

Inflammation: Chronic

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AGING AND INFLAMMATION

- Causes of Age-Related Inflammation

Chronic systemic inflammation is an underlying cause of many seemingly unrelated, age-related diseases. As humans grow older, systemic inflammation can inflict devastating degenerative effects throughout the body (Ward 1995; McCarty 1999; Brod 2000). This fact is often overlooked by the medical establishment, yet persuasive scientific evidence exists that correcting a chronic inflammatory disorder will enable many of the infirmities of aging to be prevented or reversed.

The pathological consequences of inflammation are well-documented in the medical literature (Willard et al. 1999; Hogan et al. 2001). Regrettably, the dangers of systemic inflammation continue to be ignored, even though proven ways exist to reverse this process. By following specific prevention protocols suggested by the Life Extension Foundation, the inflammatory cascade can be significantly reduced.

The Causes of Age-Related Inflammation

Aging results in an increase of inflammatory cytokines (destructive cell-signaling chemicals) that contribute to the progression of many degenerative diseases (Van der Meide et al. 1996; Licinio et al. 1999). Rheumatoid arthritis is a classic autoimmune disorder in which excess levels of cytokines such as tumor necrosis factor-alpha (TNF-a), interleukin-6 (IL-6), interleukin 1b [IL-1 (b)], and/or interleukin-8 (IL-8) are known to cause or contribute to the inflammatory syndrome (Deon et al. 2001).

Chronic inflammation is also involved in diseases as diverse as atherosclerosis, cancer, heart valve dysfunction, obesity, diabetes, congestive heart failure, digestive system diseases, and Alzheimer's disease (Brouqui et al. 1994; Devaux et al. 1997; De Keyser et al. 1998). In aged people with multiple degenerative diseases, the inflammatory marker, C-reactive protein, is often sharply elevated, indicating the presence of an underlying inflammatory disorder (Invitti 2002; Lee et al. 2002; Santoro et al. 2002; Sitzer et al. 2002). When a cytokine blood profile is conducted on people in a weakened condition, an excess level of one or more of the inflammatory cytokines, e.g., TNF-a, IL-6, IL-1(b), or IL-8, is usually found (Santoro et al. 2002). (See the Suggested Reading reference list for additional citations.)

PROTECTING AGAINST INFLAMMATORY-RELATED DISEASE

The New England Journal of Medicine published several studies in the year 2000 showing that the blood indicators of inflammation are strong predictive factors for determining who will suffer a heart attack (Lindahl et al. 2000; Packard et al. 2000; Rader 2000). The January 2001 issue of Life Extension Magazine described these studies and explained how individuals could protect themselves against these inflammatory markers (such as C-reactive protein, homocysteine, and fibrinogen).

A growing consensus among scientists is that common disorders such as atherosclerosis, colon cancer, and Alzheimer's disease are all caused in part by a chronic inflammatory syndrome.

Seemingly unrelated diseases have a common link. People who have multiple degenerative disorders often exhibit excess levels of pro-inflammatory markers in their blood. Here is a partial list of common medical conditions that are associated with chronic inflammation:

Diseases Related To Chronic Inflammation

Disease	Mechanism
Allergy	Inflammatory cytokines induce autoimmune reactions
Alzheimer's	Chronic inflammation destroys brain cells
Anemia	Inflammatory cytokines attack erythropoietin production
Aortic valve stenosis	Chronic inflammation damages heart valves
Arthritis	Inflammatory cytokines destroy joint cartilage and synovial fluid
Cancer	Chronic inflammation causes many cancers
Congestive heart failure	Chronic inflammation contributes to heart muscle wasting
Fibromyalgia	Inflammatory cytokines are elevated
Fibrosis	Inflammatory cytokines attack traumatized tissue
Heart attack	Chronic inflammation contributes to coronary atherosclerosis
Kidney failure	Inflammatory cytokines restrict circulation and damage nephrons
Lupus	Inflammatory cytokines induce an autoimmune attack
Pancreatitis	Inflammatory cytokines induce pancreatic cell injury
Psoriasis	Inflammatory cytokines induce dermatitis
Stroke	Chronic inflammation promoted thromboembolic events
Surgical complications	Inflammatory cytokines prevent healing

A critical inflammatory marker is C-reactive protein. This marker indicates an increased risk for destabilized atherosclerotic plaque and abnormal arterial clotting. When arterial plaque becomes destabilized, it can burst open and block the flow of blood through a coronary artery, resulting in an acute heart attack. One of the New England Journal of Medicine studies showed that people with high levels of C-reactive protein were almost three times as likely to die from a heart attack (Ridker et al. 1997).

