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Inflammation (Chronic)

Of the ten leading causes of *mortality* in the United States, ***chronic, low-level inflammation*** contributes to the pathogenesis of at least seven. These include heart disease, cancer, chronic lower respiratory disease, stroke, Alzheimer's disease, diabetes, and nephritis (Centers for Disease Control and Prevention 2011; Bastard et al. 2006; Cao 2011, Jha et al. 2009; Ferrucci et al. 2010; Glorieux et al. 2009; Kundu et al. 2008; Murphy 2012; Singh et al. 2011).

Inflammation has classically been viewed as an *acute* (short term) response to tissue injury that produces characteristic symptoms and usually resolves spontaneously. More contemporary revelations show *chronic* inflammation to be a major factor in the development of degenerative disease and loss of youthful functions.

Chronic inflammation can be triggered by cellular stress and dysfunction, such as that caused by excessive calorie consumption, elevated blood sugar levels, and oxidative stress. It is now clear that the destructive capacity of *chronic* inflammation is unprecedented among physiologic processes (Karin et al. 2006).

The danger of chronic, low-level inflammation is that its ***silent*** nature belies its ***destructive*** power.

In fact, stress-induced inflammation, once triggered, can persist undetected for years, or even decades, propagating cell death throughout the body. Due to the fact that it contributes so greatly to deterioration associated with the aging process, this silent state of chronic inflammation has been coined "inflammaging".

Chronic low-level inflammation may be **threatening your health** at this very moment, without you realizing it. In this protocol you will learn about low-cost blood tests that can assess the inflammatory state within your body. You'll also discover novel approaches that combat chronic inflammation to help avoid age-related health decline.

The Inflammatory Process

The Acute Inflammatory Response

Inflammation, the adaptive immune response to tissue injury or infection, plays a central role in metabolism in a variety of organisms (Medzhitov 2008).

At its most basic level, an acute inflammatory response is triggered by 1) tissue injury (trauma, exposure to heat or chemicals); or 2) infection by viruses, bacteria, parasites, or

fungi. The classic manifestation of acute inflammation is characterized by four cardinal signs: Redness and heat result from the increased blood flow to the site of injury. Swelling results from the accumulation of fluid at the injury site, a consequence of the increased blood flow. Finally, swelling can compress nerve endings near the injury, causing the characteristic pain associated with inflammation. Pain is also important to make the organism aware of the tissue damage. Additionally, inflammation in a joint usually results in a fifth sign (impairment of function), which has the effect of limiting movement and forcing rest of the injured joint to aid in healing.

A well-controlled acute inflammatory response has several protective roles:

- It prevents the spread of infectious agents and damage to nearby tissues;
- helps to remove damaged tissue and pathogens, and;
- assists the body's repair processes

However, a third type of stimuli, **cellular stress and malfunction,** triggers *chronic inflammation*, which, rather than benefiting health, contributes to disease and age-related deterioration via numerous mechanisms.

Cellular Stress & Chronic, Low-Level Inflammation

Mitochondria – cellular organelles responsible for generating biochemical energy in the form of *adenosine triphosphate* (ATP) – are a fundamentally necessary component of life in higher organisms. In fact, in the case of sophisticated multicellular life forms, organismal viability depends upon optimal mitochondrial function. Paradoxically, mitochondrial processes can also bring about a tissue-destroying inflammatory mediator known as *the inflammasome;* this phenomenon is provoked by damaged and dysfunctional mitochondria (Green 2011).

Mitochondrial dysfunction arises consequent of exposure to exogenous (e.g. environmental toxins, tobacco smoke) and endogenous (e.g. reactive oxygen species) stressors, and as a result of the aging process itself. For example, a byproduct of mitochondrial energy generation is the creation of *free radical molecules.* Free radicals can damage cellular structures and initiate a cascade of proinflammatory genetic signals that ultimately results in cell death (apoptosis), or worse, uncontrolled cell growth - the hallmark of cancer.

Aging is associated with declining mitochondrial efficiency and increased production of free radical molecules. Recent research identifies this age-associated aberration of mitochondrial function as a principle actuator of chronic inflammation (Dinarello 2011). Specifically, mitochondrial dysfunction brings about inflammation as follows:

1. Accumulation of free radicals induces mitochondrial membrane permeability;
2. Molecular components normally contained within the mitochondria leak into the *cytoplasm* (intracellular fluid in which cellular organelles are suspended);
3. Cytoplasmic *pattern recognition receptors (PRR's)*, which detect and initiate an

immune response against intracellular pathogens, recognize the leaked mitochondrial molecules as potential threats;
4. Upon detection of the potential threat, PRR's form a complex called the inflammasome that activates the inflammatory cytokine *interleukin-1β*, which then recruits components of the immune system to destroy the "infected" cell (Tschopp 2011).

These four steps represent a simplified scheme of mitochondrial dysfunction leading to cellular destruction; however, intracellular free radicals are not the only inducers of inflammatory cell death.

Circulating sugars, primarily *glucose* and *fructose*, are culprits as well. When these "blood sugars" come in contact with proteins and lipids a damaging reaction occurs forming compounds called **advanced glycation end products (AGEs).** AGEs bind to the cell-surface receptor called *receptor for advanced glycation end products*, or RAGE. Upon activation, RAGE triggers the movement of the inflammatory mediator *nuclear factor kappa-B* (NF-kB) to the nucleus, where it activates numerous inflammatory genes (Mosquera 2010). Advanced glycation end products are primarily formed *in vivo,* and glycation is exacerbated by elevated blood sugar levels. However, dietary AGEs also contribute to inflammation; they are abundant in foods cooked at high temperatures, especially red meat (Witko-Sarsat et al. 1998; Vlassara et al. 2002).

Additional biochemical inducers of a chronic inflammatory response include:

- **Uric acid (urate)** crystals, which can be deposited in joints during gouty arthritis; elevated levels are a risk factor for kidney disease, hypertension, and metabolic syndrome (Martinon et al. 2006, Alvarez-Lario et al. 2011);
- **Oxidized lipoproteins** (such as LDL), a significant contributor to atherosclerotic plaques (Nguyen Khoa et al. 1999); and
- **Homocysteine**, a non-protein-forming amino acid that is a marker and risk factor for cardiovascular disease, and may increase bone fracture risk (Au-Yeung et al. 2006).

Together, these proinflammatory instigators promote a perpetual low-level chronic inflammatory state called **para-inflammation** (Medzhitov 2008).

Although it progresses silently, para-inflammation presents a major threat to the health and longevity of all aging humans. Chronic, low-level inflammation is associated with common diseases including cancer, type II diabetes, osteoporosis, cardiovascular diseases, and others. Thus, by targeting the myriad physiological variables that can inaugurate an inflammatory response, one can effectively temper chronic inflammation and reduce their risk for inflammatory diseases.

Markers and Mediators of Inflammation

Following is a list of some of the most prominent markers of inflammation used in research and diagnosis. Some can be detected by blood tests (see "Diagnosis and Conventional Treatment of Chronic Inflammation", below):

Tumor necrosis factor alpha (TNF-α) is an intercellular signaling protein called a cytokine, which can be released by multiple types of immune cells in response to cellular damage, stress, or infection. Originally identified as an anti-tumor compound produced by macrophages (immune cells) (Green et al. 1976), TNF-α is required for proper immune surveillance and function. Acting alone or with other inflammatory mediators, TNF-α slows the growth of many pathogens. It activates the bactericidal effects of neutrophils, and is required for the replication of several other immune cell types (Sethi et al. 2008). Excessive TNF-α, however, can lead to a chronic inflammatory state, can increase thrombosis (blood clotting) and decrease cardiac contractility, and may be implicated in tumor initiation and promotion (Kundu et al. 2008).

