

LE Magazine January 2002

AS WE SEE IT

Chronic Inflammation The Epidemic Disease of Aging

Why do aging people suffer from so many seemingly unrelated disorders? Mainstream medicine attributes these multiple diseases to old age and fails to adequately address them. The sad fact is that people are needlessly suffering and dying from a common problem that is easily correctable.

In what will soon become a medical breakthrough, Life Extension has identified a reversible culprit (systemic inflammation) that is involved in the development of age-related diseases.

This role of inflammation has been 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.

Conventional doctors often tell their patients to accept the fact that they are not young anymore. Now that we know that systemic inflammation is a prime reason for the development of degenerative disease,[1-8] safe steps can be taken to suppress the inflammatory cascade that destroys cells throughout the aging body.

Aging and inflammation

Chronic inflammation inflicts devastating effects, especially as humans grow older. The pathological consequences of inflammation are fully documented in the medical literature.[9-21] Regrettably, the dangers of systemic inflammation continue to be ignored, even though proven ways exist to reverse this process.

Many people join The Life Extension Foundation (LEF) because they suffer from various degenerative diseases. A common culprit we find in these frail individuals is systemic inflammation.

The good news for healthy members is that our disease prevention protocols[22] significantly reduce the inflammatory cascade. Not all members follow our complete recommendations and their blood tests sometimes reveal elevated inflammatory markers (such as C-reactive protein). New members who come to us with multiple age-related diseases tend to present with very high inflammatory blood levels. LEF strives to identify the molecular reasons to explain why our aging population suffers from so many degenerative diseases. We use the fruits of our research to design therapeutic approaches to circumvent these disorders. In the case of chronic inflammation, LEF now has enough drugs, hormones and nutrients in its arsenal to help those suffering from chronic inflammation...the epidemic disease of aging!

What Causes Age-Related Inflammation?

Aging results in an increase of inflammatory cytokines (destructive cell-signaling chemicals) that contribute to many degenerative diseases. Rheumatoid arthritis is a classic autoimmune disorder where excess levels of cytokines such as tumor necrosis factor-alpha(TNF- α), interleukin-6(IL-6), interleukin 1(b)(IL-1b), and/or leukotriene B4(LTB4) are known to cause or contribute to the inflammatory syndrome.

Chronic inflammation is also involved in diseases as diverse as atherosclerosis, cancer, heart valve dysfunction, diabetes, congestive heart failure and Alzheimer's. In aged people with multiple degenerative diseases, C-reactive protein is often sharply elevated, indicating the presence of an underlying inflammatory disorder. When a cytokine blood profile is conducted in these feeble people, we usually find excess levels of one or more of the inflammatory cytokines (TNF- α , IL-6, IL-1 (b), LTB(4)).



William Faloon

Scientists have identified dietary supplements and prescription drugs that can reduce levels of the pro-inflammatory cytokines. The docosahexaenoic acid (DHA) fraction of fish oil is the best documented supplement to suppress TNF- α , IL-6, IL-1 (b) and LTB(4).[21-33] Studies on healthy humans and those with rheumatoid disease show that fish oil suppresses these dangerous cytokines by up to 90%.[31]

Other cytokine-lowering supplements are DHEA,[34-40] vitamin K,[41, 42] GLA (gamma linolenic acid)[43-46] and nettle leaf extract.[47] Antioxidants (such as vitamin E and n-acetyl-cysteine) may also lower pro-inflammatory cytokines[48, 49] and protect against their toxic effects.[50-55]

Prescription drugs like Enbrel (\$10,000.00/year) directly bind to TNF- α 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.[32]

When Conventional Drugs Are Not Enough

A problem recently identified by LEF is that high levels of TNF- α may persist even in people receiving Enbrel drug therapy. Even if Enbrel brings TNF- α down to a safe range, other inflammatory cytokines (such as IL-6, IL-1b) may continue to wreak havoc throughout the body.

High levels of tumor necrosis factor (TNF- α) 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.⁵⁶ In order to prevent and treat the multiple diseases of aging, it is critical to keep these destructive immune chemicals (cytokines) in safe ranges. The chart on the next page relates the currently determined safe ranges of inflammatory cytokines as measured by blood levels.

The following acronyms represent the most dangerous pro-inflammatory cytokines. Health conscious people should become familiar with these terms since these 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
 LTB (4) = Leukotriene B(4)

Inflammatory Cytokine Blood Reference Ranges

There are at least three different methods of testing blood levels of the pro-inflammatory cytokines. We have listed below, the standard reference ranges for each different type of test. To protect against diseases associated with chronic inflammation, people should be within or below these reference cytokine ranges.

