% of the population over 60 years of age.”

The next quote makes the interesting suggestion that PD is a matter of accelerated aging of a localized, specific part of the body:

“…it could be hypothesized that PD is, at least in part, a type of ‘segmental’ ageing, in which specific, localized, and accelerated aging mechanisms, which for reasons at present largely unknown, markedly affect dopaminergic (DA) neurons in the pars compacta region of the midbrain substantia nigra (SnPC).”

Further complicating the picture is the fact that this progressive decline can also occur with “normal” aging where no observable signs of symptoms of PD occur:

“Indeed, even physiological aging is characterized by a progressive decline of motor abilities and patho-anatomic features of neuronal degeneration in the brain, which in many ways are similar to key characteristics of PD (but which do not evoke clinically-relevant signs of PD).”

Specifically, post-mortem analysis of people who died in old age but had no suggestion of PD demonstrated the following:

“…data collected from 2500 aged persons who were annually assessed for PD revealed global Parkinsonism was 18.6%. However, post-mortem patho-anatomical studies of 744 of these subjects (who did not have PD; mean age at death: 88.5 yrs.) showed that: a) about 1/3 had mild or more severe nigral neuronal loss; b) about 17% had Lewy bodies; and c) 10% showed both nigral neuronal loss and Lewy bodies.”

So how can we differentiate Parkinson’s versus non-Parkinson’s patients if anatomic findings are not a reliable indicator? As you will see, the authors suggest that, even though neuronal degradation occurs with both symptomatic and asymptomatic patients, there is a subtle distinction between physiologic aging and age-related neurodegenerative disorders. Furthermore, as you will also see, it is hypothesized that this subtle difference is most closely related to inflammatory status. Before bringing up the subject of inflammation, though, Calabrese et al (1) state:

“These findings suggest that there is an apparent continuum between physiological aging and age-related neurodegenerative motor disorders.”

Given that the difference between the PD and non-PD individual is sometimes a matter of subtle and far from distinct physiologic, anatomic, and
biochemical states of being, the authors suggest the following to explain PD:

“…we propose that lifelong exposure to (exogenous and endogenous) stressors can stimulate local and systemic adaptive responses, including activation of the immune system to incur ‘physiological inflammation.’ This inflammatory response, which can be considered as ‘inflammatory tone’, is highly conserved in evolution, and appears to be critical for survival. Thus, it may be that a sustained systemic inflammatory state represents a particular aging phenotype, which results from exposure to chronic stressors, perdurable inflammatory responses, and/or some combination of both. This condition, conceptualized as an important example of adaptive remodeling, is now referred to as ‘inflammaging.’”

Long time readers of my newsletters may recognize the term “inflammaging” because I have discussed it many times before in relation to why the combination of aging and chronic environmental stress leads to a state of chronic, low-grade inflammation that is a foundational factor for virtually all chronic illnesses. In the next quote Calabrese et al (1) provide their definition of inflammaging:

“Recently, inflammaging was recognized as one of the seven pillars underpinning the aging process, and influential to many (if not all) major age-related diseases including those that are neurodegenerative. It has been proposed that inflammaging can be regarded as both an age-related increase in inflammation, and a concomitant adaptive activation of anti-inflammatory processes.”

Before continuing please note again the last line of the above quote. The current definition of inflammaging includes both pro-inflammatory and anti-inflammatory mediators. Furthermore, as is pointed out in the following quote, healthy aging is not necessarily a state of low inflammation but a state of a balance between pro- and anti-inflammatory mediators:

“…increased levels of pro-inflammatory mediators were also frequently accompanied by a concomitant elevation in anti-inflammatory markers (i.e., adiponectin, Transforming Growth Factor (TGF)-b1, IL-1 receptor antagonist (IL-1RA), cortisol, and anti-inflammatory arachidonic acid-derived compounds…”

With the above in mind, the authors suggest:

“These findings suggest that those who age ‘well’ demonstrate anti-inflammaging mechanisms (and biomarkers) that likely counteract the adverse immune response of inflammaging.”

Furthermore, in terms of treatment and prevention:

“Modulating this crucial balance of pro- and anti-inflammatory processes has become a major focus of new geroscientific approaches that are attempting to more successfully treat – or prevent – major age-related diseases.”

With the above in mind, the authors suggest that even though aging will demonstrate a certain level of neurologic degeneration, those who demonstrate symptoms of neurodegeneration will do so because of significant imbalances between pro- and anti-inflammatory factors.