The Life Extension Foundation long ago advised members to have an annual C-reactive protein blood test to detect systemic inflammation that could increase the risk of heart attack, stroke, cancer and a host of age-related diseases. In fact, on January 28, 2003, the American Heart Association and Centers for Disease Control & Prevention (CDC) jointly endorsed the C-reactive protein test to screen for coronary-artery inflammation to identify those at risk for heart attack.

WHAT CAUSES ELEVATED C-REACTIVE PROTEIN?

- Elevated C-Reactive Protein and Interleukin-6 Predict Type II Diabetes

While some doctors are finally catching on to the fact that elevated C-reactive protein increases heart attack and stroke risk, they still know little about its other dangers. Even fewer practicing physicians understand that pro-inflammatory cytokines are an underlying cause of systemic inflammation that is indicated by excess C-reactive protein in the blood.

In an abstract published in the March 6, 2002 issue of the Journal of the American College of Cardiology (JACC), tumor necrosis factor-alpha (TNF-a) levels were measured in a group of people with high blood pressure and a group with normal blood pressure (Verdecchia et al. 2002). The objective of this study was to ascertain if arterial flow mediated dilation was affected by hypertension and chronic inflammation as evidenced by high levels of the pro-inflammatory cytokine TNF-a.

The hypertensive subjects taking anti-hypertensive medications had about the same blood pressure as the healthy test subjects. Arterial flow mediated dilation, however, was significantly impaired in the hypertensives and this group also showed higher levels of TNF-a, indicating persistent inflammation despite blood pressure control. This study showed that even when blood pressure is under control, hypertensives still suffer from continuous damage to the inner lining of the arterial wall (endothelial dysfunction) caused by a chronic inflammatory insult. The doctors who conducted this study concluded by stating:

"Antihypertensive therapy alone may be insufficient to improve endothelial dysfunction in hypertensives with high plasma levels of inflammatory markers. Additional therapy to target inflammation may be necessary to improve endothelial function and to prevent progression of coronary atherosclerosis in high-risk hypertensives with subclinical inflammations."

A sensitive index to evaluate how much endothelial damage is occurring is the measurement of TPA (tissue-type plasminogen activator), a clot-dissolving enzyme found in the blood. This same study showed elevated TPA levels in hypertensives, indicating

continued endothelial damage despite blood pressure reduction. These findings indicate that hypertensives should have their blood tested for both TNF-a and TPA to assess how much inner wall (endothelial) arterial damage is occurring (Vardecchia et al. 2002). If TNF-a and/or TPA levels are high, aggressive therapies to suppress the inflammatory cascade should be considered.

Elevated C-Reactive Protein and Interleukin-6 Predict Type II Diabetes

In a study published in the July 18, 2001 issue of the Journal of the American Medical Association, a group from the famous Women's Health Study was evaluated to ascertain what risk factors could predict future development of Type II diabetes (Pradhan et al. 2001). The findings showed that baseline levels of C-reactive protein and interleukin-6 (IL-6) were significantly higher among those who subsequently developed diabetes compared to those who did not.

When comparing the highest versus lowest quartile, women with the higher IL-6 levels were 7.5 times more likely to develop diabetes while those in the higher C-reactive protein ranges were 15.7 times more likely to become diabetic. After adjusting for all other known risk factors, women with the highest IL-6 levels were 2.3 times at greater risk, while those with the highest C-reactive protein levels were 4.2 times more likely to become diabetic. It should be noted that these other diabetic risk factors (such as obesity, estrogen replacement therapy and smoking) all sharply increase inflammatory markers in the blood. The doctors who conducted this study concluded by stating:

"Elevated C-reactive protein and IL-6 predict the development of Type II diabetes mellitus. These data support a possible role for inflammation in diabetogenesis."

C-REACTIVE PROTEIN AND IL-6 PREDICT DEATH

■ Frailty in Elderly Linked to Inflammation

It is well established the elevated C-reactive protein, IL-6 and other inflammatory cytokines indicate significantly greater risks of contracting or dying from specific diseases (heart attack, stroke, Alzheimer's disease, etc.).

A group of doctors wanted to ascertain if C-reactive protein and IL-6 could also predict the risks of all-cause mortality. In a study published in the American Journal of Medicine, a sample of 1,293 healthy elderly people were followed for a period of 4.6 years (Harris et al. 1999). Higher IL-6 levels were associated with a twofold greater risk of death. Higher C-reactive protein was also associated with a greater risk of death, but to a lesser extent than elevated IL-6. Subjects with both high C-reactive protein and IL-6 were 2.6 times more likely to die during follow up than those with low levels of both of these measurements of inflammation. These results were independent of all other mortality risk factors. The doctors concluded by stating:

"These measurements (C-reactive protein and IL-6) may be useful for identification of high-risk subgroups for anti-inflammatory interventions."