Pro-Inflammatory Cytokine	Where You Want To Be		
	LabCorp	ISI	DPC
Tumor Necrosis Factor-alpha (TNF-a)	<8.1 pg/mL	10-50 pg/mL	0-8.1 pg/mL
Interleukin-6 (IL-6)	<12.0 pg/mL	2-29 ng/mL	0-9.7 pg/mL
Interleukin 1 beta (IL-1(b))	<15.0 pg/mL	0-150pg/mL	0-5 pg/mL
Leukotriene B(4) (LTB(4))	NA	300-750 pg/mL	NA

(Other blood testing lab methods may have different reference ranges)

The cost of these cytokine tests is outrageously expensive. Life Extension is in the process of negotiating an affordable Cytokine Profile blood test for Foundation members. You can find out about when these tests will be available by calling 1-800-208-3444. In the meantime, if you have health insurance, you may ask your doctor to prescribe and perform these tests and hope your medical insurance will pay for them.

Please note that an inexpensive C-reactive protein (high-sensitivity) blood test (CRP-hs) can help reveal if you suffer from 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 suffer from a disease associated with chronic inflammation) should consider using a supplement protocol and/or prescription drugs known to suppress elevated pro-inflammatory cytokines. Using the Cytokine Profile blood test can help monitor their progress.

A high-sensitivity C-reactive protein blood test can be ordered by calling 1-800-208-3444. The cost to Foundation members is \$43.00.

Supplements used by Life Extension members (such as DHA fish oil, nettle leaf extract, vitamin K and DHEA) have been shown to suppress the dangerous cytokines, TNF-a, IL-6, IL1(b), LTB(4). For those whose blood tests reveal persistently high inflammatory cytokine levels despite taking these supplements, we have identified a low cost prescription drug that may be of enormous benefit.

The generic name of this drug is pentoxifylline (PTX); the brand name is Trental®. It was first used in Europe in 1972 and long ago came off patent (meaning it is not cost-prohibitive). PTX is prescribed to improve the flow properties of blood by decreasing its viscosity. It works by improving red blood cell flexibility, decreasing platelet aggregation and reducing fibrinogen levels.[56-60] It has fallen out of favor because no drug company has the economic incentive to market it to physicians. PTX is primarily prescribed to patients with peripheral artery disease, though we believe it has potential efficacy in treating a wide range of diseases relating to chronic inflammation.

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Protecting Against Inflammatory-Related Disease

The New England Journal of Medicine published several studies in year 2000 [61] showing that the blood indicators of inflammation are strong predictive factors for determining who will suffer a heart attack. In the January 2001 issue of Life Extension magazine, we described these studies and told members how they could protect themselves against these inflammatory markers (such as C-reactive protein, homocysteine and fibrinogen).

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

Supplements used by most Life Extension members appear to suppress these dangerous inflammatory components of blood.

One of the inflammatory markers the New England Journal of Medicine identified is a protein called fibrinogen. High fibrinogen levels can induce a heart attack via several mechanisms, including increased platelet aggregation, hyper-coagulation and excessive blood thickening. The New England Journal of Medicine studies showed that those with high levels of fibrinogen were more than twice as likely to die of a heart attack.

Another inflammatory marker reported on was 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.

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 TNF- α or IL-6) that are promoting the inflammatory cascade.

In the first addendum that appears after this article, we discuss dietary modifications that can also help suppress pro-inflammatory factors in the body.

Numerous studies show that pentoxifylline (PTX) is a potent inhibitor of TNF- α , IL-1(b), IL-6 and other pro-inflammatory cytokines.[62-69] A similar number of studies show that DHA fish oil suppresses these same cytokines.[23-30, 31-32] In people suffering from a chronic disease involving elevated levels of the inflammatory cytokines, the daily administration of 400 mg to 800 mg of PTX and/or 1000 mg to 2000 mg of DHA fish oil could be of enormous benefit.

We have previously published information showing that cytokine-suppressing nutrients such as fish oil and nettle leaf prevent and treat a wide range of diseases. In the second addendum that appears at the end of this editorial, we review studies that substantiate the potential off-label benefits of PTX in protecting against inflammatory cytokine-induced diseases.

What You Should Do?