Nuclear factor kappa-B (NF-kB) is important in the initiation of the inflammatory response. When cells are exposed to damage signals (such as TNF-α or oxidative stress), they activate NF-kB, which turns on the expression of over 400 genes involved in the inflammatory response (Sethi et al. 2008). These include other inflammatory cytokines, and pro-inflammatory enzymes including ***cyclooxygenase-2*** (COX-2) and ***lipoxygenase***. COX-2 is the enzyme responsible for synthesizing pro-inflammatory prostaglandins, and is the target of non-steroidal anti-inflammatory drugs (ibuprofen, aspirin) and COX-2 inhibitors (Celebrex®).

Interleukins are cytokines that have many functions in the promotion and resolution of inflammation. Pro-inflammatory interleukins that have been the subject of most research include IL-1β, IL-6, and IL-8. IL-1β helps immune cells to move out of blood vessels and into damaged or dysfunctional tissues. IL-6 has both pro-inflammatory and anti-inflammatory roles, and coordinates the production of compounds required during the progression and resolution of acute inflammation. IL-8 is expressed by both immune and non-immune cells, and helps to attract neutrophils (immune cells that can destroy pathogens) to sites of injury.

C-reactive protein (CRP) is an acute-phase protein, one of several proteins rapidly produced by the liver during an inflammatory response. Its primary goal in acute inflammation is to coat damaged cells to make them easier to recognize by other immune cells (Meyer 2010). CRP elevation above basal levels is not diagnostic on its own, as it can raise in several cancers, rheumatologic, gastrointestinal, and cardiovascular conditions, and infections (Windgassen et al. 2011). Elevation of CRP (as determined by a high-sensitivity CRP assay or hs-CRP) has a strong association with elevated risk of cardiovascular disease and stroke (Emerging Risk Factors Collaboration et al. 2010).

Eicosanoids. The cytokine factors mentioned above (interleukins, TNF-α) are "long-distance messages". They are produced by cells at the site of inflammation and released

into the blood, carrying information about the inflammatory response throughout the body. In contrast, eicosanoids are "local" messages; they are produced by cells that are proximal to the site of inflammation, and are meant to travel short distances (locally within the same organ, to neighboring cells, or sometimes only to different parts of the same cell) in order to elicit immune defenses (Luo et al. 2011). There are several families of eicosanoids (including prostaglandins, prostacyclins, leukotrienes, and thromboxanes) that are created by most cell types in all major organ systems. Aside from their roles in inflammation (and anti-inflammation), prostaglandins have a variety of functions in cell growth, kidney function, digestion, and the constriction and dilation of blood vessels. Thromboxanes are important mediators of the blood clotting process. Pro-inflammatory leukotrienes are important for recruiting and activating white blood cells during inflammation, and are best studied for their role in airway constriction and anaphylaxis.

Cells produce eicosanoids using unsaturated fatty acids that are part of their cell membranes. The fatty acid starting materials for eicosanoid synthesis are the essential fatty acids linoleic acid (omega-6) and its derivative arachidonic acid (AA); and alpha-linolenic acid (an omega-3) and its derivatives eicosapentaenoic acid (EPA) and *docosahexaenoic* acid (DHA). While generalizations about roles of these fatty acids in eicosanoid synthesis should be approached cautiously, the most potent inflammatory eicosanoids are produced from omega-6 fatty acids (linoleic and arachidonic acids). Diets high in omega-3 fatty acids are associated with lower biomarkers of inflammation and cardiovascular disease risk; proposed mechanisms include the production of less inflammatory or anti-inflammatory eicosanoids and through the cyclooxygenase and lipoxygenase enzymes (see below) (Serhan et al. 2001).

Cyclooxygenases and Lipoxygenases. The eicosanoids (above) require several enzymatic steps to be synthesized from unsaturated fatty acids; the cyclooxygenase (COX) and lipoxygenase (LOX) enzymes catalyze the first steps in these reactions. Cyclooxygenases initiate the conversion of omega-3 and omega-6 derivatives into one of the many prostaglandins or thromboxanes. The interest in COX enzyme metabolism comes from the fact that its inhibition leads to decreased prostaglandin synthesis, and therefore a reduction in inflammation, fever, and pain. The analgesic and anti-inflammatory activity of aspirin and the non-steroidal anti- inflammatory drugs (NSAIDS, like ibuprofen and naproxen) is due to their inhibition of COX enzymes. There are two COX enzymes with well-defined roles in humans (COX-1 and COX-2). COX-2 has the most relevance to the inflammatory process: it is normally inactive, but is turned on during inflammation and stimulates this process of inflammation by creating pro-inflammatory prostaglandins and thromboxanes.

Lipoxygenases convert fatty acids into proinflammatory *leukotrienes*, important local mediators of inflammation. Several potent inflammatory leukotrienes are produced by 5-LOX in mammals. Lipoxygenase enzymes, and the pro-inflammatory factors they produce, have a fundamental role in the inflammatory process by aiding in the recruitment of white blood cells to the site of inflammation. They also stimulate local cells to produce cytokines, which amplifies the inflammatory response (Luo et al. 2011). Thus, LOX enzymes may be involved in a wide variety of inflammatory conditions, and

represent an additional target for anti-inflammatory therapy

While COX and LOX enzymes are most often associated with pro-inflammatory processes, it is important to remember that both enzymes also produce factors that inhibit or resolve inflammation and promote tissue repair (including the prostacyclins and lipoxins), The proper transition from the pro- to anti-inflammatory activities of the COX and LOX enzymes is an important for the progression of a healthy inflammatory response.

Risk Factors for Chronic Inflammation

There are several risk factors which increase the likelihood of establishing and maintaining a low-level inflammatory response. These include:

Age. In contrast to younger individuals (whose levels of inflammatory cytokines typically increase only in response to infection or injury), older adults can have consistently elevated levels of several inflammatory molecules, especially IL-6 and TNF-α (Singh et al. 2011). These elevations are observed even in healthy older individuals. While the reasoning for this age-associated increase in inflammatory markers is not thoroughly understood, it may reflect cumulative mitochondrial dysfunction and oxidative damage, or may be the result of other risk factors associated with age (such as increases in visceral body fat or reductions in sex hormones; see below).

Obesity. Fat tissue is an endocrine organ, storing and secreting multiple hormones and cytokines into circulation and affecting metabolism throughout the body. For example, fat cells produce and secrete both TNF-α and IL-6, and visceral (abdominal) fat can produce these inflammatory molecules at levels sufficient to induce a strong inflammatory response (Trayhurn et al. 2005; Schrager et al. 2007). Visceral fat cells can produce three times the amount of IL-6 as fats cells elsewhere (Fried et al. 1998), and in overweight individuals, may be producing up to **35%** of the total IL-6 in the body (Mohamed-Ali et al. 1997). Fat tissue can also be infiltrated by macrophages, which secrete pro-inflammatory cytokines. This accumulation of macrophages appears to be proportional to BMI, and appear to be a major cause of low-grade, systemic inflammation and insulin resistance in obese individuals (Ortega Martinez de Victoria et al. 2009, Weisberg et al. 2003).

Diet. A diet high in saturated fat is associated with higher pro-inflammatory markers, particularly in diabetic or overweight individuals (Nappo et al. 2002) (Peairs et al. 2011). This effect was absent in healthy individuals (Myhrstad et al. 2011, Poppitt et al. 2008, Payette et al. 2009). Diets high in synthetic trans- fats (such as those produced by hydrogenation) have been associated with increases in inflammatory markers (IL-6, TNF-α, IL-8, CRP) in some studies (Mozaffarian et al. 2004) (Lopez-Garcia et al. 2005), but had no effect in others (Nielsen et al. 2011, Bendsen et al. 2011). The increases in markers of inflammation due to synthetic trans- fats may be more pronounced in individuals that are also overweight (Nielsen et al. 2011).