Frailty in Elderly Linked to Inflammation

In a study of almost 5,000 elderly people, scientists discovered that frail seniors were more likely to have signs of increased inflammation than their more active counterparts. This study was published in the Archives of Internal Medicine (Walston et al. 2002) and showed that these frail seniors with elevated blood inflammatory markers also tended to show more clotting activity, muscle weakness, fatigue and disability than active elderly people.

Findings from these studies should motivate every health conscious individual to have their blood tested for C-reactive protein. If it is elevated, then the Inflammatory Cytokine Test Panel is highly recommended. Those who suffer from any type of chronic disease may also consider the Inflammatory Cytokine Test Panel in order to identify the specific inflammatory mediator that is causing or contributing to their problem.

GLYCATION'S ROLE IN INFLAMMATION

■ Cooking and Aging Have Similar Biological Properties

Eating high temperature cooked food is another contributor in the production of inflammatory cytokines. In fact, it has been shown that eating high temperature cooked food leads to the formation of advanced glycation end (AGE) products. Glycation can be described as the binding of a protein molecule to a glucose molecule resulting in the formation of damaged protein structures. Many age-related diseases such as arterial stiffening, cataract and neurological impairment are at least partially attributable to glycation. These destructive glycation reactions render proteins in the body cross-linked and barely functional. As these degraded

proteins accumulate, they cause cells to emit signals that induce the production of inflammatory cytokines.

The glycation process is presently irreversible, though an important study indicates a drug in clinical trials may be partially effective. According to a Proceedings of the National Academy of Sciences study, consuming foods cooked at high temperature accelerates the glycation process, and the subsequent formation of advanced glycation end products.

A more succinct descriptive term for "advanced glycation end products" is "glycotoxin," since "advanced glycation end products" are toxic to the body. We will use the word "glycotoxin" from here on to describe the term "advanced glycation end products."

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Inflammation: Chronic

Cooking and Aging Have Similar Biological Properties

Cooking foods at high temperatures results in a "browning" effect, where sugars and certain oxidized fats react with proteins to form glycotoxins in the food. Normal aging can also be regarded as a slow cooking process, since these same glycotoxins form in the skin, arteries, eye lenses, joints, cartilage, etc. of our body.

The Proceedings of the National Academy of Sciences study shows that consuming foods high in glycotoxins might be responsible for the induction of a low-grade, but chronic state of inflammation. In addition, the glycotoxins in food cooked at high temperatures also promote the formation of glycotoxins in our living tissues. The implication of these findings is profound.

What one eats plays a major role in chronic inflammatory processes. Consuming low glycemic foods prevents the insulin surge that contributes to chronic inflammatory processes. It is also important to avoid over consumption of foods high in arachidonic acid (beef, egg yolk, dairy, etc.).

We now know that eating too much over-cooked food causes an increase in inflammatory cytokines. Since most "junk" foods are cooked at extremely high temperatures, it makes sense to avoid French fries, hamburgers, potato chips, fried food and other snacks. These foods not only contain lots of glycotoxins, they also create other metabolic disorders that can induce degenerative disease.

Consuming at least 1000 mg a day of carnosine, and/or 300 mg of the European drug aminoguanidine can inhibit pathological glycation reactions in the body. Eating high temperature cooked foods also induces the formation of glycotoxins. Avoiding foods cooked at high temperature not only reduces pathological glycation processes, but also prevents the formation of numerous gene-mutating toxins that are known carcinogens.

Food is cooked to destroy bacteria and other pathogens that could cause a serious illness. It is important not to eat undercooked food, but avoiding food unnecessarily cooked at higher temperatures is desirable. Certain foods (like fried foods) have to cook at high temperatures. Health conscious people are increasingly avoiding fried foods because they are associated with many health risks.

With the availability of cytokine blood profile tests, it is now possible to ascertain the underlying cause of chronic inflammatory disease. The appropriate drugs, nutrients, dietary change(s) and/or hormones can then be used to suppress the specific cytokines (such as IL-6 or TNF-a) that are promoting the inflammatory cascade.

