Homocysteine Reduction
How Much Is Safe?

Since its discovery in 1932, homocysteine's journey into mainstream medicine has been rocky. For the first 36 years after its discovery, little was understood about it. Then in 1968 a Harvard researcher named Dr. Kilmer McCully noticed that children with genetically elevated homocysteine levels experienced heart disease similar to the heart disease found in middle-aged patients. He proposed that homocysteine might be an independent risk factor for heart disease. Like many medical pioneers, McCully's proposal concerning homocysteine was met with scorn.

McCully's homocysteine theory has since been proven beyond a doubt: people with elevated homocysteine levels are more likely to have strokes, Alzheimer's disease and dementia, kidney disease, diseases of the eye, erectile dysfunction, and, especially, heart disease (De Bree A et al 2002).

Conventional medicine, however, has still been slow to react to this news. Even today, the message on homocysteine from major mainstream medical groups is murky. Not so for the Life Extension Foundation, which has been alert to the dangers of elevated homocysteine levels since 1981. In that year, the Foundation published an article suggesting that people take aggressive action to lower their homocysteine levels (Life Extension Foundation 1981). It took conventional medicine another 15 years to catch up, when studies first appeared in major medical journals advocating the use of supplements, especially the B vitamins, to lower homocysteine levels.

Scientists have worked hard to understand why our homocysteine level increases throughout life, and how that impacts our health. Homocysteine level is affected by a number of influences, including lifestyle, dietary choices, and genetics. As we age, our ability to absorb nutrients decreases. As a result, less of the important B vitamins are available to help metabolize homocysteine. Homocysteine level is also increased by certain pharmaceuticals, an aging metabolism, smoking, drinking too much alcohol or coffee, lack of exercise, obesity, and stress.

There are various interpretations of how much homocysteine is dangerous. The Life Extension Foundation prefers an aggressive stance: based on numerous published studies, we advocate relatively low homocysteine levels to help lower risk of disease. By ages 40 to 42, mean homocysteine levels are about 11 micromoles per liter (µmol/L) in men and 9 µmol/L in women. Even homocysteine levels this low has been associated with disease. The Life Extension Foundation recommends homocysteine level between 7 µmol/L and 8 µmol/L.

For the vast majority of people, a high homocysteine level is related to the gradual breakdown of the body's ability to metabolize homocysteine. However, some people have a high homocysteine level because of a rare genetic defect. This condition, called homocystinuria, is associated with developmental delays, osteoporosis, diseases of the eye, stroke, and severe heart disease that can occur at a young age

Now that you know some of the conditions associated with high homocysteine levels, we will discuss in detail its effects and how to lower this disease marker.

What You Have Learned So Far

- An elevated homocysteine level is linked to heart attack and atherosclerosis.
- Other diseases and conditions—including vascular disease, diseases of the eye, stroke, Alzheimer's disease and dementia, erectile dysfunction, and poor outcome in pregnancy—have also been associated with having elevated homocysteine.
- Homocysteine level rises as we age, along with the incidence of diseases associated with this elevation.
- The Life Extension Foundation prefers an aggressive stance on homocysteine, striving for a level between 7 µmol/L and 8 µmol/L.

HOMOCYSTEINE AND HEART DISEASE: A CLEAR CONNECTION

The evidence is clear that having an elevated homocysteine level is an independent risk factor for heart disease. One large study conducted among physicians who had no history of heart disease showed that having a highly elevated homocysteine level was associated with a more than 3-fold increase in the risk of heart attack over a 5-year period (Stampfer MJ et al 1992).

Homocysteine has a number of direct effects on the arteries that help explain its association with heart disease. It causes thickening of the intima, or inner wall of the arteries. And it encourages blood platelets to accumulate, which may lead to the formation of blood clots (Harker LA et al 1976). In animal studies, homocysteine has been shown to affect the production of nitric oxide, a substance that causes arteries to relax and blood flow to increase (Stuhlinger MC et al 2001).

Having an elevated homocysteine level has been associated with:

- First and second heart attacks (Al-Obaidi MK et al 2000; Matetzky S et al 2003)
- Coronary artery disease (Nygard O et al 1997)
- Total cardiovascular mortality (Anderson JL et al 2000)
- Adverse outcomes after coronary balloon angioplasty (Schnyder G et al 2002)
- Heart failure (Vasan RS et al 2003)

In 1999, the American Heart Association recognized the role of homocysteine in atherosclerosis when it issued an advisory statement emphasizing the importance of reducing homocysteine blood levels and of screening people who are at high risk (Malinow MR et al 1999). The New England Journal of Medicine (Oakley GP 1998) and the Journal of the American Medical Association (Tucker KL et al 1996) suggested that vitamin supplements could be used to lower homocysteine levels.

