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## AS WE SEE IT

### Startling New Findings About Homocysteine

Several years ago, we made an alarming discovery! People who had previously been in safe ranges were calling us to report that their new blood tests revealed markedly higher homocysteine levels.

We expected to see some elevation, as homocysteine levels are known to rise during normal aging. What startled us was the magnitude of increase that occurred in as little as one year. In some cases, this sharp rise in homocysteine was accompanied by the onset of a degenerative disorder (angina, stroke, renal impairment, aortic stenosis, memory loss, depression, etc.).

In response to our findings, we alerted members about the importance of testing their blood annually to guard against unexpected surges in cardiovascular risk factors such as homocysteine, C-reactive protein, and low-density lipoprotein (LDL).



William Faloon



Newly published studies are confirming the observations we first made in the late 1990s. In the latest study, a startling 100% of French elderly hospitalized patients showed higher than desired homocysteine levels, with 45% suffering from severe hyperhomocysteinemia (blood homocysteine greater than 18 mmol/L).<sup>1</sup>

Some physicians still define excess homocysteine as blood levels greater than 15-18 mmol/L. Published studies, on the other hand, indicate that keeping homocysteine below 7-8 mmol/L is ideal for reducing the risk of lethal diseases.<sup>2</sup>

In a three-year study of 600 Italian elderly hospitalized patients, the mean fasting homocysteine level was a frighteningly high 16.8 mmol/L. Patients with hyperhomocysteinemia in this study showed a greater prevalence of serious disease states, such as vascular and cognitive disorders.<sup>3</sup>

In a German paper titled Hyperhomo-cysteinemia In Advanced Age, the following conclusions were made as it relates to homocysteine and age-related disease:<sup>4</sup>

- Hyperhomocysteinemia often occurs with advanced age
- Impairment of physical condition or social situation seems to increase the risk of hyperhomocysteinemia
- Administration of vitamins B6 and B12, and folate, causes a significant decrease of elevated serum homocysteine concentrations in older persons
- Homocysteine-lowering treatment should improve the prevention of chronic diseases.

### The Homocysteine “Hypothesis” of Degenerative Disease

Life Extension members were warned about the dangers of high homocysteine way back in 1981 and were advised to take folic acid, along with vitamins B12 and B6, to reduce it.

Throughout the 1980s, many doctors debunked the “hypothesis” that homocysteine was a risk factor for heart attack.<sup>5-7</sup> Beginning in the mid-1990s, however, the findings from large human trials concluded that high homocysteine levels were associated with a significantly greater risk of heart attack and stroke.

### No Safe Range

The clear message from scientific findings is that there is no safe “normal range” for homocysteine. While commercial laboratories state that normal homocysteine can range from 5 to 15 micromoles per liter (mmol/L) of blood, epidemiological data reveal that homocysteine levels



More recent studies not only confirm the cardiovascular dangers of homocysteine, but also its toxic effect on the brain. It turns out that high blood levels of homocysteine increase the incidence of depression, memory impairment, and even Alzheimer's disease.

The latest findings reveal that elderly people with common degenerative diseases frequently present with very high levels of homocysteine.

The medical establishment woke up to the dangers of homocysteine when The New England Journal of Medicine and The Journal of the American Medical Association (JAMA) published articles suggesting that vitamin supplements be used to lower homocysteine levels.<sup>8-9</sup>

The evidence that homocysteine increased heart attack risk was substantial in 1981. It is regrettable that 22 years later, most doctors still do not recognize homocysteine as a toxic amino acid that should be reduced in the bloodstreams of all their aging patients.