THE DETRIMENTAL EFFECTS OF SLEEP DEPRIVATION

On June 22, 2002, researchers at the annual meeting of the Endocrine Society held in San Francisco reported that sleep deprivation markedly increases inflammatory cytokines. This finding helps explain why pain flare-up occurs in response to lack of sleep in a variety of disorders. According to the researchers, even modest sleep restriction adversely affects hormone and cytokine levels. In this carefully controlled study, sleep deprivation caused a 40% to 60% average increase in the inflammatory marker IL-6 in men and women, while men alone showed a 20% to 30% increase in TNF-a. Both IL-6 and TNF are potent pro-inflammatory cytokines that induce systemic inflammation (Vgontzas et al. 1999; Vgontzas et al. 2001).

The study results were presented by Dr. Alexandros Vgontzas, professor of psychiatry at The Pennsylvania State University in Hershey. Dr. Vgontzas stated that the findings indicate that getting a full night's rest of eight hours is not just a nice bonus, but a necessity. He stated that people who are missing even two to three hours of sleep function poorly the next day.

Dr. Vgontzas added that the finding that lack of sleep may stimulate an increase in chronic inflammatory response is worrisome because inflammation has been linked to the most common lethal conditions affecting humans today. Vgontzas warned: "Restriction of sleep a few hours is a major risk for public safety."

This study has significant implications for the treatment of chronic pain and inflammatory disorders. For many, following the recommendations in Life Extension's Insomnia Protocol could provide considerable relief from pain and other disorders by preventing the increase of pro-inflammatory cytokines.

THE DANGEROUS PRO-INFLAMMATORY CYTOKINES

- Reducing Inflammation
- Lowering Elevated C-Reactive Protein
- Blood Testing
- The Importance of Cytokine Testing
- Pentoxifylline Studies
- When to Avoid PTX and Other Anti-Inflammatories
- Sources of Pentoxifylline
- Diet and Inflammation

The following acronyms represent the most dangerous pro-inflammatory cytokines. Health-conscious persons should become familiar with these terms because excess levels of these cytokines cause or contribute to many diseases states:

TNF-a tumor necrosis factor-alpha

IL-6 interleukin-6

IL-1(b) interleukin-1 beta

IL-8 interleukin-8

Reducing Inflammation

The docosahexaenoic acid (DHA) fraction of fish oil is well documented as to its ability to suppress TNF-a, IL-6, IL-1(b), and IL-8 (Jeyarajah et al. 1999; James et al. 2000; Watanabe et al. 2000; Yano et al. 2000). A recent scientific study shows that fish oil suppresses these dangerous cytokines by up to 90% (James et al. 2000).

Other cytokine-lowering supplements are DHEA (Casson et al. 1993), vitamin K (Reddi et al. 1995; Weber 1997), GLA (gamma linolenic acid) (Purasiri et al. 1994), and nettle leaf extract (Teucher et al. 1996). Antioxidants, such as vitamin E (Devaraj et al. 2000) and N-acetyl-cysteine (Gosset et al. 1999), may also lower pro - inflammatory cytokines and protect against their toxic effects.

Prescription drugs like Enbrel (\$10,000 a year) directly bind to TNF-a and block its interaction with TNF cell surface receptors. Enbrel has demonstrated significant clinical improvement in rheumatoid arthritis patients, as have high-dose fish oil supplements (Kremer 2000). High levels of TNF-a may persist even in people receiving Enbrel drug therapy. Even if Enbrel brings TNF-a down to a safe range, other inflammatory cytokines such as IL-6 and IL-1(b) may continue to wreak havoc throughout the body. High levels of tumor necrosis factor (TNF-a) are destructive to many vital tissues such as joint cartilage (e.g., rheumatoid arthritis) and heart muscle (e.g., congestive heart failure).

Excess IL-6 and other inflammatory cytokines attack bone and promote the formation of fibrinogen that can induce a heart attack or stroke (di Minno et al. 1992). To prevent and treat the multiple diseases of aging, it is critical to keep these destructive immune chemicals (cytokines) in safe ranges.

Methods of Lowering Elevated C-Reactive Protein

Those who are in relative good health, but have elevated C-reactive protein, can try to lower it using a variety of diet modifications, supplements and/or drugs. Supplements such as vitamin E, borage oil, fish oil, DHEA, vitamin K and nettle leaf extract can lower C-reactive protein. Diets low in arachidonic acid, omega-6 fatty acids, saturated fats, high-glycemic food and overcooked food can suppress inflammatory factors in the body.