The number of inflammatory-related diseases that could be successfully treated with cytokine-lowering therapy is staggering. Pentoxifylline (PTX) is a cytokine-suppressing drug that has been overlooked by most of the medical establishment. Supplements such as fish oil, nettle leaf, DHEA and vitamin K

Diseases Related To Chronic Inflammation

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

Disease	Mechanism
Cancer	Chronic inflammation causes most cancers
Heart Attack	Chronic inflammation contributes to coronary atherosclerosis
Alzheimer's disease	Chronic inflammation destroys brain cells
Congestive Heart Failure	Chronic inflammation causes heart muscle wasting
Stroke	Chronic inflammation promotes thrombo-embolic events
Arthritis	Inflammatory cytokines destroy joint cartilage and synovial fluid
Aortic Valve Stenosis	Chronic inflammation damages heart valves
Kidney failure	Inflammatory cytokines restrict circulation and damage nephrons
Lupus	Inflammatory cytokines induce an autoimmune attack
	Inflammatory

possess mechanisms of suppressing inflammatory cytokines similar to PTX. There are no side-by-side comparisons that would enable us to categorically state whether PTX or natural agents (such as DHA fish oil) work better.

For those suffering from multiple degenerative diseases, we recommend the cytokine profile blood test. This can be done by your own doctor or you can inquire about it by calling 1-800-208-3334. If your cytokine test reveals excess levels of cytokines such as TNF- α and/or IL-1b, you may consider supplements such as DHA fish oil (1000-2000 mg/day). If you have been taking DHA fish oil, nettle leaf extract, vitamin K and DHEA, and blood tests show that you still have high levels of inflammatory cytokines, you should consider 400 mg to 800 mg a day of pentoxifylline (PTX) or Enbrel (if you can afford it).

We have previously published articles about the multiple degenerative diseases caused by chronic inflammation. The sheer volume of new confirmatory data mandates that those seeking to avoid age-related health catastrophes suppress their inflammatory cytokines.

I know most members reading this column will not have their blood tested and will instead, use some of the supplements that have been shown to suppress these dangerous cytokines. For most healthy people, this should work. If you suffer from a degenerative disease(s) associated with chronic inflammation, I urge you to take the Cytokine Profile or the C-reactive protein blood test we recommend. When you get your results, use the appropriate supplements and/or drugs to bring your inflammatory markers down to a safe range. This is a matter of life or death for many aging humans!

If you have questions about this pioneering new anti-aging protocol, call our advisors at 1-800-226-2370.

For longer life,



William Faloon

Caution: PTX should not be used in those with bleeding disorders such as those with recent cerebral or retinal hemorrhage (Physicians Desk Reference, 2001). Patients taking Coumadin should have more frequent monitoring (once a week) of prothrombin times.^{70, 71} Those suffering from other types of bleeding should receive frequent physician examinations. According to two studies, PTX should be avoided by Parkinson's patients.^[72, 73]

It is important to note that the body uses tumor necrosis factor-alpha (TNF-a) to acutely fight infections. If patients are showing any sign of infectious disease, drugs like 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- α inhibiting therapy (infliximab). Since PTX, fish oil and nettle directly suppress TNF- α , perhaps these agents should be temporarily discontinued during the time when one has an active infection.

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Asthma	cyokines close the airways
Psoriasis	Inflammatory cytokines induce dermatitis
Pancreatitis	Inflammatory cytokines induced pancreatic cell injury
Allergy	Inflammatory cytokines induce autoimmune reactions
Fibrosis	Inflammatory cytokines attack traumatized tissue
Surgical complications	Inflammatory cytokines prevent healing
Anemia	Inflammatory cytokines attack erythropoietin production
Fibromyalgia	Inflammatory cytokines are elevated in fibromyalgia patients

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Addendum One Diet and Inflammation

In addition to toxic cytokines, there are other inflammatory pathways that can be mediated via diet modification. A common problem involves over-production of pro-inflammatory hormone-like "messengers" (such as prostaglandin E2) and under-production 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.[1,2] Gamma linolenic acid (GLA) induces production of the anti-inflammatory prostaglandin E1.[3, 4] 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.

Since prostaglandin E2 is a culprit in inflammation, reducing foods that are high in omega-6 fatty acids and increasing 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)].[5] Another dietary factor that can lead to high levels of arachidonic acid is the over-consumption of high-glycemic index carbohydrates that causes excess production of insulin.[6]

Foods that may contribute to chronic inflammation are foods with a high glycemic index (things that you digest quickly) like fruit juices or rice cakes, food heavy in polyunsaturated fats or saturated fats, and foods high in arachidonic acid

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Addendum Two

Pentoxifylline Studies

Pentoxifylline (PTX) is a prescription drug approved by the FDA to treat peripheral vascular disease. The standard dose is 1200 mg a day to improve circulation. To suppress pro-inflammatory cytokines, a lower dose of 400 mg to 800 mg a day can be used. What follows is a brief description of studies showing benefits to PTX that extend beyond its FDA-approved use. Please note that it is illegal for the manufactures of PTX to distribute this off-label information to the public. Life Extension can provide this information because we do not sell PTX.