**Inflammation and Parkinson’s disease (PD)**

With the above in mind, how does chronic inflammation relate to PD? Calabrese et al (1) point out:

“It has been shown that the age-related increase of both peripheral inflammation and neuroinflammation contribute to the prodromal phase of PD. We hypothesize that peripheral and/or central inflammatory stimuli affecting the brain could induce inflammatory changes that shift microglial function toward neurodegeneration, are inductive for, and operative in PD, and thereby lead to PD signs, symptoms and progression. Data reveal that peripheral immune system activation exacerbates inflammatory responses in the brain, and may incur or increase neurodegenerative processes.”

Next, the authors discuss in more detail the role of microglial cells in CNS inflammation. Recall from past newsletters that microglia are the primary immune cells in the brain that are responsible for much, if not most, of the creation of CNS inflammatory mediators when ill-health due to
significant environmental stress occurs. Calabrese et al (1) state:

“Activation of microglial cells is, on one hand, beneficial for neuronal tissue, as it stimulates clearance of cell debris and prompts secretion of several neurotrophic factors. But on the other, microglial inflammatory mediators modulate immune cells, act on neurons, and have been shown to contribute to neurodegenerative effects. Thus, while activation of inflammatory responses is fundamental for tissue functioning and homeostasis, it can also contribute to neuronal insult.”

Given that much of what I have written and quoted in past newsletters emphasized the negative aspects of microglial function, the above quote is well placed. For, as with so many aspects of human physiology that occupy a responsive role to environmental stressors, with short term stressors, microglia function as health promoting agents by, as noted above, removing cellular debris and promoting neurologic repair. In contrast, with chronic stress, the allostatic load, catabolic aspects of microglial function come to the forefront by, in this case, increasing CNS inflammation. Thus, as with virtually all endocrine and immune aspects of the allostatic response, microglia can exhibit both health promoting and health depleting functions depending on the duration of the environmental stress.

The next quote I would like to feature from the Calabrese et al (1) paper addresses the common misconception that the blood-brain barrier and other factors will protect the brain from the ravages of systemic inflammation:

“Until quite recently, the brain was considered to be an immunologically privileged organ due to the presence of the blood-brain barrier (BBB), the low expression of major histocompatibility complex class II (MHCII) proteins, and the apparent lack of cerebral lymphatic vessels. Currently, however, this view has changed. Louveau and colleagues have demonstrated the presence of lymphatic vessels in mouse brain, which could support the possibility of bi-directional peripheral-CNS entry and exit of immune cells; these findings have implications for neurodegeneration.”

With the above in mind, the authors state:

“Indeed, several neurodegenerative diseases evidence an infiltration of inflammatory and immune mediators from the periphery to the CNS.”

As you may recall, in the previous two newsletters I discussed one way “immune mediators from the periphery” can affect the CNS – from a dysfunctional, dysbiotic, leaky gut. However, as suggested in the above quote, evidence is now making it clear that systemic inflammation originating in virtually any part of the body can conceivably infiltrate the CNS. Therefore, it is imperative that all of the previous dogma that may have influenced our clinical decisions which infers the CNS somehow stands apart either anatomically or physiologically from the rest of the body must now be discarded.

Of course, the above discussion is referring to the situation where a healthy blood-brain barrier exists. Unfortunately, evidence is now demonstrating that, with chronic neurologic illness, along with suboptimal function of the brain per se, there is also suboptimal functioning of the blood-brain barrier. Calabrese et al (1) comment:

“...while findings of brain lymphatics are compelling, the role – and dysfunction – of the BBB must still be considered. A number of CNS pathologies, inclusive of neurodegenerative diseases incur increased BBB permeability and dysfunction, and this loss of a protective barrier allows relatively free entry of circulating blood macromolecules in the CNS. Therefore we posit that direct lymphatic access and/or compromised BBB function enable immunologically active cells and mediators to access and affect the brain, which if and when chronic, may be contributory to both inflammaging and particular neurodegenerative changes and diseases, including PD.”

Oxidative stress and PD

Of course, as we all know, whenever we see chronic inflammation it is almost inevitable that increased oxidative stress will be accompanying it. The next few quotes feature comments on PD and oxidative stress by Calabrese et al (1). First, does PD, in fact, involve increased oxidative stress? The authors state:
“There is evidence of increased oxidative stress in brain tissue of patients with PD.”

Where does this increased oxidative stress primarily originate? Mainly the mitochondria:

“Reactive oxygen and nitrogen species (ROS and RNS, respectively) are produced mainly in mitochondria as a by-product of aerobic metabolism.”

