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## REPORT

### Predict Your Risk of Future Disease

The verdict is in. It is C-reactive protein, and not cholesterol that puts people at their greatest risk for developing heart disease, stroke and other age-related ailments.

C-reactive protein is an inflammatory marker produced in response to acute injury, infection or other inflammatory stimuli. Chronically elevated levels of C-reactive protein can reveal a state of systemic inflammation that causes or contributes to many different kinds of lethal diseases.

The most immediate danger of chronic inflammation is that it induces plaques along arterial walls to become more vulnerable to rupture.<sup>1</sup> When an atherosclerotic plaque ruptures, it releases chunks of tissue that may then become lodged in the arteries that feed the heart muscle, or in the vessels that oxygenate brain cells. The end result is a heart attack or stroke as blood vessels become choked from lack of oxygen.

A C-reactive protein blood test can serve to reveal the existence of vascular disorders in their earliest stages, so that appropriate anti-inflammatory therapies can be administered to lower C-reactive protein expression.

The following new studies provide examples of the different disorders associated with elevated C-reactive protein:

1. C-reactive protein is elevated in those who suffer from Alzheimer's disease, and high levels have also been correlated with loss of cognitive ability in seemingly healthy people. One study published in the January 2003 issue of the *Journal of Neuroimmunology* found that in a healthy population from the Netherlands, C-reactive protein levels at the study's outset were predictive of poorer scores on a test of learning and recall during the six years of the study's follow-up.<sup>2</sup>
2. Elevated inflammatory markers are characteristic of type II diabetes. Dr. Paul Ridker, who has conducted many of the studies that support C-reactive protein's relationship to chronic age-related disease, indicates that the extent of the inflammatory process known to exist in diabetics can be measured with the C-reactive protein test.<sup>3</sup>
3. Some evidence indicates that C-reactive protein elevation could be linked with depression in aging people, which may at least partially explain why chronic depression increases heart disease risk in this population. In the December 2002 issue of the *American Journal of Cardiology*, researchers at Washington University in St. Louis, Missouri reveal that depressed subjects exhibited significantly higher levels of C-reactive protein and other markers of inflammation than did subjects who were not depressed. The depressed patients were also more likely to be obese-not surprising, in light of the fact that obesity causes elevations in C-reactive protein as well.<sup>4</sup>
4. Smoking, high blood pressure and the use of synthetic female hormones (in the form of oral contraceptives or hormone replacement therapy)-all of which increase the risk of adverse cardiovascular events-also have been found to cause elevations in C-reactive protein levels.



Consensus is building that C-reactive protein measurements are superior to any type of blood test when it comes to predicting the risk of heart disease or stroke. It follows that C-reactive protein measurement should be added to the usual blood tests administered to assess such risks.

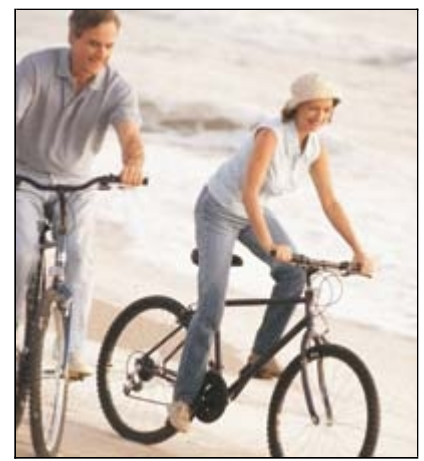
The reason most people consider blood testing is to ascertain their cardiovascular risk factors. It has become evident that prediction of heart disease risk goes far beyond cholesterol counts and blood pressure measurements.

Most physicians still do not routinely test for C-reactive protein, despite the fact that it is inexpensive and highly accurate. Instead, they continue to base evaluations of cardiac risk on traditional measurements of LDL/HDL cholesterol and triglycerides. While there is a place for these measurements in the overall scheme of laboratory testing for cardiac disease prevention, they should by no means stand alone. (Tests to evaluate homocysteine and fibrinogen are also important for those who wish to gain an accurate picture of what's going on inside their arteries.)

Neglecting to test levels of this inflammatory marker once a year could rob you of the chance to take early, aggressive steps to reverse the cardiac disease processes.

What causes elevated C-reactive protein

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*<sup>5</sup>, 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. 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 (endothelial dysfunction) to the inner lining of the arterial wall 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."