If diet and supplements fail, drugs such as ibuprofen, aspirin, pentoxifylline or one of the statins (such as Pravachol®) should be tried. If the modified diet, nutrients and/or drugs lower C-reactive protein to below 1.3 (mg/L) of blood, then this is an indication that the underlying inflammatory fire has been extinguished. (The high-sensitivity C-reactive protein blood test is recommended to measure this indicator.)

For those whose blood tests reveal persistently high inflammatory cytokine levels despite taking the supplements mentioned above, a low-cost prescription drug may be of enormous benefit.

The generic name of this low-cost prescription drug is pentoxifylline (PTX); the brand name is Trental. This drug was first used in Europe in 1972 and long ago was removed from patent status (meaning it is not cost-prohibitive). PTX is prescribed to improve blood flow properties by decreasing its viscosity. It works by improving red blood cell flexibility, decreasing platelet aggregation, and reducing fibrinogen levels (de la Cruz et al 1993; Gara 1993; Gaur et al. 1993). PTX has fallen from favor because no drug company has the economic incentive to market it to physicians. PTX is primarily prescribed to patients with peripheral artery disease, although it may have potential efficacy in treating a wide range of diseases relating to chronic inflammation.

Numerous studies show that pentoxifylline (PTX) is a potent inhibitor of TNF-a, IL-1(b), IL-6, and other pro-inflammatory cytokines (Neuner et al. 1994; Noel et al. 2000; Pollice et al. 2001; Ventura et al. 2001). Similarly, studies also show that DHA fish oil suppresses these same cytokines (Das 2000; Yano et al. 2000). In people who have a chronic disease involving elevated levels of the inflammatory cytokines, the daily administration of 400-800 mg of PTX and/or 1000-2000 mg of DHA fish oil could be of enormous benefit.

Individuals with chronic disease sometimes find it difficult to suppress C-reactive protein. In these cases, it is important to identify the specific inflammatory cytokines that are responsible for the destructive inflammatory processes that is causing or contributing to the underlying disease state. This enables a custom tailored program to be implemented, and its success measured by suppressing the pro-inflammatory cytokine culprits. For instance, if levels of TNF-a levels are elevated, and natural approaches fail to lower it, the prescription drug Enbrel should be considered.

Inflammatory Cytokine Blood Testing

People suffering from chronic disease often have elevated levels of C-reactive protein in their blood. C-reactive protein indicates an inflammatory process is going on in the body, but does not identify the specific pro-inflammatory cytokine that may be the underlying cause.

Testing for pro-inflammatory cytokines has been prohibitively expensive because there has been so little demand for it. The Life Extension Foundation offers an inflammatory cytokine profile at an affordable price. Below is the cytokine panel for this test along with the optimal anti-inflammatory ranges:

Pro-Inflammatory Cytokine	Optimal Anti-Inflammatory Range	
	Quest	LabCorp
Tumor necrosis factor alpha (TNF-a)	0-25 pg/mL	<8.1 pg/mL
Interleukin-1 beta (IL-1b)	0-150 pg/mL	<15.0 pg/mL
Interleukin-6 (IL-6)	2-29 pg/mL	<12.0 pg/mL
Interleukin-8 (IL-8)	10-80 pg/mL	<32.0 pg/mL

Note: Quest and LabCorp are blood testing facilities. Other blood testing laboratory methods may have different ranges.

As stated earlier in this chapter, an inexpensive C-reactive protein (high-sensitivity) blood test (CRP-hs) can help reveal if you have systemic inflammation. If your C-reactive protein level is over 1.3 (mg/L), this is an indication that you have an inflammatory event occurring in your body. Those with elevated CRP-hs levels (and who have a disease associated with chronic inflammation) should consider using a supplement protocol and/or prescription drugs known to suppress elevated pro-inflammatory cytokines.

The Importance of Cytokine Testing for Those Suffering From Chronic Illness

There are many chronic disease states that can now be managed by the proper utilization of the Inflammatory Cytokine Blood Panel. If you are elderly, or suffer from any serious disorder, these cytokine tests can enable your doctor to prescribe therapies that specifically target the inflammatory cytokine responsible for your poor state of health.

From a practical standpoint, if you suffer from congestive heart failure, and your levels of TNF-a remain persistently high, you may ask your doctor to prescribe the drug Enbrel®, which specifically counteracts the destructive effects of TNF-a.

If you suffer from cancer and your levels of IL-6 remain persistently high, you may consider high dose DHEA or asking your doctor to prescribe a bisphosphonate drug (such as Zometa® that protects against bone destruction that releases excess IL-6 into the body. Those with prostate, certain types of breast cancer, and other hormonally driven cancer should consider other IL-6 lowering therapies (such as high dose DHA fish oil extract) in lieu of DHEA.