According to the authors, the main free radicals produced in this scenario are superoxide radical (O2-), hydrogen peroxide (H2O2), nitric oxide (NO) and peroxynitrite (ONOO-). As we age, not only do we tend to produce more inflammatory mediators via the inflammaging process but we also tend to produce more free radicals:

“….mitochondria of older organisms are fewer in number, larger in size and less efficient, and have been shown to produce less energy and more superoxide.”

Furthermore, as you might expect, mitochondrial dysfunction is an issue with PD:

“Mitochondrial dysfunction has been strongly associated with PD.”

What is also important to note is that increased oxidative stress and inflammation are not isolated entities that function independently with PD. In contrast they work together to contribute to the development of PD:

“Reactive radical species may also be involved in signaling responses, which subsequently stimulate pathways related to pro-inflammatory gene expression, cell senescence, and cell death. This inflammatory cascade is more active during aging, and has been linked to age-associated pathologies, inclusive of neurodegenerative diseases, and PD more specifically. Thus, we believe that the oxidative theory of aging should be complemented by, and integrated to the inflammatory theory of aging. To be sure, inflammation has a host of characteristics that can be reciprocally interactive with oxidative stress and aging. Notably, ROS can directly or indirectly activate transcription factors such as NF-κκ κκ and AP-1 that can promote inflammation.”

Of course, as with inflammation, oxidative phenomena play a valuable role in the brain, with only prolonged or excessive production being a problem:

“Generally, brain cells have relatively high metabolic activity and use discrete oxidative damage-repair mechanisms to remove end-products of intracellular damage. But defects of the DNA repair system in brain cells could contribute to the accumulation of potentially disruptive and toxic metabolites of cellular insult, and lead to neurological dysfunction.”

The specific impact of oxidative stress on nigral dopaminergic (DA) neurons

As was mentioned in the beginning of this monograph, Parkinson’s disease essentially involves dysfunction of the DA neurons in the pars compacta region of the midbrain of the substantia nigra. The following quotes from the Calabrese et al (1) paper discuss how oxidative stress contributes to this dysfunction:

“There are a number of possible explanations for the apparent vulnerability of nigral DA neurons to metabolic and oxidative stress. First, these neurons have particularly long (up to 4.5 m), unmyelinated axons, with numerous synapses, which require considerable metabolic energy to be sustained. Second, they exhibit autonomous pace making activity, involving cytosolic calcium oscillations and calcium extrusion, both of which require expense of energy. Third, increased levels of cytosolic DA and its metabolites can cause toxic oxidative stress. Lastly, mitochondrial dysfunction and increased oxidative stress can lead to the depletion of lysosomes and functional impairment of the lysosomal autophagy system (LAS), and it is possible, if not likely, that several of these putatively pathogenetic pathways in PD are concomitantly involved and interactive. In contrast, DA neurons in the adjacent ventral tegmental area are relatively resilient in PD.”

More information on the cell types involved with PD

Microglia

As was mentioned above, microglia can play both healing and destructive roles in the brain. The
following quote from the Calabrese et al (1) discusses how microglia can transform from healing to destructive entities:

“Microglia function as the first line of immunological response to CNS insult and/or pathological conditions. Following CNS damage, microglia change from a surveillant to a reactive state, displaying alterations in cell morphology and phenotypes that vary based upon the type and extent of (insulting) stimulus to which they are exposed and respond. Observations of reactive microglia in postmortem brain samples of PD patients led to suggestions that microglia are involved in the neuropathological changes in DA neurons that are inherent to this disease.”

Astrocytes

According to the authors:

“Astrocytes primarily are involved in control of water distribution, vascular integrity, maintenance of the integrity of the BBB, ionic (e.g.-calcium and potassium) buffering, ROS scavenging, trophic factor release, regulation of synaptogenesis, synaptic pruning, modulation of the tripartite synapse, and support of brain microarchitecture. Astrocytes have also been shown to play a prominent role in the regulation of neuroinflammation in PD. Studies of primary cell cultures reveal that astrocytes are important for both protection and survival of DA neurons, affording protection to DA neurons through removal of toxic molecules from the extracellular space or through the release of antioxidant molecules and trophic factors.”

Interestingly, it has also been found that astrocytes can work with microglia to create inflammation:

“…Zhang and Barres reported that inflammatory responses in microglia are amplified by astrocytes.”

What is the best way to assess the nature of inflammation in the PD patient?