These findings indicate that hypertensives should have their blood tested for TNF-a to assess how much inner wall (endothelial) arterial damage is occurring. If the level of TNF-a is 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 (JAMA)*<sup>6</sup>, a group from the famous Women's Health Study were evaluated to ascertain what risk factors could predict future development of type II diabetes. 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 that, "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

It is well established that 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*<sup>7</sup>, a sample of 1,293 healthy elderly people were followed for a period of 4.6 years. Higher IL-6 levels were associated with a two-fold 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*<sup>8</sup> and showed that these frail seniors with elevated blood inflammatory markers also tend 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.

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# REPORT

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### Interpreting results obtained from The Inflammatory Cytokine Test Panel

There are many chronic disease states that can now be managed by the proper utilization of the Inflammatory Cytokine Test 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.

For example, 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 ask your doctor to prescribe a bisphosphonate drug (such as Zometa® that protects against bone destruction) that releases excess IL-6 from 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 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.

### Low-cost cytokine testing

Few physicians have recognized the critical importance of suppressing pro-inflammatory cytokines in the treatment of degenerative disease. As a result, there has been little demand for cytokine tests and commercial blood laboratories have been charging exorbitant prices for the four most important inflammatory cytokine tests.

The good news is that Life Extension Buyers Club has been able to establish a relationship with the largest blood-testing laboratory in the United States to offer an inflammatory cytokine profile at an affordable price.

The standard commercial price for the four most dangerous inflammatory cytokines is around \$645.00. The Life Extension Buyers Club has negotiated a retail price for the complete inflammatory cytokine panel of only \$435.00. The cost of individual cytokine tests to Life Extension members is then discounted as follows:

### Identifying the underlying cause of elevated C-reactive protein

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.

In order to enable members to identify the specific cytokine that may be causing a chronic inflammatory condition, a new blood test panel is available that detects abnormally high levels of the most dangerous pro-inflammatory cytokines. Here is the new Inflammatory Cytokine Test Panel showing optimal anti-inflammatory ranges:

Pro-inflammatory Cytokine	Anti-Inflammatory Range
Tumor necrosis factor alpha (TNF-a)	No more than 25 pg/mL
Interleukin-1 beta (IL-1b)	No more than 150 pg/mL
Interleukin-6 (IL-6)	No more than 29 pg/mL
Interleukin-8 (IL-8)	No more than 80 pg/mL

Tumor Necrosis Factor alpha (TNF-a)	\$99.00
Interleukin-6 (IL-6)	\$99.00
Interleukin 1(b) (IL1(b))	\$99.00

If all four of these tests are ordered at once, the member's price is reduced to \$295.00.

Life Extension has medical doctors available by phone to assist members in understanding what the results of inflammatory cytokine tests indicate. There is no additional charge for this consultation service.

To order a high sensitivity C-reactive protein blood test, the Inflammatory Cytokine Blood Panel, or any other blood tests by mail order, call 1-800-208-3444. Until June 1, 2003, the price of a high-sensitivity C-reactive protein test is only \$42.00.

Why annual blood tests are crucial to protecting one's health

### How to lower 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 medication. 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. Some doctors recommend that men's C-reactive protein levels be kept under 0.55 mg/L of blood. (Make sure to always ask for the high-sensitivity C-reactive protein blood test).

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- $\alpha$  levels are elevated, and natural approaches fail to lower it, the prescription drug Enbrel should be considered.

Health conscious people often fail to appreciate the critical importance of regular blood screening as part of their overall disease prevention program. The most comprehensive blood test is called the CBC/Chemistry Profile. This low-cost profile measures over 40 different blood parameters that can have a dramatic impact on one's state of health.

One of the many serious disorders that can be detected by the CBC/Chemistry Profile is calcium overload. This condition is caused when too much calcium is removed from the bone and deposited into the vascular system. Unless discovered by a blood test, people often don't find out about calcium imbalance until after they suffer a crippling bone fracture, a painful kidney stone (renal calculi) or heart valve failure (due to excess valvular calcification). These diseases often manifest years after the calcium imbalance first begins; yet, a low-cost CBC/Chemistry Profile can detect this problem early and enable the person to take relatively simple nutritional steps to correct the calcium imbalance before it causes a disease state.

Another disorder people encounter as they grow older is elevated serum glucose that can contribute to the development of arterial and neurological disease and accelerate aging through a process known as glycation. If high glucose is discovered, there are lifestyle changes, drug and nutrient therapies available to bring these levels into normal ranges.