Some cancer and patients display elevated levels of IL-8, which induces cancer cells to express growth factors that fuel their propagation. In hepatitis C, elevated IL-8 signals interferon drug resistance. An IL-8 suppressing therapy will soon be available to Americans (it is already used in Japan).

Those with systemic inflammatory disease often manifest high levels of IL-1b. If diet, the anti-inflammatory supplements (fish oil, borage oil, DHEA, etc.) and cytokine-suppressing drugs (pentoxifylline, 400 mg twice a day) fail to suppress this destructive cytokine, then ask your doctor to prescribe the drug Arava (leflunomide), starting at the low dose of 10 mg a day.

Inflammation: Chronic

Pentoxifylline Studies

This section discusses the positive results obtained in numerous studies when pentoxifylline was administered to reduce the damaging effects of chronic inflammation.

PTX is a prescription drug approved by the FDA to treat peripheral vascular disease. The standard dose is 1200 mg daily to improve circulation. To suppress pro-inflammatory cytokines, a lower dose of 400 mg twice a day can be used. A brief description of studies showing benefits of PTX extending beyond its FDA-approved use follows.

A controlled study on human diabetics with advanced renal failure showed that 400 mg daily of PTX reduced TNF-a levels by approximately 35%. In the PTX group, a measurement of kidney impairment was reduced 59%. There were no changes in those given placebo. The researchers noted that inflammatory cytokines such as TNF-a have long been implicated in the development and progression of diabetic kidney failure (Navarro et al. 1999a). Organ failure induced by TNF-a has also been confirmed by other studies (Boldt et al. 2001).

Aging causes a progressive decline of blood delivery to the tissues. Those who have diabetes experience accelerated circulatory deficit. In a study on diabetic rats, just 2 weeks of PTX administration resulted in a correction of nerve conduction deficit, amounting to 56.5% in the sciatic motor nerve and 69.8% in the saphenous sensory nerve. PTX restored the microvascular deficit by 50.4% (Flint et al. 2000). This study indicates that PTX may be of particular benefit to diabetics, especially those suffering from neuropathy, kidney disease, and other vascular disorders.

It is not just age-related disease that has been linked to chronic inflammation. A growing body of evidence points to a chronic inflammatory state as an underlying cause of kidney failure, asthma, pancreatitis, lupus, certain skin diseases, and other conditions.

In a study on human asthmatics (Entzian et al. 1998), PTX was shown to be almost 6 times more effective in suppressing TNF-a than the popular anti-asthma drug theophylline. The doctors concluded that PTX may be an especially promising candidate as an asthma therapy.

Lupus is an autoimmune disease. About 90% of its victims develop kidney problems. In a group of pediatric lupus patients, PTX helped to stop the deterioration of kidney function (Vazquez Garcia et al. 2000). The clinical manifestations of experimental systemic lupus erythematosus (SLE) correlate with an increased secretion of TNF-a and IL-1(b). In a mouse study, PTX significantly reduced the production of IL-1b and TNF-a. The result was significantly lower anti-DNA antibodies (a blood marker of lupus activity) and a substantially lower rate of protein in the urine (indicating reduced kidney damage). The scientists concluded that the early administration of PTX improves the clinical status of mice with this autoimmune disease (lupus) (Segal et al. 2001).

In advanced kidney failure, anemia can be induced by an inflammatory cytokine attack on erythropoietin, the major natural hormone responsible for red blood cell (RBC) production. In a group of seven anemic patients with advanced renal failure, PTX suppressed TNF-a and reversed the anemic state (Navarro et al. 1999b).

Free radicals and inflammatory cytokines have been implicated in pancreatitis. Inflammation of the pancreas is associated with a greater risk of pancreatic cancer. Many of the antioxidants used by Foundation members reduce the incidence of pancreatitis. In one study on acute pancreatitis, PTX was shown to reduce pancreatic inflammation and attenuate the depletion of pancreatic glutathione. PTX also inhibited the expected increase in TNF-a levels and prevented mitochondrial damage. Mitochondria are the power plants within all of our cells. The scientists suggested that PTX be considered as an adjuvant treatment of acute pancreatitis (Gomez-Cambronero et al. 2000).

Psoriasis is characterized by abnormal cell proliferation, inflammation, and increased levels of inflammatory cytokines. In an experiment on nude mice, PTX was shown to reduce cell proliferation and thickening of skin. Improvement was seen in the classical signs of psoriasis (Gilhar et al. 1996). A study on dogs showed that PTX was one of several drugs helpful in treating atopic dermatitis (Marsella et al. 2001). In mice, a study showed PTX to be effective in treating contact- and irritant-induced dermatitis by suppressing excess production of TNF-a (Schwarz et al. 1993).