While it may not be practical for many patients, examination of cerebrospinal fluid (CSF) is best to specifically define the nature of inflammation in the PD patient:

“Cerebrospinal fluid (CSF) reflects metabolic and pathological alterations of the CNS more directly than any other body fluid, and therefore affords a viable and valuable resource for obtaining and assessing neuroinflammatory and neurodegenerative biomarkers of PD.”

What was found in PD patients? Consider the following:

“Elevated levels of IL-6 and IL-1β have been found in the CSF of PD patients. Furthermore, higher concentrations of IL-2, IL-4, IL-1β and transforming growth factor- (TGF-α) were found in ventricular CSF in juvenile PD patients (vs healthy controls).”

An expanded discussion of Parkinson’s disease as a manifestation of allostatic load

As I briefly mentioned above and discussed extensively in past newsletters and lectures, allostasis, which is the total body response to any environmental stressor or set of environmental stressors, is a positive, anabolic phenomenon when stressors are short term and low in intensity. However, when stressors are long term and even moderate intensity, the allostatic response increases in magnitude to the point where it is no longer a positive, anabolic entity but a negative, catabolic entity that contributes to or creates virtually every chronic illness we see in our practices today. This excessive allostatic response has been termed “allostatic load.” Therefore, whether the allostatic response functions positively or negatively is largely a matter of degree or dosage. The idea that any health related factor has a differential effect on health based primarily on dose or amount has been termed “hormesis.” Long time readers may recall that I discussed this concept extensively in previous newsletters.

Calabrese et al (1), in the remainder of their paper, discuss PD and inflammaging as an issue of hormesis. They introduce this discussion in the following quote:

“Given the aforementioned findings, we believe – and propose – that inflammation may be regarded as a type of hormetic stress; exerting potential for positive outcomes at low levels (physiological inflammation) at young and adult ages, and becoming increasingly detrimental
later, in the post-reproductive period (i.e. – inflammaging), especially in those people who, as a result of genetic background and/or unhealthy lifestyle, cannot maintain an optimal balance between inflammaging and anti-inflammaging (viz. – unsuccessful remodeling). However, the strength of hormetic processes lies in their potentially adaptive capacity throughout the lifespan. Like young and healthy middle-aged individuals, centenarians also have high levels of anti-inflammatory molecules to counteract the increased levels of inflammation that can occur with age.”

In the next quote, Calabrese et al (1) discuss hormesis more specifically:

“Hormesis in aging is defined as ‘life-supporting beneficial effects resulting from the cellular responses to single or multiple rounds of mild stress.’ Various stressors have been reported to have hormetic characteristics, including heat shock, irradiation, heavy metals, pro-oxidants, acetalddehyde, alcohols, hypergravity, and repeated physical exercise.”

Before continuing, please note again the last sentence of the above quote. Traditionally, virtually everyone in alternative medicine and health care in general has defined every stressor mentioned in that sentence, with the exception of “repeated physical exercise,” as “bad.” In reality, as suggested by the authors, none of these are inherently bad. Rather “badness” is a matter of dosage, with low doses actually being beneficial because of the positive, low-grade, anabolic allostatic response they engender. Of course, we know this about exercise, but what of the others?. As noted by Calabrese et al (1), we need to check our agendas at the door about current functional medicine touchstone issues such as heavy metals, alcohol, irradiation, etc., and accept the research-based reality that low dose exposure is not only not harmful but actually beneficial. How does this translate to clinical practice and patient management? In my opinion, we also need to check our “all or none” warnings and hystericis at the door when we talk to patients and speak in terms of moderation, variety, and common sense.

In the next quote Calabrese et al (1) continue this fascinating and controversial discussion on the idea that small of amounts of “toxic” substances can promote health by optimizing allostatic, adaptive response elements by addressing what are known as “hormetins”:

“Any conditions that induce biologically beneficial effects by initially causing low-level damage that consequently stimulate various adaptive mechanisms and pathways are termed hormetins. Recently, it has been postulated that a Mediterranean diet (MedDiet) exerts healthy effects through hormetic mechanisms, as specific components (e.g. – phytochemicals, vitamins, lipids, particular carbohydrates and fibers) likely counteract the effects of inflammatory stimuli by acting as hormetins. Longitudinal exposure to the MedDiet may incur both a leftward shift and decreased amplitude of pro-inflammatory processes, thereby facilitating physiological inflammation and suppressing unbalanced inflammation/inflammaging that has been however, with the above in mind, we still need to institute measures that reduce allostatic load when the above mentioned factors and other environmental stressors are clearly excessive. In the next quote Calabrese et al (1) discuss this in terms of reducing inflammaging:

“Approaches aimed at reducing inflammaging (e.g. – systemic reduction of stress/antigenic burden, eradication of chronic infections, nutritional modulation, use of free radical scavenging compounds, vaccinations, and treatment with anti-inflammatory drugs) might each and all prove to be effective in delaying the onset of a number of age-related diseases. As well, these approaches may be synergized by a hormetic strategy, which involves repeated exposure to low levels of particular stressors to induce activity of physiological mechanisms of maintenance and repair.”