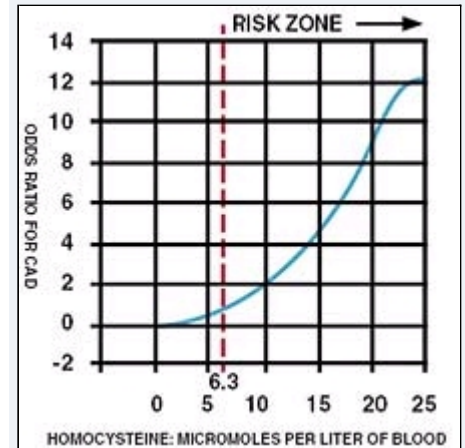
### What Doctors Are Overlooking

Optimal blood homocysteine levels are under 7 mmol per liter of blood, yet newly published research findings confirm that as humans grow older, homocysteine levels increase substantially. High homocysteine has been linked to many common age-related diseases including vascular occlusion, kidney failure, and dementia. A consistent finding in these studies is that hyperhomocysteinemia is associated with poor nutritional status.

Some doctors now recognize the lethal role that homocysteine plays in the development and progression of common degenerative diseases. These doctors, however, seldom treat their patients in a scientific manner. For instance, patients with high homocysteine levels are sometimes told to take a folic acid supplement or moderate doses of vitamin B12, vitamin B6, and folic acid. Homocysteine blood levels are rarely checked again. These vitamin-prescribing doctors assume that homocysteine will be adequately lowered as long as the patient takes the recommended dose of vitamins, which is often the same dose recommended for all their patients.

above 6.3 cause a steep progressive risk of heart attack (see the American Heart Association's journal Circulation).<sup>2</sup> One study found that each 3-mmol/L increase in homocysteine caused a 35% increase in heart attack risk.<sup>10</sup>

One reason Life Extension recommends homocysteine levels be kept below 7-8 mmol/L is that this is about the best an aging person can realistically accomplish, even when taking high doses of vitamin B6, TMG, and other homocysteine-lowering nutrients.



The chart above illustrates the results of the American Heart Association study: incremental increases in homocysteine levels correlate with increased risk for coronary artery disease. Levels of risk: 15.0=high risk; 9.0=moderate risk; 7.0=low risk.

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Original research conducted by Life Extension years ago, however, showed that there is a huge individual variability in the amount of B vitamins needed to keep homocysteine in optimal (safe) ranges. Life Extension found that a substantial percentage of members who were taking the recommended potencies of B vitamins were not achieving adequate homocysteine control. In these members with elevated homocysteine, higher doses of vitamin B6 and/or TMG (trimethylglycine) were needed to bring homocysteine down to the safe range.

Doctors who fail to check their patients' blood for homocysteine regularly and adjust the B vitamin dose accordingly are not going to reduce homocysteine to safe ranges in most of their patients. It is usually up to the patients themselves to take the initiative to inform their doctors that they intend to maintain their blood homocysteine levels below 7-8 mmol/L of blood.

### What Causes Homocysteine Overload

Some people have high blood homocysteine early in life, while others don't manifest dangerous levels until they grow older. According to every scientific study we could find, most aging people accumulate too much homocysteine in their blood. One reason for this is that the methylation detoxification system that normally disposes of homocysteine becomes defective with aging. Healthy methylation reactions convert homocysteine back into its amino acid precursor, methionine. Supplements that facilitate healthy methylation reactions in the body include folic acid, vitamin B12, and TMG.

#### Homocysteine Overload Increases Heart Attack Risk by 300%

Data from a study of healthy U.S. physicians with no prior history of heart disease show that highly elevated homocysteine levels were associated with a more than three-fold increase in the risk of heart attack over a five-year period.

This finding was published as part of the Physicians' Health Study that included 14,916 male physicians.<sup>11</sup> The Framingham Heart Study (and other studies) has confirmed that elevated homocysteine is an independent risk factor for heart disease.



Another way the body rids itself of excess homocysteine is through the trans-sulfuration pathway, which is dependent on vitamin B6. As long as adequate levels of vitamin B6 are present, homocysteine is converted into beneficial cysteine in the body via this trans-sulfuration pathway.