An increase in TNF-a has been implicated in leprosy skin reactions. PTX has also been shown to work with other drugs in producing a quick response to this inflammatory cytokine-induced condition (Sampaio et al. 1998; Welsh et al. 1999).

Fibrosis is a common problem for cancer patients undergoing radiation therapy. PTX in combination with vitamin E has been shown to help heal these lesions. Scientists have speculated that the efficacy of this treatment is probably due to a combination

of blood flow stimulation and reduction in inflammatory cytokines (Fischer et al. 2001). Other studies show that PTX helps to prevent the fibrosis (Moser et al. 2000).

Inflammation plays a pivotal role in the pathogenesis of organ injury after cardiopulmonary bypass. Elderly patients appear to be especially prone to developing systemic inflammation. In a controlled study, patients undergoing cardiopulmonary bypass were given PTX before and right after surgery. Compared to the group receiving PTX, the control group showed a greater increase in C-reactive protein, IL-6, and other inflammatory cytokines. The PTX-treated patients recovered faster than the controls (Boldt et al. 2001). The researchers conducting the study stated the PTX group showed less inflammatory response than the controls and urged that more studies be done.

When it comes to healing after surgery, several factors are involved including restoration of microcirculation and strength of the inflammatory response. In a study on rats, PTX significantly shortened the time needed for healing in colonic anastomoses (reconnecting the large intestine after removing a section of it as occurs for colon cancer patients). In the rats receiving PTX, inflammatory response was markedly reduced and restoration of circulation improved. The scientists concluded by stating that PTX administration could prevent failures of colonic anastomoses (Schwarz et al. 1993). This study provides further evidence that PTX can be of significant benefit to the surgical patient by speeding the healing process. High DHA fish oil may also provide these benefits.

Some surgeons might be concerned that PTX could cause excess bleeding, yet one study showed that by modulating the dose of various anti-clotting agents (including PTX), the risk of surgical bleeding and abnormal blood clots could be reduced (Schwarz et al. 1993). The real value to PTX may be its long-term use after surgery to protect against the chronic inflammatory syndrome, to which so many of the elderly are vulnerable. The maintenance dose of PTX needed may be as low as 400 mg daily. (Remember: High-dose fish oil and other nutrients have shown similar benefits to PTX.)

When to Avoid PTX and Other Anti-Inflammatories

PTX should not be used by individuals with bleeding disorders such as a recent cerebral or retinal hemorrhage (PDR 2001). Patients taking Coumadin should have more frequent monitoring (once a week) of prothrombin times (White et al. 1989; Stigendal et al. 1999). Those with other types of bleeding should receive frequent physician examinations. According to two studies, PTX should be avoided by Parkinson's disease patients (Godwin-Austen et al. 1980; Serrano-Duenas et al. 2001).

It is important to note that the body uses TNF-a to acutely fight infections. If patients show any sign of infectious disease, drugs such as Enbrel (that inhibit the effects of TNF-a), are temporarily discontinued. A new FDA advisory states that patients should be tested and treated for inactive tuberculosis prior to therapy with another TNF-a inhibiting therapy (infliximab). Because PTX, fish oil, and nettle directly suppress TNF-a, these agents should be temporarily discontinued during the time when one has an active infection.

Sources of Pentoxifylline

Pentoxifylline can be obtained from any pharmacy with a physician's prescription. Here are sample prices for 100 tablets of the three available brands (prices obtained from a Walgreen's pharmacy located in Ft. Lauderdale, FL in January 2002):

Trental 400 mg
(name brand) \$80.59

Pentoxil 400 mg
(generic) \$53.09

Pentoxifylline 400 mg
(extended-release generic) \$53.09

Because only 1-2 tablets daily are taken, pentoxifylline is a relatively inexpensive drug.

Diet and Inflammation

In addition to toxic cytokines, there are other inflammatory pathways that can be mediated via diet modification. A common problem involves overproduction of pro-inflammatory hormone-like "messengers" (such as prostaglandin E2) and underproduction of anti-inflammatory "messengers" (such as prostaglandin E1 and E3).

The good news is that omega-3 fatty acids found in fish oil help to suppress the formation of undesirable prostaglandin E2 and promote synthesis of beneficial prostaglandin E3 (Kelley et al. 1985; Watanabe et al. 2000). Gamma-linolenic acid (GLA) induces production of the anti-inflammatory prostaglandin E1 (Das et al. 1989; Fan et al. 1997). What you eat can significantly

affect whether you have more of the beneficial prostaglandins (E1 and E3) as opposed to the pro-inflammatory prostaglandin E2.