General dietary over-consumption is a major contributor to inflammation and other detrimental age-related processes in the modern world. Therefore, eating a calorie-restricted diet is an effective means of relieving physiologic stressors. Indeed, several studies show that calorie restriction provides powerful protection against inflammation (Ahmadi 2011; González 2012). For more information about the metabolic benefits of eating fewer calories, readers should refer to the caloric restriction protocol.

Low sex hormones. Amongst their many roles in biology, sex hormones also modulate the immune/inflammatory response. The cells that mediate inflammation (such as neutrophils and macrophages) have receptors for estrogens and androgens that enable them to selectively respond to sex hormone levels in many tissues (Gilliver 2010). A notable example is that of *osteoclasts*, the macrophages that reside in skeletal tissue and are responsible for breaking down and recycling old bone. Estrogens turn down osteoclast activity. Following menopause, lowered estrogen levels cause these bone depleting cells to maintain their activity, breaking down bone faster than it is rebuilt. This is one of the factors in the progression of osteoporosis.

Experiments in cell culture have demonstrated that testosterone and estrogen can repress the production and secretion of several pro-inflammatory markers, including IL-1β, IL-6, TNF-α, and the activity of NF-kb (Keller et al. 1996; Ray et al. 1997; Deshpande et al. 1997). These observations have been corroborated by observational studies that have linked lower testosterone levels in elderly men to increases in inflammatory markers (IL-6 and IL-6 receptor) (Maggio et al. 2006, Khosla et al. 2002). Several studies have shown an increase in inflammatory IL-1β, IL-6, and TNF-α following surgical or natural menopause (reviewed in Gameiro et al. 2010) (Singh et al. 2011). Conversely, the preservation of sex hormone levels is associated with reductions in the risk of several inflammatory diseases, including atherosclerosis, asthma in women, and rheumatoid arthritis in men (reviewed in (Gilliver 2010). Hormone replacement therapy (HRT) may partially exert its protective effects through an attenuation of the inflammatory response. Reductions in the risks of coronary heart disease and inflammatory bowel disease in some individuals, as well as levels of some circulating inflammatory cytokines (including IL-1B, IL-8, and TNF-α) has been observed in some studies of women on hormone replacement therapy (Kane et al. 2008, Vural et al. 2006, Anderson et al. 2004).

Smoking. Cigarette smoke contains several inducers of inflammation, particularly reactive oxygen species. Chronic smoking increases production of several pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8), while simultaneously reducing production of anti-inflammatory molecules (Arnson et al. 2010). Smoking also increases the risk of periodontal disease, an independent risk factor for increasing systemic inflammation (Lee et al. 2011).

Sleep Disorders. Production of inflammatory cytokines (TNF-α and IL-1β) appears to follow a circadian rhythm and may be involved in the regulation of sleep in animals and humans (Vgontzas et al. 1997). Disruption of normal sleep can lead to daytime elevations of these pro-inflammatory molecules. Plasma levels of TNF-α and/or IL-6 were elevated in patients with excessive daytime sleepiness, including those with sleep apnea and

narcolepsy (Vgontzas et al. 1997). These elevations in cytokines were independent of body mass index or age (Vgontzas et al. 2000, Vgontzas et al. 2003), although persons with higher visceral body fat were more likely to have sleep disorders. (Trakada et al. 2007)

Other Inciting Factors

Periodontal disease can produce a systemic inflammatory response that may affect several other systems, such as the heart and kidneys (Slade et al. 2003, Pradeep et al. 2011). It is by this mechanism that periodontal disease is thought to be a risk factor for cardiovascular diseases (Vaishnava et al. 2011)

Stress (both physical and emotional) can lead to inflammatory cytokine release (IL-6); stress is also associated with decreased sleep and increased body mass (stimulated by release of the stress hormone cortisol), both of which are independent causes of inflammation (Pervanidou et al. 2011).

The maintenance of a proper inflammatory response may also involve the central nervous system. The recently identified vagal immune reflex senses inflammatory molecules through a network of nerves (branches of the vagus nerve), and sends this information to the brain. If the brain determines that the inflammatory response is too great, it sends signals to the site(s) of inflammation to attenuate the response (van Westerloo 2010). Preliminary data suggests that depressed nerve activity may be associated with exaggerated inflammatory responses seen in sepsis (Pontet et al. 2003). Smoking, itself a risk factor for inflammation, also decreases activity of the vagus nerve (Taylor et al. 2011).

Excess Blood Glucose Fuels Inflammatory Fires

When glucose is properly utilized, our cells produce energy efficiently. As cellular sensitivity to **insulin** diminishes, excess glucose accumulates in our bloodstream. Like spilled gasoline, excess blood glucose creates a highly combustible environment from which oxidative and inflammatory fires chronically erupt.

Excess glucose not used for energy production converts to **triglycerides** that are either stored as unwanted **body fat** or accumulate in the blood where they contribute to the formation of **atherosclerotic plaque**.

As an aging human, you face a daily onslaught of excess **glucose** that poses a grave risk to your health and longevity. Surplus glucose relentlessly reacts with your body's proteins, causing damaging ***glycation*** reactions while fueling the fires of **chronic inflammation** and inciting the production of destructive **free radicals** (Basta 2004; Uribarri 2005; Toma 2009).

Avert Glycation and Inflammation by Controlling Glucose Levels with Green Coffee

Extract

Unroasted coffee beans, once purified and standardized, produce high levels of ***chlorogenic acid*** and other beneficial polyphenols that can suppress excess blood glucose levels. Human clinical trials support the role of ***chlorogenic acid***-rich green coffee bean extract in promoting healthy blood sugar control and reducing disease risk.

Scientists have discovered that ***chlorogenic acid*** found abundantly in **green coffee bean extract** inhibits the enzyme *glucose-6-phosphatase* that triggers new glucose formation and glucose release by the liver (Henry-Vitrac 2010; Andrade-Cetto 2010). Glucose-6-phosphatase is involved in dangerous postprandial (after-meal) spikes in blood sugar.

In another significant mechanism, ***chlorogenic acid*** increases the signal protein for insulin receptors in liver cells (Rodriguez de Sotillo 2006). That has the effect of increasing ***insulin sensitivity***, which in turn drives down blood sugar levels.

In a clinical trial, 56 healthy volunteers were challenged with an oral glucose tolerance test before and after a supplemental dose of green coffee extract. The oral glucose tolerance test is a standardized way of measuring a person's after-meal blood sugar response. In subjects not taking green coffee bean extract, the oral glucose tolerance test showed the expected rise of blood sugar to an average of 144 mg/dL after a 30 minute period. But in subjects who had taken 200 mg of the green coffee bean extract**,** that sugar spike was significantly reduced, to just *124 mg/dL—a 14% decrease* (Nagendran 2011). When a higher dose (400 mg) of green coffee bean extract was supplemented, there was an even *greater* average reduction in blood sugar—up to nearly 28% at one hour.

Ensuring that fasting glucose levels stay **between 70 and 85 mg/dL**, and that two hour post-meal glucose levels remain **under 125 mg/dL** can help combat chronic inflammation.

Diseases Associated with Chronic Inflammation

Cardiovascular diseases (CVD). Inflammation is an integral part of atherosclerosis (recall that oxidized low-density lipoprotein cholesterol stimulates the inflammatory response). Circulating inflammatory cytokines are predictive of peripheral arterial disease, heart failure, atrial fibrillation, stroke, and coronary heart disease (Singh et al. 2011, Emerging Risk Factors Collaboration et al. 2010).