Those with moderate homocysteine elevation may respond to the daily intake of 800 mcg of folic acid, 600 mcg of vitamin B12, 100 mg of vitamin B6, and 500 mg of TMG. Life Extension has found that aging members sometimes require vitamin B6 in doses ranging from 250 to 1000 mg a day\* and/or 1500 to 3000 mg of TMG a day to reduce homocysteine to a safe range (below 7-8 mmol/L of blood). Reducing consumption of foods that contain lots of methionine (such as red meat and chicken) can lower homocysteine.

Scientific studies point to aging, vitamin deficiency, and chronic disease states (such as kidney failure) as common causes of hyperhomocysteinemia.

### Scientific Publications Recognize Homocysteine

When looking back at the scientific literature, we could find only 37 published papers about homocysteine and degenerative disease risk in the 1980s.<sup>12</sup> Many of these papers stated that homocysteine was not a heart attack risk factor.

In the 1990s, however, the number of published studies swelled to 648, and most of them pointed to homocysteine as a culprit in the development of coronary artery disease and coronary thrombosis (heart attack).<sup>13</sup>

The last several years have seen an exponential increase in the number of scientific studies about homocysteine. From 2000 to the present, an astounding 553 papers were published about the significant role of homocysteine in the development of multiple age-related diseases.<sup>14</sup> In fact, more studies have been published about homocysteine so far in 2003 than in the entire decade of the 1980s.

An example of the kind of recently published research can be found in the August 22, 2003 issue of the journal *Circulation Research*. This study revealed how relatively low levels of homocysteine (10 mmol/L) can inflict massive damage to the arterial wall via several destructive molecular mechanisms.<sup>15</sup>

## Folic Acid Is Not the Solution

Supplementation with folic acid reduces homocysteine levels in the blood. Folic acid works by facilitating youthful methylation patterns that enable homocysteine to be transformed (remethylated) into the amino acid methionine. Healthy methylation also requires vitamin B12. Many doctors prescribe only folic acid and neglect to provide their patients with adequate vitamin B12. Without vitamin B12, the remethylation process is severely impaired.

Life Extension discovered many years ago that high doses of folic acid by themselves do not sufficiently lower homocysteine levels. In one case, a member taking 20,000 mcg a day of folic acid saw his homocysteine level remain persistently high.

A new study on kidney failure patients reveals just how critical vitamin B12 is in protecting against homocysteine overload. People suffering from end-stage kidney disease often manifest very high levels of homocysteine. In this study, doctors gave one group of patients oral supplements that contained 5000-6000 mcg of folic acid, 6-10 mcg of vitamin B12, and 5-10 mg of vitamin B6. The other group received a (1-mg) B-12 injection weekly in addition to the daily oral supplements.<sup>16</sup>

In the group receiving the weekly B-12 shot, homocysteine levels decreased by 32%, while the group receiving the oral folic acid, B12, and B6 did not show a change over the 8-16 week study period. What was so impressive about this study is that the subjects initially had normal blood levels of folic acid and vitamin B12. In response to the vitamin B12 injections, serum B12 levels increased more than 60-fold from 625 to 40,400 pmol/L, which resulted in a reduction of homocysteine by an average of 32%. This study showed a direct linear correlation between increased blood levels of vitamin B12 and decreased levels of homocysteine.

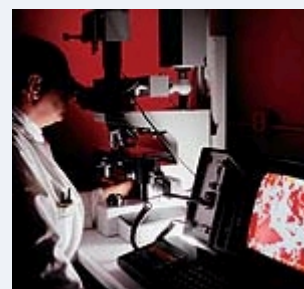
One flaw in this study was that the oral dose of vitamin B12 (6-10 mcg) in the control group was very low. Most Life Extension members obtain over 600 micrograms a day of B12. The oral dose of vitamin B6 (5-10 mg/day) used in this study was also below the higher amounts (100 mg and above) taken by most Life Extension members. It is possible that if higher oral doses of vitamins B12 and B6 had been used in this study that compared B12 injections to folic acid-B12-B6 supplements, a reduction in homocysteine may have occurred.