A controlled study on human diabetics with advanced renal failure showed that 400 mg a day of PTX reduced TNF- α levels by approximately 35%. In the pentoxiphylline 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- α have long been implicated in the development and progression of diabetic kidney failure.[1] Organ failure induced by TNF- α has been confirmed by other studies.[2]

Aging causes a progressive decline of blood delivery to the tissues. Those afflicted with diabetes suffer from accelerated circulatory deficit. In a study on diabetic rats, just two 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 saphenous sensory nerve. PTX restored the micro-vascular deficit by 50.4%. 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 afflictions.

In a study on human asthmatics, PTX was shown to be almost six times more effective in suppressing TNF- α than the popular anti-asthma drug theophylline. The doctors concluded that PTX may be an especially promising candidate as an asthma therapy.[3]

Lupus is an autoimmune disease and about 90% of its victims develop kidney problems. In a group of pediatric lupus patients, PTX helped to stop the deterioration of kidney function.¹⁹ The clinical manifestations of experimental systemic lupus erythematosus(SLE) correlate with an increased secretion of TNF- α and IL-1. In a mouse study, PTX significantly reduced the production of TNF- α and IL-1. The result was significantly lower anti-DNA antibodies (a blood marker of lupus activity) and substantial 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).[4]

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 7 anemic patients with advanced renal failure, PTX suppressed TNF- α and reversed the anemic state.[5]

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 tumor necrosis factor-alpha 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.[6]

Psoriasis is characterized by abnormal cell proliferation, inflammation and increased levels of inflammatory cytokines. In an experimental on nude mice, PTX was shown to reduce cell proliferation and thickening of skin. Improvement was seen in the classical signs of psoriasis.[7] A study on dogs showed that PTX was one of several drugs helpful in treating atopic dermatitis.[8] A mouse study showed PTX to be effective in treating contact- and irritant-induced dermatitis by suppressing excess production of TNF- α . [9]

Pentoxifylline Sources

You can obtain pentoxifylline from any pharmacy with a doctor's prescription. Here is the price for 100 tablets of the three available brands:

Trental 400 mg (name brand)	\$80.59
Pentoxil 400 mg (generic)	\$53.09
Pentoxifylline 400 mg (extended release generic)	\$53.09

Prices obtained from a Walgreen's pharmacy located in Ft. Lauderdale, Florida.

Since you will only take one to two tablets a day of pentoxifylline, this is a relatively inexpensive drug.

An increase in TNF-a has been implicated in leprosy skin reactions and PTX has been shown to work with other drugs in producing a quick response to this inflammatory cytokine-induced condition.[10,11]

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 inflammatory cytokines.[12] Other studies show that PTX helps to prevent the fibrosis.[13]

Inflammation plays a pivotal role in the pathogenesis of organ injury after cardiopulmonary bypass. Elderly patients appear to be especially prone to develop 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.[7] The doctors 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 micro-circulation 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.[9] 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 may 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.⁹ We believe that the real value to PTX may be its long-term use after surgery to protect against the chronic inflammatory syndrome that so many of the elderly are vulnerable to. The maintenance dose of PTX needed may be as low as 400 mg a day. Please note that high-dose fish oil and other nutrients have shown similar benefits to PTX.

Caution: PTX should not be used in those with bleeding disorders such as those with recent cerebral or retinal hemorrhage. Patients taking Coumadin should have more frequent monitored of pro-thrombin time. Those suffering from other types of bleeding should receive frequent physician examinations. Furthermore, we would consider evaluating the individual patient's coagulation status to see what effect PTX has on the template bleeding time. This is an inexpensive test that relates the biological effect of PTX (or other agents like aspirin, non-steroidal anti-inflammatory agents) on the function of platelets. All of these agents affect platelet aggregation and this effect can be manifested in a prolonged template bleeding time. According to two studies, PTX should be avoided by Parkinson's patients. It is important to note that the body does use tumor necrosis factor-alpha (TNF- α) to acutely fight infections. If patients are showing any sign of infectious disease, drugs like Enbrel (that inhibit the effects of TNF- α) are temporarily discontinued. A new FDA advisory states that patients should be tested and treated for inactive, or latent, tuberculosis prior to therapy with another TNF- α inhibiting therapy (infliximab). Since PTX, fish oil and nettle directly suppress TNF- α , perhaps these agents should be temporarily discontinued during the time when one has an active infection.

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