Cancer. Several studies have established links between chronic low-level inflammation and many types of cancer, including lymphoma, prostate, ovarian, pancreatic, colorectal and lung (Aggarwal et al. 2006).(Kundu et al. 2008) There are several mechanisms by which inflammation may contribute to carcinogenesis, including alterations in gene expression, DNA mutation, epigenetic alterations, promotion of tumor vascularization, and the expression of pro-inflammatory cytokines that have roles in cancer cell proliferation (Kundu et al. 2008, Balkwill 2009)

Diabetes. The infiltration of macrophages into fat tissue and their subsequent release of pro-inflammatory cytokines into circulation occur at a greater rate in type II diabetics than in non-diabetics (Pickup et al. 2000, Nappo et al. 2002, Ortega Martinez de Victoria et al. 2009). Pro-inflammatory cytokines clearly decrease insulin sensitivity (Bastard et al. 2006).

Age-related macular degeneration (AMD). An evaluation of 11 population-based studies encompassing over 41,000 patients demonstrated a clear association between elevated serum CRP levels (> 3 mg/L) and the incidence of late onset AMD (Hong et al. 2011). The risk of AMD in these high-CRP patients was increased over 2-fold compared with patients with CRP levels < 1 mg /L.

Chronic kidney disease (CKD). The chronic, low-grade inflammation in CKD can lead to the retention of several pro-inflammatory molecules in the blood (including cytokines, AGEs, and homocysteine) (Glorieux et al. 2009). The reduced excretion of pro-inflammatory factors by the diseased kidney can accelerate the progression of chronic inflammatory disturbances elsewhere in the body, such as the cardiovascular system.

Osteoporosis. Inflammatory cytokines (TNF-α, IL-1β, IL-6) are involved in normal bone metabolism. Osteoclasts, the cells that break down (resorb) bone tissue, are a type of macrophage and can be stimulated by pro-inflammatory factors. Systemic elevations in pro-inflammatory cytokines push bone metabolism towards resorption, and have been observed to induce bone loss in persons with periodontal disease, pancreatitis, inflammatory bowel disease, and rheumatoid arthritis (Cao 2011). An increase in the levels of inflammatory cytokines is also a mechanism by which menopause stimulates bone loss.

Depression. There is a small, but significant association between elevated IL-6 and CRP in depressed patients, which has been observed in many population studies (Dantzer 2012). It is unclear whether inflammation leads to stress or vice versa, and there is data supporting both hypotheses (Gimeno et al. 2009) (Copeland et al. 2012).

Cognitive decline. Several observational studies have linked chronic low-level inflammation in older adults to cognitive decline and dementia, including vascular dementia and Alzheimer's disease (Singh et al. 2011). One study found that people with the highest CRP and IL-6 levels (> 2.4 pg/mL) had a ~30-40% increased risk of cognitive decline compared to those with the lowest levels (< 1.4 pg/mL). (Yaffe et al. 2003). Inflammatory markers can be elevated before the onset of cognitive dysfunction, indicating their potential relevance as a prognostic tool in high-risk individuals (Singh et al. 2011).

Others. Elevations in circulating inflammatory cytokines are associated with several other conditions, both inflammatory (rheumatoid arthritis, IBD/Crohn's disease, pancreatitis) and non-inflammatory (anemia, fibromyalgia, frailty, sacropenia/cachexia/muscle wasting) (Kaser et al. 2011) (Jha et al. 2009) (Ferrucci et al. 2010, Kadetoff et al. 2011, Rolland et al. 2011). Again, whether inflammation incites

these conditions or results from them is unclear, and requires further investigation.

Conventional Medicine Typically Overlooks Chronic Inflammation

Chronic inflammation or para-inflammation is generally not treated on its own by mainstream physicians. Interventions in conventional medicine are usually only undertaken when the inflammation occurs in association with another medical condition (such as arthritis). Currently, conventional preventive medical approaches to inflammation are limited to the use of CRP to predict cardiovascular disease in high-risk subjects, and the prophylactic use of drugs like aspirin to inhibit the inflammatory cascade linked to thrombosis (uncontrolled blood clotting). Indeed, the potentially asymptomatic nature of low grade inflammation is such that elevations of pro-inflammatory cytokines may progress undetected for some time, only being discovered after they have had time to cause enough cellular damage to produce disease symptoms. As future studies solidify the association between inflammatory mediators and different diseases, early detection of cytokine aberrations and anti-inflammatory therapy to reduce disease risk may gain more mainstream acceptance.

Testing Blood for Inflammatory Factors

The following two blood tests are inexpensive and are good markers of systemic inflammation. They can be used to detect the presence of chronic inflammation and monitor the success or failure of various anti-inflammatory regimens:

Pro-Inflammatory Marker	**Optimal Ranges**
High-sensitivity C-reactive protein (CRP);	Under 0.55 mg/L in men
	Under 1.0 mg/L in women
Fibrinogen	200 - 300 mg/dL

The following blood tests are expensive and help identify specific factors that are causing systemic inflammation:

Cytokine Testing	Normal Ranges **(LabCorp)**
Tumor necrosis factor alpha (TNF-α)	<8.1 pg/mL
Interleukin-1 beta (IL-1β)	<15.0 pg/mL
Interleukin-6 (IL-6)	2-29 pg/mL
Interleukin-8 (IL-8)	<32.0 pg/mL

Drug Strategies to Combat Chronic Inflammation

Pentoxifylline. Pentoxifylline is a drug used to treat conditions involving poor circulation to the brain, limbs, and other areas perfused by small blood vessels. The drug effectively modulates properties of both blood vessels *and* red blood cells thanks to its action as a non-selective *phosphodiesterase* inhibitor. Phosphodiesterase inhibition is a clinically important mechanism in many additional aspects of human physiology as well, so pentoxifylline has been studied in a wide range of applications ranging from diabetic complications and non-alcoholic liver disease, to endometriosis and cardiac surgery (Groesdonk et al. 2009; Li et al. 2011; Lopes de Jesus et al. 2008; Lv et al. 2009).

The potent anti-inflammatory properties of pentoxifylline were a secondary discovery, and still are not fully understood. Studies have revealed, though, that pentoxifylline modulates TNF-α signaling, which probably contributes to the considerable suppression of inflammation it has evoked in several human trials (Hepgul et al. 2010). In a recent trial, 400 mg of pentoxifylline taken twice daily significantly suppressed hs-CRP, fibrinogen, and TNF-α levels in patients with chronic kidney disease; subjects' renal function improved with treatment as well (Goicoechea et al. 2012). In patients with HIV-related vascular dysfunction, pentoxifylline lessened leukocyte adhesion – a process that contributes to cardiovascular disease by allowing inflammatory cells to infiltrate the endothelial lining of blood vessels (Gupta et al. 2010). Given by IV-infusion, pentoxifylline lowered TNF-α levels and pain intensity following surgical removal of kidney stones (Izadpanah et al. 2009).

Pentoxifylline dosage varies depending on individual circumstances and clinical application, however, 400 mg taken twice daily has consistently tempered inflammation in diverse human trials. For example, administered at this dose for one month to 30 diabetic individuals with high blood pressure, not only did pentoxifylline quell inflammation (20% reduction in CRP levels and an 11% improvement in erythrocyte sedimentation rate [measure of inflammatory tendency of a blood sample]), but it also bolstered plasma antioxidant status, as evidenced by a 20% reduction in malondialdehyde levels (measure of oxidative stress) and a nearly 5% increase in glutathione levels, a powerful antioxidant (Maiti et al. 2007).