Because prostaglandin E2 is a culprit in inflammation, reducing the consumption of foods that are high in omega-6 fatty acids and increasing the consumption of omega-3 rich foods, such as salmon and other fish, can be beneficial. Limiting foods that convert to arachidonic acid can help reduce inflammation. Arachidonic acid is a precursor to both prostaglandin E2 and the pro-inflammatory cytokine leukotriene B(4) (Brock et al. 1999). Another dietary factor that can lead to high levels of arachidonic acid is the overconsumption of high-glycemic index carbohydrates that cause excess production of insulin (Kreisberg et al. 1983). These quickly digestible foods include fruit juices or rice cakes. Food heavy in polyunsaturated fats or saturated fats can also increase prostaglandin E2.

Additionally, a study of elderly patients with heart disease requiring elective surgery (Tepaske et al. 2001) found that nutritional supplements containing omega-3 polyunsaturated fatty acids (as well as yeast and L-arginine) improved the outlook for high-risk patients when given a minimum of 5 days prior to surgery.

The number of inflammatory-related diseases that could be successfully treated with cytokine-lowering therapy is staggering. PTX and supplements such as fish oil, nettle leaf, DHEA, and vitamin K possess mechanisms of suppressing inflammatory cytokines. Unfortunately, there are no side-by-side comparisons to enable us to categorically state whether PTX or natural agents (such as DHA fish oil) work better.

Foods cooked at high temperatures can produce a browning effect in which glycotoxins are formed from the reaction of sugars and oxidized fats with protein. Glycotoxins may contribute to low-grade chronic inflammation. High glycemic foods may also contribute to the inflammatory process. Dietary modifications to reduce inflammation should include elimination of foods and cooking processes that contribute to a chronic state.

For those who have multiple degenerative diseases, the cytokine profile blood test and the C-reactive protein blood test are highly recommended. This may be done through your own physician or the Life Extension Foundation. If your cytokine test reveals excess levels of cytokines such as TNF-a, IL-1(b), or both, nutritional supplementation, dietary modifications, and low-cost prescription medications such as PTX are advised.

The following supplements are suggested:

- The docosahexaenoic acid (DHA) fraction of fish oil may be the most effective nonprescription supplement to suppress pro-inflammatory cytokines. Gamma-linolenic acid (GLA) is a precursor of PGE1, a potent anti-inflammatory agent. A product called Super EPA/DHA provides 1400 mg of EPA and 1000 mg of DHA in 4 capsules.
- DHEA is a hormone that decreases with age. DHEA has been shown to suppress IL-6, an inflammatory cytokine that often increases as people age. Typical doses of DHEA are 25-50 mg daily, although some people take 100 mg daily. Refer to the DHEA Replacement protocol for suggested blood tests to safely and optimally use DHEA.
- Nettle leaf has been shown to suppress the proinflammatory cytokine TNF-a. Take 1000 mg daily.
- Vitamin E and N-acetyl-cysteine (NAC) are protective antioxidants with anti-inflammatory properties. Vitamin E that contains gamma-tocopherol and tocotrienols provides the most broad-spectrum protection. Take 1 capsule daily of Gamma E Tocopherols with Sesame Lignans and Tocotrienols with Sesame Lignans. NAC is an amino acid with antiviral and liver protectant properties. One 600 mg capsule daily is recommended.
- Vitamin K helps reduce levels of IL-6, a pro-inflammatory messenger. Vitamin K also helps in the treatment of osteoporosis by regulating calcium and promoting bone calcification. One 10 mg capsule daily is recommended for prevention purposes. Do not take vitamin K if you are taking Coumadin or some other type of anticoagulant medicine.
- Consuming at least 1000 mg per day of carnosine and/or 300 mg of the European drug aminoguanidine can inhibit pathological glycation reactions in the body.

Note: It is illegal for the manufacturers of PTX to distribute this off-label information to the public. Life Extension can provide this information because it does not sell PTX.

PRODUCT AVAILABILITY

Super EPA/DHA with Sesame Lignans, DHEA, nettle leaf, Gamma E Tocopherol with Sesame Lignans, NAC, Super Carnosine, and Super K with K2 are available by telephoning (800) 544-4440 or by ordering online. Call (800) 208-3444 for more information on blood testing. Pentoxifylline (PTX) and Enbrel are prescription medications.



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