The value of higher oral doses of vitamins B12 and B6 was shown in another published study<sup>17</sup> on end-stage kidney disease patients. Those receiving 100 mg of vitamin B6, 1000 mcg of vitamin B12, and 16,000 mcg of folic acid showed a 30% reduction in homocysteine levels—comparable to the 32% reduction seen in patients receiving weekly B12 shots.

While most people can adequately lower homocysteine levels by increasing their oral intake of TMG and vitamins B12 and B6, elderly people sometimes suffer absorption difficulties and need weekly B12 shots that require a doctor's prescription. For those whose homocysteine levels remain above 7-8 mmol/L despite taking the recommended oral doses of folic acid, TMG, and vitamins B12 and B6, a weekly 1-mg vitamin B12 shot is strongly recommended.

## A Sad Case History

A 48-year-old business associate of Life Extension recently stopped by to see one of our doctors. He was concerned because his recent blood test showed a homocysteine reading of 21.2. The doctor warned him about the heart attack risk he faced and advised him to initiate an aggressive homocysteine-lowering program immediately. This busy executive promised he would do so soon but said he had to run out to make an appointment. Three weeks later, while working out in a gym, this man suffered a massive heart attack and died. His untimely death in August 2003 came as a shock to many who had known him for the past 15 years.



We know that homocysteine not only causes chronic damage to the arterial wall, but also increases the risk of an acute arterial blood clot forming. It is possible that had this 48-year-old man's homocysteine level been brought under control, he might not have suffered this fatal heart attack.

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Life Extension has consistently found that taking very large doses of folic acid does not lower homocysteine much more than moderate folic acid intakes. When members present with stubbornly high homocysteine levels, we have seen significant reductions when the dose of vitamin B6 and/or TMG is increased, but not when folic acid intake is increased. If homocysteine levels remain high despite higher intakes of TMG and B6, there is now the option of taking a weekly 1-mg vitamin B12 shot or trying very high sublingual doses of vitamin B12.

#### AMA Takes One Step Backward

Since 1990, the Journal of the American Medical Association (JAMA) has published dozens of articles documenting the cardiovascular dangers of homocysteine, C-reactive protein, and fibrinogen.

Three new articles published in JAMA advise doctors to take the easy way out in helping patients to reduce heart attack risk. The consensus of these articles is that while homocysteine and other cardiovascular blood markers contribute to heart attacks, physicians should concentrate prevention efforts on controlling the following four areas:

**Cigarette Smoking**  
**High Cholesterol**  
**Hypertension**  
**Diabetes**

JAMA suggests that doctors go back to knowledge that is 30 years old in an effort to better reduce heart attack risk today.

Of course people shouldn't smoke. One reason is that cigarette smoking boosts homocysteine levels in the blood. The trouble is that doctors have only minimal control over their patients' smoking habits.



Hypertension can be better controlled if physicians made a greater effort. The August 2003 Life Extension magazine describes what doctors are not doing to optimally control blood pressure. Controlling hypertension better, however, does not mean that the proven dangers of homocysteine should be ignored.

Diabetes is an absolute cardiac risk factor, but conventional medicine focuses too much on treating hyperglycemia (high blood glucose) and not enough on suppressing excess insulin levels. Type II diabetics suffer from hyperinsulinemia (excess blood insulin) years before hyperglycemia manifests. During this period when the pancreas is secreting too much insulin, severe damage is being inflicted on the arterial wall, the eyes, kidneys, nerves, etc. (Refer to the Diabetes protocol in the 2003 edition of *Disease Prevention and Treatment* for complete information about lowering excess serum insulin.) Preventing diabetic vascular complications should include—not exclude—aggressive steps to lower homocysteine.