Metformin. The regulation of energy metabolism and inflammation are closely associated; this is evidenced by the co-incidence of metabolic disorders (obesity, diabetes) and low-grade inflammation (Molavi et al. 2007). Metformin may reduce the activity of inflammatory cytokines by increasing the production of IL-1βreceptor *antagonist (IL1Rn)*, a protein factor which interferes with pro-inflammatory signaling of IL-1β (Buler et al. 2012). It may also promote favorable CRP levels, although not to the same extent as weight loss (Molavi et al. 2007, Sobel et al. 2011). A randomized controlled trial of hypertensive and dyslipedemic patients taking 1700 mg/day of

metformin for 12 weeks demonstrated a 26.7% reduction in IL-6 and 8.3% reduction in TNF-α from baseline levels, a degree of reduction similar to that of the potent statin drug rosuvastatin (Crestor®)(Gómez-García et al. 2007). The anti-inflammatory effects of metformin appear to be rapid; reductions in circulating TNF-α, IL-1β, CRP, and fibrinogen were observed after only 30 days in a larger study of 128 type II diabetic patients with dyslipidemia (Pruski et al. 2009).

Aspirin. Aspirin has been used as an anti-inflammatory therapy long before the molecular mechanics of inflammation had been discovered; it is now well characterized as an inhibitor of cyclooxygenase enzymes. The modification of COX molecules by aspirin has important implications for cardiovascular health. Blood platelets use cyclooxygenase to produce thromboxane A2, a pro-inflammatory molecule that is an important signal during the initial stages of the clotting process. The inhibitory effect of aspirin on COX enzymes in platelets can partially explain its protective effects against the complications of several disorders, including hypertension, heart attack, and stroke (Patrono et al., 2008). Aspirin's inhibition of cycloxygenase also helps explain its potential effect on cancer risk reduction as observed in several studies (Rothwell et al., 2011; Rothwell et al., 2010; Salinas et al., 2010; Flossmann et al., 2007), as COX-2 also appears to have roles in increasing the proliferation of mutated cells, tumor formation, tumor invasion, and metastasis, and may contribute to drug resistance in some cancers(Sobolewski et al. 2010). Aspirin has also been shown to reduce the activity of NF-kb in vitro (Weber et al. 1995), and lower levels of multiple inflammatory markers (TNF-α,CRP, IL-6) in patients with cardiovascular disease (Ikonomidis et al. 1999, Chen et al. 2006, Solheim et al. 2003, Solheim et al. 2006).

Unlike many other non-steroidal anti-inflammatory drugs (NSAIDS), the effects of aspirin on COX enzymes are permanent for the life of the COX enzyme. Interestingly, it appears that rather than rendering the enzyme inactive, aspirin modifies the function of COX. Aspirin stops the enzyme from producing pro-inflammatory prostaglandins, and enables it to begin producing anti-inflammatory molecules called resolvins (Serhan et al. 2002).

Low-Dose Statin Drugs. Statins are thought to reduce inflammation by a mechanism distinct from their effects on cholesterol metabolism; they interfere with the function of cytokine receptors on the surface of white blood cells. Therefore, pro-inflammatory signals in the blood are unable to provoke a response from white blood cells, and they are prevented from further stimulating inflammation (Stancu et al. 2001) (Bu et al. 2011). Results of the JUPITER trial presented the strongest evidence for statins as anti-inflammatory therapy; in this study of over 17,000 healthy middle-aged men and women with elevated levels of the inflammatory marker CRP but normal levels of blood lipids, 20mg/day of rosuvastatin (Crestor®) reduced CRP levels by over half, in addition to reducing heart attack and stroke incidence (Ridker et al. 2008). Smaller studies have looked at the effect of statins on other inflammatory markers as well. A randomized controlled trial of hypertensive and dyslipedemic patients taking a lower dose (10 mg/day) of rosuvastatin for 12 weeks demonstrated a ~22% reduction in IL-6 and 13% reduction in TNF-α from baseline levels (Gómez-García et al. 2007). A second

uncontrolled study of simvastatin demonstrated more modest reductions in IL-6, but no changes in TNF-α from the statin treatment (Bulcão et al. 2007). To generate a substantial anti-inflammatory effect using statin drugs alone requires a high dose that is more likely to induce side effects than lower dose statin therapy.

Dietary Approaches to Reduce Chronic Inflammation

Inflammation itself is not a disease, but is featured, to varying degrees, in adverse health conditions. Information on strategies and research regarding the reduction of inflammation characteristic to specific health conditions are featured in their respective Life Extension Protocols: Allergies; Age-related Macular Degeneration; Cancer Adjuvant therapy; Cardiovascular Disease; Gout; Inflammatory Bowel Disease; Osteoarthritis and Rheumatoid Arthritis; Osteoporosis. What follows is a summary of dietary and supplemental approaches to addressing general chronic inflammation and para-inflammation. As many types of general inflammation often occur without additional symptoms, most of the strategies listed below are based on their ability to reduce circulating inflammatory cytokines, the hallmark of the para-inflammatory state.

Macronutrients and Energy Balance. Macronutrient content (particularly the types and levels of carbohydrates and fats) can have a significant effect on the progression of inflammation (as measured by increases in pro-inflammatory markers). Diets with relatively high glycemic index (GI) and glycemic load (GL) have been associated with elevated risk of coronary heart disease, stroke, and type 2 diabetes mellitus, particularly among overweight individuals, and have been associated with modest increases in proinflammatory markers in multiple studies (Galland 2010). In a study of over 18,000 healthy women ≥45 years old without diagnosed diabetes, high GI and GL diets resulted in a small but significant increase in hs-CRP (+12% for high GI) over low GI diets (Levitan et al. 2008). In the Danish Hoorne study (Du et al. 2008), for every 10 unit increase in dietary glycemic index, circulating CRP was increased by 29%. As discussed previously, some dietary fats (particularly saturated and synthetic trans- fats) increase inflammation occurrence, while omega-3 polyunsaturated fats appear to be anti-inflammatory (Mozaffarian et al. 2004).

Since fat tissue (especially abdominal fat) expresses inflammatory cytokines, obesity can be a major cause of low-grade, systemic inflammation (Ortega Martinez de Victoria et al. 2009, Weisberg et al. 2003). Thus, it is important that total energy intake be proportional to energy expenditure, to avoid the deposition of abdominal fat. Obesity-induced increases in inflammatory cytokines appear to be reversible with fat loss (North et al. 2009). In a dramatic example, weight loss (by adjustable gastric banding) in a group of 20 severely obese individuals reduced IL-6 by 22% and CRP by almost half (Moschen et al. 2010).

An inflammatory index, developed by a group from the Arnold School of Public Health at the University of South Carolina, scored 42 common dietary constituents based on their ability to raise serum CRP (Cavicchia et al. 2009). Constituents (such as saturated fat, tea polyphenols, or vitamin D) were given either a positive (anti-inflammatory) or

negative (pro-inflammatory) score, the magnitude of which was weighted based on the volume of inflammation research on the isolated ingredient. Human clinical data was weighted more than animal data, and clinical trials more than observational studies. The scores were then verified by comparing them to nutrient intakes and CRP levels from a group of 494 volunteers over the course of 1 year. Amongst the most anti-inflammatory nutrients (based on the model and study data) are magnesium, beta-carotene, turmeric (curcumin), genistein, and tea; the most pro-inflammatory included carbohydrates, total- and saturated fat, and cholesterol. The index may provide a useful metric for accessing the overall inflammatory potential of an individual diet.

Exercise. Energy expenditure through exercise lowers multiple cytokines and pro-inflammatory molecules independently of weight loss. While muscle contraction initially results in a pro-inflammatory state, it paradoxically lowers systemic inflammation. This effect has been observed in dozens of human trials of exercise training in both healthy and unhealthy individuals across many age groups (reviewed in Bruunsgaard 2005).

Fiber. In an analysis of 7 studies on the relationship between weight loss and hs-CRP, increased fiber consumption correlated with significantly greater reductions in hs-CRP concentrations (North et al. 2009). In these studies, daily fiber intakes ranging from 3.3 to 7.8 g/MJ (equivalent to about 27 to 64 g/day for a standard 2000 kcal diet) reduced CRP from 25%-54% in a dose-dependent fashion. These results should be interpreted carefully, as only two of the seven studies were specifically designed to examine the effects of fiber independently (North et al. 2009). The Women's Health Initiative failed to detect an effect of fiber consumption on hs-CRP, but found that greater intake of dietary soluble and insoluble fiber (over 24 g/day) was associated with lower levels of IL-6 and TNF-α (Ma et al. 2008).