Of course, I’m sure most of you are familiar with the above mentioned interventions, some of which are also quite controversial. However, before you dismiss them completely, please keep in mind hormesis or, in more basic terms, moderation, variety, and common sense.
implied (or demonstrated) in a number of age-related diseases.”

How does this apply to neurodegenerative diseases such as PD? The authors continue:

“Animal studies suggest that a diet rich in phytochemicals may enhance neuroplasticity and resistance to neuroinflammation, mitigating or preventing neurodegenerative changes in the brain that are typical in a number of age-related CNS disorders (including PD). Such effects may occur through a process of ‘neurohormesis’ in which cellular components of the CNS respond to exogenous and endogenous toxic agents (e.g. – H2S, NO, CO, glutamate, calcium) that act as mild stressors to facilitate neuronal resistance against stronger insults.”

For me, this intriguing discussion gives a much clearer view of what foods and supplements containing various phytonutrient-based compounds are actually doing. In addition, this hormetic viewpoint of these compounds answers an important question about the actual impact of natural agents that we have long defined as “anti-inflammatory.” If these compounds are “anti-inflammatory” would it not be true that there is a risk of over suppression of inflammatory mediators? Calabrese et al (1) explain to us that this is not possible because, in reality, these substances are not “anti-inflammatory” in the traditional way we have considered them. Rather, they have hormetic (and what we traditionally described as adaptogenic) properties which produce a weak, short term effect on allostatic responses, particularly on those involving inflammatory mediators. This leads to the kind of allostatic response that is positive, anabolic, ultimately balancing pro- and anti-inflammatory pathways.

**Parkinson’s disease, gut microflora, and the gut-brain axis**

Of course, based on our current knowledge base, no discussion on PD would be complete without addressing gut microflora and the gut-brain axis. Calabrese et al (1) begin their discussion on this important relationship by stating the following:

“One of the most advanced and appealing hypotheses of age-related neurodegeneration posits that environmental stressors may contribute to senescence of glia, thus creating a chronically pro-inflammatory milieu in the brain. It is likely that environmental and dietary factors induce peripheral changes that affect CNS function, and it is interesting to speculate if and how the recognized bi-directional gut-brain axis (and gut microbiota) may be involved in a variety of CNS effects and disorders. Recent studies have shown that PD is associated with gut dysbiosis. The fecal concentration of short chain fatty acids (SCFA) is significantly reduced in PD patients as compared to healthy controls, and this could both contribute to gastrointestinal dysmobility and impact CNS alterations in PD.”

The authors go on to state that the relationship between PD and gut-brain axis should be viewed as part of a larger picture of what happens in general to gut microflora as we age:

“While the gut-brain relationship remains the topic of ongoing study, extant data on PD microbiome should be interpreted within the context of the changes that occur in the gut microbiome during healthy aging. For example, it has been shown that the gut microbiome undergoes profound changes with age. These likely contribute to inflammaging and alteration of redox status, which can exert effects on the brain through the age-related increase in bacteria involved in the tryptophan metabolism pathway; findings supported by the demonstrated reduction of tryptophan in the serum of centenarians. As well, there is evidence that the age-related dysbiosis is involved in inflammaging, oxidative damage, apoptosis and neural dysfunction that are contributory to decreased neurological activity and capacity.”

Before continuing, please notice again the word “tryptophan” in the above quote. Along with a discussion on PD and the gut-brain axis, no discussion on PD or any other neurodegenerative disease would be complete, as I hope I have demonstrated in previous newsletters, without a discussion on the connection with aberrant tryptophan/kynurenine metabolism. I will feature
the comments on this important relationship made by Calabrese et al. (1) shortly.