High cholesterol is only one of many heart attack risk factors that can be identified in the blood. Published studies indicate that other blood markers (such as C-reactive protein and homocysteine) may be more dangerous than high cholesterol.

The American Medical Association has proclaimed that doctors should focus on only four areas of heart attack prevention. This edict is a loud and clear signal that people who are truly concerned about their risk of heart attack should take matters into their own hands and follow a program that keeps ALL the known cardiac risk factors—including homocysteine—in safe ranges.

#### Why Homocysteine Blood Testing Is So Crucial

It has become clear that homocysteine levels increase with age and with the onset of degenerative disease. A spike in homocysteine not only accelerates damage to the arterial wall and neurons, but also increases the risk of sudden death heart attack or stroke.

As humans age, they sometimes need to increase their intake of homocysteine-lowering nutrients because their natural detoxification systems are no longer adequate.

It is not possible to “guess” what one's homocysteine levels may be. The only way to maintain safe ranges of homocysteine is to have your blood tested, follow the appropriate homocysteine-lowering program, and then retest your blood 30-90 days later to make sure you have reduced homocysteine to a safe range (below 7-8 mmol/L). Any other approach is the equivalent of throwing

darts with your eyes blindfolded.

### **Medicare Will Not Pay for Homocysteine Blood Testing**

Based on the fact that those with lower homocysteine have a reduced risk of disease, you would think that Medicare would mandate annual homocysteine blood testing in order to lower its outlays for expensive procedures such as coronary bypass surgery and nursing home care.

Instead, Medicare classifies homocysteine as a “non-covered” test. We were told that Medicare always refuses to pay for the test because it considers the test “not medically reasonable and necessary.”

The homocysteine blood test is FDA approved and the scientific literature conclusively links elevated homocysteine to increased risk of disease in the elderly. Yet Medicare denies payment for it. We believe that these kinds of illogical rules will accelerate Medicare’s collapse into insolvency in the not-too-distant future.

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#### Dramatic Reduction in Blood Testing Prices

The high cost of laboratory testing has kept some people from undergoing comprehensive annual blood tests that could save their lives. The good news is that prices on almost all blood tests for Life Extension members have come down sharply beginning October 1, 2003.

The retail price of a homocysteine blood test at a commercial laboratory is over \$180. Life Extension members used to pay \$85 for it. Under the new lower pricing structure, members of The Life Extension Foundation can obtain a homocysteine blood test for only \$64.

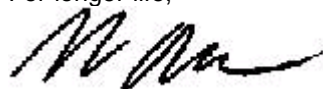
We are pleased to announce these price reductions because we know that blood tests provide a solid scientific basis for keeping Foundation members alive longer. I cannot tell you how many early-stage prostate cancers have been diagnosed because of the convenient mail-order blood-testing service we offer.

I urge all Foundation members to have their blood tested at least once a year. If homocysteine levels are elevated, aggressive actions should be undertaken to lower it. After higher amounts of nutrients such as TMG and vitamin B6 have been taken for 30-90 days, another homocysteine blood test should be done to make sure levels are below 7-8 (mmol/L).

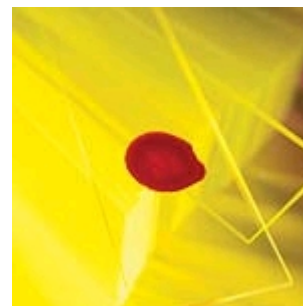
While people often fear cancer more than cardiovascular disease, the irrefutable fact is that heart attack and stroke kill far more Americans than cancer and most other diseases combined. Overwhelming evidence suggests that keeping blood markers such as homocysteine in safe ranges can dramatically reduce the risk of vascular disease.

I personally have been a beneficiary of having my blood tested and always recommend it on my media appearances. View information on the most important annual blood test for men and women to consider.

For longer life,



William Faloon.



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