Micronutrients

Magnesium. In two large observation studies (the Women's Health Initiative and Harvard Nurses Study), greater magnesium (Mg) intake was associated with lower hs-CRP, IL-6, and TNF-α receptor, a measure of TNF-α activity (Galland 2010, Chacko et al. 2010). Data from the Multi-Ethnic Study of Atherosclerosis failed to find significant differences in IL-6 or CRP levels between individuals with the highest and lowest magnesium intakes, but did find a significant association between greater dietary magnesium and the lower levels of the inflammation-associated proteins homocysteine and fibrinogen (de Oliveira Otto et al. 2011). Magnesium was rated as the most anti-inflammatory dietary factor in the Dietary Inflammatory index, which rated 42 common dietary constituents on their ability to reduce CRP levels based on human and animal experimental and observation data (Cavicchia et al. 2009).

Vitamin D. Vitamin D appears to exert anti-inflammatory activity by the suppression of pro-inflammatory prostaglandins, and inhibition of the inflammatory mediator NF-κβ (Krishnan et al. 2010). Although intervention studies of its anti-inflammatory activity in humans are lacking, several observational studies suggest vitamin D deficiency may promote inflammation. Vitamin D deficiencies are more common amongst patients with

inflammatory diseases (including rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and diabetes) than in healthy individuals (Guillot et al. 2010). They also occur more frequently in populations that are prone to low-level inflammation, such as obese individuals and the elderly (Awad et al. 2012). Vitamin D levels can drop following surgery (a condition associated with acute inflammation), with a concomitant rise in CRP (Reid et al. 2011). Low vitamin D status was associated with elevated CRP in a study of 548 heart failure patients (Liu et al. 2011), and with increases in IL-6 and NF-κβ in a group of 46 middle-aged men with endothelial dysfunction (Jablonski et al. 2011).

Vitamin E. Vitamin E functions as an antioxidant in the body. Specifically, vitamin E is incorporated into low-density lipoprotein (LDL) particles and protects them against oxidative damage; it seems to guard against atherosclerosis via other mechanisms as well (Meydani 2001. The **gamma-tocopherol** form of vitamin E appears to complement the anti-inflammatory action of **alpha-tocopherol**. Gamma-tocopherol has been shown to inhibit COX-2 and attenuate IL-1β signaling (Jiang 2000; Sjoholm 2001). In a small clinical trial on subjects with metabolic syndrome, the combination of gamma-tocopherol and alpha-tocopherol effectively suppressed C-reactive protein and TNA-α levels compared to placebo (Devaraj 2008). In this study, the combination of both tocopherols performed better than either alone, prompting the investigators to remark "*the combination of [alpha-tocopherol] and [gamma-tocopherol] supplementation appears to be superior to either supplementation alone on biomarkers of oxidative stress and inflammation and needs to be tested in prospective clinical trials...*"

Zinc and Selenium. Zinc- and Selenium-containing antioxidant proteins (such as superoxide dismutase and glutathione peroxidase) reduce reactive oxygen species (free radicals), which indirectly inhibits NF-κβ activity and prevents the production of several inflammatory enzymes and cytokines. Zinc can also inhibit NF-κβ in a more direct manner (Prasad 2009, Duntas 2009). Zinc supplementation is associated with decreases in inflammation in populations that are prone to zinc deficiency, such as children and the elderly (Kelishadi et al. 2010, Wong et al. 2011). Low level inflammation and circulating pro-inflammatory factors (CRP, TNF-α, IL-6, and IL-8) were reduced in elderly subjects by moderate zinc supplementation in several studies (Bao et al. 2010, Kahmann et al. 2008, Mariani et al. 2006). Like zinc, selenium deficiencies are common in chronic inflammatory states associated with disease (such as sepsis) (Maehira et al. 2002), where selenium supplementation has been associated with reductions in inflammation and better patient outcomes (Duntas 2009).

Other Dietary Factors

Resveratrol and Pterostilbene. The exact mechanism by which resveratrol exerts anti-inflammatory activity has not been established, although it inhibits a variety of pro-inflammatory compounds (cyclooxygenase, TNF-α, IL-1β, IL-6, NF-κβ) in animal models and human cell culture (Jha et al. 2010; Khanduja et al. 2004). The related compound pterostilbene has demonstrated similar inhibition of inflammatory markers in cell culture (Pan et al. 2008). Modulation of the inflammatory immune response likely

contributes to resveratrol's protective role in animal models of heart disease, cancer, acute pancreatitis and inflammatory bowel disease (Clarke et al. 2008). Resveratrol may be protective against general, low-level para-inflammation as well: when taken with a single high-fat, high-carbohydrate meal (930 kcal), resveratrol (100 mg) prevented the sharp post-meal increases in markers of oxidation and inflammation in a small crossover study of 10 healthy volunteers. For example, synthesis of IL-1β increased by 91% over 5 hours following the test meal; with resveratrol, this increase was significantly less (29%) (Ghanim et al. 2011).

Curcumin. Extensive in vitro and animal studies have examine the effects of curcumin on experimentally-induced inflammatory diseases (atherosclerosis, arthritis, diabetes, liver disease, gastrointestinal disorders, and cancers) and disease markers (lipoxygenase, cyclooxygenase, TNF-α, IL-1β, NF-κβ, and others) (Chainani-Wu 2003, Bengmark 2006). Fewer human studies have examined curcumin's effects on patient-oriented outcomes in inflammatory diseases, but most of the small randomized controlled trials of curcumin have consistently shown patient improvements in several inflammatory diseases, including psoriasis, irritable bowel syndrome, rheumatoid arthritis, and inflammatory eye disease (Epstein et al. 2010)(reviewed in White et al. 2011).

Tea polyphenols. The anti-inflammatory effects of green and black tea polyphenols have been substantiated by dozens of in vitro and animal studies (Singh et al. 2010) The polyphenols EGCG and theaflavin exert their anti-inflammatory effects through the inhibition of the NF-κβ signaling pathway, which decreases expression of several inflammatory proteins (lipoxygenase, cyclooxygenase, TNF-α, IL-1β, IL-6, and IL-8) in cell culture experiments (de Mejia et al. 2009). EGCG also inhibits the production and release of histamine, a key mediator of allergic and inflammatory response, in vitro (Melgarejo et al. 2010). In observational studies of tea consumption, >2 cups of tea/day (black or green) was associated with a nearly 20% reduction in CRP compared to non-tea drinkers, and significantly lower levels of two other inflammatory markers (serum amyloid A and haptogen, which are elevated in coronary heart disease) (De Bacquer et al. 2006). In clinical interventions, black tea appears to be more successful in reducing inflammatory markers than green (Galland 2010). A 25% reduction in CRP was also observed in a small trial of healthy, non-smoking men consuming a black tea extract (equivalent to 4 cups of tea/day) for 6 weeks (Steptoe et al. 2007). A similar average reduction was observed in a larger study of healthy, individuals at high risk for coronary heart disease, but revealed a more dramatic 40-50% reduction in CRP amongst individuals with the highest starting CRP values (>3 mg/L) (Bahorun et al. 2010).

Carotenoids. In the Women's Health and Aging Study, participants with the highest blood levels of α-carotene and total carotenoids were significantly more likely to have the lower IL-6 levels than participants with low carotenoid levels at the onset of the study (Walston et al. 2006). Participants with the lowest blood levels of α- and β-carotene, lutein/zeaxanthin, or total carotenoids were more likely to experience increases in IL-6 over a period of 2 years.