Excess amounts of serum iron will generate massive free radicals throughout the body that significantly increase the risk of cancer, atherosclerosis and probably neurological disorders such as Alzheimer's and Parkinson's disease. If a blood test shows iron levels are too high, there are many ways to bring it down. It seems illogical to wait for an iron overload-induced disease to manifest just because you did not want to "bother" getting an annual CBC/Chemistry Profile.

The CBC/Chemistry Profile includes measurements of total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides. If you are taking a statin drug or a cholesterol-lowering supplement like policosanol, it is imperative that you ascertain if the proper dose is being taken.

Some people taking cholesterol-blocking agents actually reduce their cholesterol to dangerously low levels (below 150 mg/dL). The findings from a CBC/Chemistry can provide a basis for the dose of a cholesterol-blocking agent to be increased or decreased in order to achieve optimal benefits. Anyone taking a cholesterol-blocking agent should check his or her blood levels at least once a year, not only to maintain optimal cholesterol levels, but to also guard against liver toxicity.

If triglyceride levels are above 100 mg/dL, high-dose fish oil supplements can normally reduce levels of this artery-clogging lipid.

Protecting against drug-induced toxicities

The average person over age 60 takes several prescription drugs every day to treat or



prevent chronic medical conditions. Toxic side effects from medication result in the death of 125,000 to 189,000 Americans each year. According to the American Medical Association, adverse reactions to prescription drugs are a leading cause of death in the United States. The American Medical Association emphasizes that these deaths are occurring even though doctors, who are supposed to monitor patients to prevent these drug-induced deaths, are prescribing the drugs.

The fact is, HMOs are seeking to save money in the short-term and are often not recommending CBC/Chemistry Profiles that would help detect drug-induced liver and kidney impairment in time to prevent disability and death. If you are taking certain prescription medications, regular blood testing is mandatory according to the FDA, yet doctors routinely fail to prescribe the recommended blood tests and their patients pay the "ultimate" price.

It's not just prescription drugs that can cause irreversible liver or kidney damage. There are many factors (alcohol, over-the-counter drugs, excess niacin, hepatitis C) that can make a person susceptible to liver or kidney damage. For most people, these conditions smolder for years until a life-threatening medical crisis occurs. Due to a phenomenon known as "individual variability," some people are especially vulnerable to liver and kidney damage. In these cases a CBC/Chemistry Profile can detect an underlying problem in time to take corrective actions.

### Maintaining a youthful hormone balance

Aging causes significant alterations in hormone balance.

In aging men, beneficial hormones such as testosterone, DHEA and growth hormone decline, while less desirable hormones such as estrogen and insulin often increase. The effects of these hormone imbalances can manifest as clinical depression, increased abdominal obesity, diminished mental and physical energy levels and loss of libido.

Aging females often suffer a progesterone and DHEA deficit, while levels of estrogen and testosterone can become too high or low. The clinical effects of these hormone imbalances in females often manifest as the symptoms associated with menopause, depression, loss of bone mass and loss of libido. In both men and women, the failure to correct hormone imbalance can directly contribute to cardiovascular disease, certain forms of cancer, type II diabetes, osteoporosis and neuronal degeneration.

Fortunately, once hormone status is ascertained, through blood testing, definitive corrective action can be taken to safely restore hormone balance to a youthful range.

### The rationale for blood testing

Annual blood testing is a cornerstone of any scientific program designed to extend the healthy human life span. Conventional doctors often refuse, or don't know how to order the type of blood tests that can reveal correctable underlying risk factors for developing degenerative disease.

The Life Extension Foundation initiated a program in 1996 to enable its members to request any blood test and to receive the actual results of these tests. This service has enabled members to detect abnormalities that can be brought to the attention of their physician, or corrected by lifestyle changes. Life Extension members save more than 50% compared to the prices charged by commercial blood testing laboratories, and avoid having to pay for a doctor's visit just to order the tests.

People too often fall victim to a disease that could have been prevented if their blood was tested every year. When a blood test reveals an abnormality, corrective actions can often be taken to prevent a serious disease from developing. Refer to the next page for information about mail order blood testing, including the recommended Male and Female Panels.

For further information and scientific references about using blood tests to protect against aging-related disease, refer to the following protocols in the Life Extension Foundation's Disease Prevention and Treatment reference book, or web site at [www.lef.org](http://www.lef.org):

- Male Hormone Modulation Protocol
- Female Hormone Modulation Protocol

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- Atherosclerosis Protocol
- Homocysteine Protocol
- Fibrinogen Protocol
- Depression Protocol
- DHEA Protocol
- DHEA Replacement Therapy Protocol
- Cardiovascular Protocol
- Inflammation (chronic) Protocol

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