In the next featured quote, Calabrese et al. (1) discuss all the interesting and intricate ways the gut and the brain interact in relation to neurologic dysfunction:

“It is important to recognize the reciprocity of gut-brain effects: changing activity of the CNS can also modify function of the gut and gut microbiota; and the integrity of the gut microbiota is essential for the bioavailability of polyphenols, unsaturated fatty acids, and anti-oxidants, which exert protective actions against cellular and neuronal insult, and which can sustain healthy aging. As previously noted, the gut microbiota may also regulate brain function via modulation of tryptophan, an essential dietary amino acid, which is metabolized in the gut, and can cross the blood-brain barrier to contribute to the synthesis of serotonin (5-hydroxytryptamine; 5-HT). Age-related changes in the amygdala, hippocampus, and frontal cortex, as well as cognitive and behavioral processes mediated by these brain regions have been related to alterations in 5-HT function, which may occur as a result of disrupted gut-microbiome-dependent metabolism.”

Parkinson’s disease and tryptophan/kynurenic metabolism

Calabrese et al. (1) state the following about the relationship between PD and tryptophan/kynurenic metabolism:

Tryptophan is also metabolized via the kynurenine pathway (KP), which can lead to the production of nicotinamide adenosine dinucleotide (NAD+), as well as quinolinic and kynurenic acids. These latter compounds are neuroactive metabolites that act on N-methyl-D-aspartate (NMDA) and alpha 7 nicotinic acetylcholine receptors (nAChR) in the CNS and enteric nervous system (ENS). In the CNS, kynurenic acid has been long viewed as neuroprotective, while quinolinic acid is primarily considered an excitotoxic NMDA receptor agonist.”

Next the authors mention the relationship between the gut, kynurenine metabolism, and the overall impact on neurologic function and PD specifically:

“The balance between bacterial tryptophan utilization, metabolism, and synthesis, and 5-HT/kynurenic production is likely important to 5-HT transmission in both the enteric nervous system (ENS) and CNS. Alterations of the kynurenine pathway have been assessed in PD (as well as other neurodegenerative diseases). PD patients have higher L-kynurenine/tryptophan ratios in serum and CSF as compared to controls, suggesting up-regulated activity of enzymes involved in catalyzing tryptophan to kynurenine (i.e. – indoleamine-2,3-di-oxygenase (IDO); tryptophan 2,3-dioxygenase (TDO)).”

Parkinson’s disease and genetic function

Since many, if not most of you, are now seriously considering genetic aberrations when evaluating the needs of chronically ill patients, it is appropriate to feature the comments by Calabrese et al. (1) on the PD connection with genetic dysfunction:

“Findings to date reveal that inflammation causes DNA damage through the disruption of telomere function. Specifically, chronic inflammation (inflammaging) induces telomere dysfunction by increasing oxidative stress. This accelerates cell senescence, which leads to increased pro-inflammatory and pro-oxidant signaling by the senescence associated secretory phenotype (SASP) response, and induction of mitochondrial dysfunction, thereby propagating DNA damage and senescence to bystander cells. These processes of ‘senescence-induced senescence’ and ‘inflammation-induced inflammation’ appear to be important mechanisms in aging and the induction and progression of neurodegeneration and other age-associated diseases.”

As noted in the above quote, what makes chronic illness in general, and neurodegenerative disease in particular, so challenging to address is the “vicious circle” aspects. Most especially, the fact that inflammation leads to more inflammation is a central issue. Therefore, optimization of the pro- and anti-inflammatory mediators through the interventions mentioned above plus reducing cumulative
environmental stress, which certainly includes but is not limited to diet (It may also include chronic infection, toxic exposure, excessive worry, etc.), is crucial for gaining meaningful prevention or resolution.

**Final conclusions from Calabrese et al**

Calabrese et al (1) conclude their outstanding paper with two summations. First, concerning aging and inflammaging:

“Aging and inflammaging are now thought to represent the progressive increase and spread of inflamed local (i.e.-micro) and systemic (i.e.-macro) environments of aged bodies. These effects are evoked and sustained by: 1) endogenous and exogenous stress, 2) toxic and cellular debris factors; 3) decreased clearance of intracellular debris,…and 4) increased activation of NF-κκκκ and inflammasomes.”

Second, how does this all relate to PD:

“…we posit that PD may be hypothetically viewed as aberrantly augmented mechanisms of the aging process, which involve a convergence of the proposed ‘transmission hypothesis’ of neurodegenerative disease, and the propagation hypothesis of the aging process/phenotype. According to this view, clinical PD could be considered as an accelerated brain aging, which is due, in part, to an interaction of genetic and non-genetic risk factors.”

**REFERENCES**