DHEA. Low levels of sex hormones are associated with systemic increases in inflammatory markers (Singh et al. 2011); DHEA (dehydroepiandrosterone) an adrenal steroid hormone, the precursor to the sex steroids testosterone and estrogen. DHEA is abundant in youth, but steady declines with advancing age and may be partially responsible for age-related decreases sex steroids (Heffner 2011). In cell culture and animal models, DHEA can suppress inflammatory cytokine activity, in some cases more effectively than either testosterone or estrogen (Gordon et al. 2001). Chronic inflammation may itself reduce DHEA levels (Ernestam et al. 2007). DHEA supplementation in elderly volunteers (50 mg/day for 2 years) significantly decreased TNF-α and IL-6 levels, as well as lowered visceral fat mass and improved glucose tolerance (both associated with inflammation) in a small study (Weiss et al. 2011).

Fish Oil, is the best source of the omega-3 fatty acids eicosapentaenoic acid -- EPA, and docosahexaenoic acid – DHA that can only be synthesized to a limited extent in humans, which is why fish oil supplementation is so critical. Omega-3 fatty acids have been well studied for their prevention of cardiovascular disease and mortality in tens of thousands of patients; the anti-inflammatory effects of omega-3's contribute to this activity (Marik et al. 2009). They have also proven successful at improving patient outcomes in scores of studies of other inflammatory diseases, particularly asthma, inflammatory bowel disease, and rheumatoid arthritis (Calder 2006) (Giugliano et al. 2006).

The association between greater fish oil/omega-3 consumption and reduced systemic inflammation is substantiated by data from several large observational trials. In 855 healthy participants from the Health Professionals Follow-Up Study, intake of omega-3 fatty acids was associated with lower plasma levels of markers of TNF-α activity; interestingly, high intake of both omega-3 and omega-6 fatty acids (which are usually assumed to be pro-inflammatory) was associated with the lowest level of inflammation (Pischon et al. 2003). The Nurses' Health Study I cohort of 727 women revealed lower concentrations of inflammatory markers (including CRP and IL-6) amongst those in the top 20% of omega-3 consumption, when compared to those who consumed least amount (Lopez-Garcia et al. 2004). In the ATTICA study of over 3000 Greek men and women without any evidence of cardiovascular disease, participants who consumed over 300 g of fish per week had, on average, 33% lower CRP, 33% lower IL-6, and 21% lower TNF-α than participants who did not consume fish (Zampelas et al. 2005). In a sample of 5,677 men and women without cardiovascular disease from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, long-chain omega-3 intake (from fish or supplements) was associated with reduced plasma concentrations of multiple inflammatory markers (including CRP, IL-6, and TNF-α receptor, a measure of TNF-α activity)(He et al. 2009)

N-acetyl cysteine (NAC). Activation of the NF-κB pathway plays a central role in the activation of inflammatory cytokine genes; N-acetyl cysteine inhibits NF-κβ in cell culture, lowering expression of cytokines such as IL-6 and IL-8 (Araki et al. 2007) (Radomska-Leśniewska et al. 2006). Data establishing the effects of NAC on lowering chronic inflammation in humans is limited, but shows promise. NAC supplementation for 8 weeks demonstrated modest, but statistically significant decreases in circulating IL-6 levels in patients with chronic kidney disease (Nascimento et al. 2010). The effects were

more pronounced in persons with significant inflammation at the start of the study (as measured by hs-CRP). NAC also reduced markers of systemic inflammation in a small study of patients with burn injuries (Csontos et al. 2011).

Boswellia. Boswellia serrata (frankincense) is a traditional anti-arthritic in Ayurvedic medicine; its anti-inflammatory properties have been attributed to the specific inhibition of 5-LOX and reduction in the production of pro-inflammatory leukotrienes by boswellic acids, a constituent of the Boswellia gum resin (Boswellia serrata. 2008). In cell culture, both crude and highly purified Boswellia extracts inhibited the production of pro-inflammatory TNF-α and IL-1β (Gayathri et al. 2007). One of the boswellic acids, ***Acetyl-11-keto-beta-boswellic acid (AKBA)***, was an inhibitor of NF-Kb activity in mice (Cuaz-Pérolin et al. 2008), while a topical mixture of the four most abundant boswellic acids decreased inflammation in a rodent inflammation model (Singh et al. 2008). A recent systematic review of human trials of Boswellia for inflammatory conditions revealed that the small number of randomized controlled trials on the extract have produced encouraging results for its use for asthma and osteoarthritis (Ernst 2008), warranting larger studies to confirm the extract as an effective therapy. Standardized Boswellia extracts (30% AKBA) have been effective in mitigating pain in osteoarthritis patients (Sengupta et al. 2008); when combined with non-volatile Boswellia oil, the standardized extract (called AprèsFlex™, or Aflapin®) demonstrated improved activity at a lower concentration (Sengupta et al. 2010). The use of Boswellia extracts for inflammatory bowel diseases has been investigated in multiple clinical trials, although results have been mixed (Gupta et al. 1997; Gupta et al. 2001; Holtmeier et al. 2011).

Sesame Lignans. The observation that sesame oil could decrease the production of arachidonic acid in fungi and rat liver cells led to the identification of the sesame lignans (sesamin, sesamolin, sesaminol) as specific inhibitors of Δ5 desaturase (delta-5-desaturase), one of the enzymes used in the synthesis of arachidonic acid (Shimizu et al. 1991). By inhibiting Δ5 desaturase, sesame lignans may reduce the synthesis of pro-inflammatory prostaglandin, leukotrienes, and thromboxanes, each of which require arachidonic acid as a starting material (Harikumar et al. 2010). In animal models, diets high in sesame seed oil reduced production of the pro-inflammatory prostaglandins PGE-1 and -2, as well as thromboxane B2 (Chavali et al. 1997). In humans, 5 weeks of sesamin supplementation (39 mg/day) reduced the production of the pro-inflammatory vasoconstrictor 20-hydroxyeicosatetraenoic acid (20-HETE; a product of the enzyme 5-LOX) by 30% (Wu et al. 2009). This potential anti-inflammatory property of sesame lignans may partially explain its observed hypotensive (blood pressure-lowering) activity (Miyawaki et al. 2009).

Bromelain. The anti-inflammatory activity of the proteolytic enzyme preparation bromelain has been attributed to its ability to reduce COX-2 activity, decrease prostaglandin and thromboxane synthesis, lower circulating fibrinogen levels, and reduce cellular adhesion of pro-inflammatory white blood cells to the sites of inflammation (Yuan et al. 2006). Human trials of bromelain for inflammatory conditions have yielded promising results (Bromelain Monograph 2010). In a blinded study from Germany, researchers divided 90 patients with painful osteoarthritis of the hip into two groups: one

half receiving an oral enzyme preparation containing bromelain for six weeks, while the other half received the anti-inflammatory drug diclofenac (sold under the brand name Voltaren® and generic names). They found that the bromelain preparation was as effective as diclofenac in standard scales of pain, stiffness and physical function, and better tolerated than the drug comparator. The researchers concluded, "[the bromelain preparation] may well be recommended for the treatment of patients with osteoarthritis of the hip with signs of inflammation as indicated by a high pain level" (Klein 2006).

Another study comparing a standardized commercial enzyme preparation containing bromelain with diclofenac reached the same conclusion. The study reported that the supplement containing bromelain (90 mg, three times daily) to be as effective as diclofenac (50 mg, twice daily) in improving the symptoms of osteoarthritis of the knee. Patients reported comparable reductions in joint tenderness, pain and swelling, and improvement in range of motion at the end of the study. The investigators found bromelain to be as good as diclofenac on a standard pain assessment scale and to be better than the drug in reducing pain at rest (by 41% for bromelain versus 23% for the drug), improving restricted function (by 10% for bromelain versus 0% for the drug), being rated by more patients in improving symptoms (24% for bromelain versus 19% for the drug), and being evaluated by more physicians as having good efficacy (51% for bromelain versus 37% for the drug). In summary, the investigators determined bromelain to be an effective and safe alternative to NSAIDs such as diclofenac for painful osteoarthritis (Akhtar 2004).

In further research from the United Kingdom, a three-month study looked at the dose-dependent effects of bromelain, either 200 mg or 400 mg a day in volunteers with mild acute knee pain. Pain evaluation was based on patient symptom scores, which were reduced by 41% in the 200 mg bromelain group and by 59% in those receiving 400 mg of bromelain, indicating a dose-response relationship. This was also observed for scores of stiffness and physical function, which decreased significantly in the higher-dose bromelain group compared with those receiving 200 mg. The researchers also noted that overall psychological well-being was significantly improved in both bromelain groups, leading to their conclusion that this natural therapy may be effective in improving general well-being as well as symptoms in otherwise healthy adults suffering from mild knee pain (Walker 2002).

In animal models and cell culture experiments, bromelain has consistently demonstrated a variety of anti-inflammatory properties (Fitzhugh 2008; Secor 2008; Onken 2008; Secor 2005).

Mitochondrial Support

Reactive oxygen species generated during mitochondrial respiration contribute to inflammation, as outlined above. Aging individuals are especially susceptible to mitochondria-related oxidative stress since mitochondria become increasingly dysfunctional with age. Taking steps to support mitochondrial integrity and efficiency can help alleviate some of the systemic oxidative and inflammatory burden caused by

poorly functioning mitochondria. Two nutrients, **coenzyme Q10 (CoQ10)** and **pyrrloquinoline quinone (PQQ)** are powerful mitochondrial protectants (Sourris 2012; Tao 2007), and studies support an anti-inflammatory role for these compounds.

Pyrroloquinoline quinone is a cofactor for enzymes critically important for cellular energy homeostasis and redox balance (Rucker 2009). Several studies have shown that PQQ exerts a protective effective during circumstantial mitochondrial stress and increased oxidative load (Tao 2007; Xiong 2011). In one study, rats given a diet supplemented with PQQ displayed greater energy expenditure and, remarkably, increased mitochondrial density in liver tissue. PQQ supplemented rats also had lower triglycerides and their hearts were more protected against lack of oxygen than rats that had not been given PQQ (Bauerly 2011). During periods of limited oxygen supply to cardiac tissue, a dramatic spike in oxidative stress and subsequent inflammation damages cells; the findings from this animal model indicate that PQQ can stave off this inflammatory cell destruction by preserving mitochondrial efficiency in adverse conditions.

Coenzyme Q10 is an indispensable intermediary in mitochondrial ATP production. Studies have shown that CoQ10 levels are low during inflammatory conditions. In one investigation, patients with septic shock were found to have CoQ10 levels substantially lower than healthy individuals, and, among patients, lower CoQ10 levels correlated with higher levels of an inflammatory mediator called VCAM (Donnino 2011). In an animal model in which rats were given drinking water with added fructose, an experiment that leads to obesity, diabetes, and other inflammatory complications, CoQ10 supplementation attenuated the inflammatory response by decreasing hepatic expression of CRP and other inflammatory mediators (Sohet 2009). Laboratory experiments indicate that CoQ10 modulates the expression of several hundred genes, many involved in inflammatory signaling (Schmelzer 2008). Of particular significance, one experiment showed that CoQ10, at physiologically relevant concentrations, was able to blunt induced TNF-α by more than 25% via modulation of the NF-kB signaling pathway (Schmelzer 2008).

Guarding Against Inflammatory Glycation Reactions

The role of elevated blood sugar and glycation end products in initiating an inflammatory storm has been discussed above. Fortunately, in addition to reducing caloric intake to suppress both fasting and post-meal glucose concentrations, some natural compounds ameliorate the glycation process and may help rein in the sugar-induced inflammatory cascade. Chief among these anti-glycation nutrients are **benfotiamine**, a member of the B-vitamin family, and **carnosine**, an amino acid.

Benfotiamine has been used to target diabetic complications since the mid 1990's (Stracke 1996). More recent evidence continues to support its use as a powerful protector against blood sugar-induced tissue damage. In a clinical trial, 165 subjects with diabetes were randomized to receive benfotiamine at either 300 or 600 mg per day, or a placebo for 6 weeks. After the intervention period, those taking benfotiamine exhibited improvements in neuropathic pain in a dose-dependent fashion (Stracke 2008). An animal

model found that benfotiamine relieved neuropathic pain by powerfully suppressing inflammation (Sanchez-Ramirez 2006). Moreover, laboratory experiments have shown that, in addition to blocking glycation reactions, benfotiamine may regulate inflammation more directly by modulating COX and LOX enzyme activity (Shoeb 2012).

Carnosine exerts a range of favorable biochemical effects within the body; it powerfully blunts glycation reactions and eases oxidative stress (Vistoli 2012). In addition, several experiments have revealed a marked ability of carnosine to suppress inflammation in various cell types (Fleisher-Berkovich 2009; Tsai 2010; Boldyrev 2007). Unfortunately, carnosine levels decline as much as 63% between ages 10 and 70 (Hipkiss 2009). Furthermore, in patients with type II diabetes, skeletal muscle carnosine content is markedly lower than in healthy control subjects (Gualano 2011). When carnosine is administered as a supplement to animals with chemically–induced diabetes, it is able to protect delicate retinal cells from inflammatory complications related to high blood sugar (Pfister 2011).

Life Extension Suggestions

General Support

- **Magnesium**: 100 – 800 elemental milligrams of highly-absorbable magnesium
- **Vitamin D**: 5000 – 8000 IU daily (depending on blood test results; optimal blood levels are between 50 and 80 ng/mL)
- **Vitamin A**: 500 IU acetate and 4500 IU beta-carotene daily
- **Natural Vitamin E**: 100 – 400 IU alpha-tocopherol and 200 mg gamma-tocopherol daily
- **Fish oil** (with olive polyphenols and sesame lignans): providing 1400 mg EPA and 1000 mg DHA daily
- **Zinc**: 30 mg daily
- **Selenium**: 200 mcg daily
- **DHEA**: 15 – 25 mg daily for women, and 25 – 75 mg daily for men (depending on blood test results)

Antioxidants

- ***Trans*-resveratrol**: 100 – 500 mg daily
- ***Trans*-pterostilbene**: 0.5 – 50 mg daily
- **Green tea extract**, standardized to 98% polyphenols: 725 – 1450 mg daily
- **Black tea extract**, standardized to 25% theaflavins: 350 mg daily
- **N-Acetylcysteine**: 600 – 1200 mg daily

Mechanism-Specific Support

- **Curcumin** (as highly absorbed BCM-95®): 400 – 800 mg daily
- ***Boswellia serrata* extract** (as highly absorbed AprèsFlex™), standardized to 20% AKBA: 100 mg daily

- **Bromelain** (enteric coated): 500 – 1000 mg daily

Optimizing Glucose Levels and Targeting Advanced Glycation End Products

- **Green coffee extract**, standardized to 50% chlorogenic acid: 200 – 400 mg before each meal, up to three times daily
- **Benfotiamine**: 150 – 1000 mg daily
- **L-carnosine**: 500 – 1500 mg daily

Supporting Mitochondrial Function

- **Pyrroloquinoline quinone**: 10 – 20 mg daily
- **CoQ10** (as ubiquinol): 100 – 200 mg daily

In addition, the following **blood tests** should be considered:

- **Male or Female Panel** (includes glucose, C-reactive protein, LDL, homocysteine, sex hormones, and many other important tests)
- **Fibrinogen**
- **Vitamin D** (25-hydroxyvitamin D)
- **Cytokine Panel**
- **Omega Score®**

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