TESTING HOMOCYSTEINE LEVELS

Homocysteine levels are measured directly in the blood. An acceptable level of homocysteine depends partly on your age and gender. It is clear, however, that our homocysteine level rises as we age and that (above a certain level) homocysteine is dangerous. Conventional medicine classifies homocysteine levels as follows:

- Normal—5 to 15 µmol/L
- Moderate—16 to 30 µmol/L
- Intermediate—31 to 100 µmol/L
- Severe—Above 100 µmol/L

However, because of the evidence linking homocysteine to heart disease (even at relatively low levels), the Life Extension Foundation recommends that people try to keep their homocysteine level between 7 µmol/L and 8 µmol/L. A homocysteine level over 12 µmol/L should be treated aggressively. One study found that each 3-µmol/L increase in homocysteine caused a significant increase in the risk of having a heart attack (Verhoef P et al 1996).

HOMOCYSTEINE: WHAT IS IT?

Homocysteine is an intermediary amino acid; its role in the body is complex, but very important. Homocysteine is a necessary byproduct of a healthy metabolism. Homocysteine is produced as part of the methionine cycle, in which methionine is converted to S-adenosylmethionine (SAMe). SAMe is valuable because of its ability to donate methyl groups during chemical reactions throughout the body. Homocysteine is synthesized when SAMe donates its methyl group. In scientific terms, this means the SAMe has been methylated (lost a methyl group). Methylation is crucial to the health of our cells and tissues by regulating gene expression, protein function, and RNA metabolism.

The methionine cycle is responsible for the creation of all the homocysteine in the body. Most of the resulting homocysteine is bound to plasma and considered stored, or inactive. It may be released into the bloodstream as free homocysteine in response to adverse changes in the body's biochemistry. Thus, high levels of homocysteine are linked to specific health problems. There is also evidence that homocysteine itself causes damage to the cells within blood vessels.

Homocysteine in the bloodstream is metabolized through two principal pathways. It may be remethylated back into methionine through a process that involves folic acid (folate) and vitamin B12. This is called the remethylation pathway and is responsible for consuming most of the body's free homocysteine. The remethylation pathway creates more SAMe to support healthy methylation. (Some organs, namely the kidney and liver, are able to remethylate homocysteine directly back into SAMe, but only a fraction of homocysteine is processed in this way.)

Alternatively, some of the excess homocysteine may be used to create cysteine, which is then converted into glutathione. Glutathione is an important and powerful antioxidant. The conversion of homocysteine into glutathione may be accelerated when the body is under oxidative stress. This second process is called the transsulfuration pathway because it produces sulfate byproducts that are flushed from the body in urine. The transsulfuration pathway depends on vitamin B6 to work properly.

There are many reasons free homocysteine levels might rise in the blood. We may be suffering from oxidative damage because of a

shortage of glutathione, or our methylation capacity may be decreased, which affects our cells' ability to grow, differentiate, and function properly.

HOMOCYSTEINE: LINKED TO DISEASES OF AGING

Although homocysteine's association with heart disease attracts the most attention, researchers are continually learning more about its effect on other diseases and conditions. So far, elevated homocysteine levels have been linked to the following disorders or diseases:

- **Stroke**—Homocysteine's effect on the arteries that supply the brain with blood (carotid arteries) is similar to its effect on the arteries in the heart. One study that analyzed 1077 people found that overall risk of "silent stroke" or other risk factors for a stroke were strongly associated with elevated homocysteine levels (Vermeer SE et al 2003). Larger, more focused studies are underway.
- **Vascular disease**—There is evidence that homocysteine combines with low-density lipoprotein (LDL) cholesterol and contributes to the creation of plaque inside artery walls (McCully KS 1996). Some forms of homocysteine have been shown to damage the inner walls of blood vessels directly (Jakubowski H 2003). Homocysteine has also been implicated in the formation of blood clots, which can cause a heart attack, stroke, or peripheral vascular disease.
- **Liver disease**—Elevated homocysteine and low levels of SAMe are linked to liver toxicity and cirrhosis (Martinez-Chantar ML et al 2002; Ventura P et al 2005). Homocysteine likely contributes to liver damage, leading to the formation of fibrin, clots, and vascular complications (de la Vega MJ et al 2001).
- **Kidney disease**—The kidneys filter, reabsorb, and metabolize amino acids, including homocysteine. In kidney failure, homocysteine levels rise due to improper kidney filtration (Friedman AN et al 2001). Folic acid, trimethylglycine (TMG; also known as betaine), and vitamins B6 and B12 reduce homocysteine in people with kidney failure. High doses of folic acid can normalize homocysteine levels. Once kidney failure occurs, folic acid is much less effective, and high doses of vitamin B12 are required to help normalize homocysteine levels (Righetti M et al 2004).
- **Thyroid conditions**—Elevated homocysteine levels may contribute to accelerated heart disease among people who have hypothyroidism (Morris MS et al 2001).
- **Alzheimer’s disease and dementia**—High levels of homocysteine indicate impaired methylation in the brain. Individuals with Alzheimer's disease have been shown to have elevated homocysteine levels (Joosten E et al 1997; McCaddon A et al 1998).
- **Depression**—Depression has been linked to low levels of folic acid in women (Ramos MI et al 2004). Low folic acid levels have been shown to decrease the effectiveness of the antidepressant fluoxetine (Prozac®) (Fava M et al 1997), and vitamin B6 may alleviate depression (Hvas AM et al 2004). Deficiencies in these vitamins are also closely associated with high homocysteine levels.
- **Erectile dysfunction**—Homocysteine has been shown to reduce the production of nitric oxide. Nitric oxide causes blood vessels to relax, increasing blood flow to organs and tissues. Folic acid and vitamin B12 may help lower homocysteine levels. In one case study, a man with erectile dysfunction, who also had a genetic defect that causes elevated homocysteine levels, did not initially respond to treatment with sildenafil (Viagra®). However, after treatment with 5000 micrograms (mcg) of folic acid and 1000 mcg of vitamin B12, his erectile dysfunction was successfully treated with sildenafil (Lombardo F et al 2004).
- **Diseases of the eye**—Homocysteine's ability to damage blood vessels also has implications for the tiny blood vessels in the eye. Elevated homocysteine levels are associated with serious eye conditions, including glaucoma and macular degeneration. A study showed that homocysteine levels of 11.6 µmol/L were the average concentrations in patients who had central retinal vein occlusion; the average level was 9.5 µmol/L in control subjects (Vine AK 2000).

Why Homocysteine Levels Rise

Homocysteine levels are responsive to a wide range of influences. They rise naturally as we age. Genes also play a large role in the body's metabolism of homocysteine. However, there are many lifestyle factors that can also cause homocysteine levels to rise. For instance, excessive coffee and alcohol consumption have been shown to increase homocysteine levels (De Bree A et al 2002).

Dietary choices affect homocysteine levels. Eating foods that contain large amounts of methionine, such as red meat and chicken, has been shown to increase blood levels of homocysteine. Similarly, low intake of foods rich in vitamin B, such as green leafy vegetables, may also increase homocysteine levels (Devlin TM 2002).

In addition, the following pharmaceuticals are associated with elevated homocysteine levels:

- **Fenofibrate**—Used in the treatment of high cholesterol (Dierkes J et al 1999).
- **Niacin**—Used in the treatment of lipid management (e.g. Cholesterol & Lipoprotein (a)).
- **Metformin**—Used to treat diabetes (Carlsen SM et al 1997).
- **Antiepileptic drugs**—Used to control seizures (Schwaninger MC et al 1999).

- **Levodopa**—Used to manage Parkinson's disease (Muller T et al 1999).
- **Methotrexate**—Used to treat cancer, psoriasis, arthritis, and lupus (Haagsma CJ et al 1999).

THE LIFE EXTENSION FOUNDATION APPROACH TO HYPERHOMOCYSTEINEMIA

In general, there are two strategies used to lower homocysteine: increase the rate at which it is metabolized by the body, or prevent excess homocysteine from being formed in the first place. It also makes sense to address the damage caused by an elevated homocysteine level and any underlying conditions that may be contributing to the condition. The Life Extension Foundation's approach to lowering homocysteine relies on several principles:

- Directly addressing high homocysteine levels by increasing metabolization of homocysteine. Nutrients that increase metabolization of homocysteine fall into two categories: those that increase the remethylation of homocysteine back into SAMe, and those that act along the transsulfuration pathway to remove excess homocysteine from the body.
- Routine blood testing to monitor homocysteine levels. This should include genetic testing to check for abnormalities. Slight genetic defects in as few as two enzymes may cause moderate hyperhomocysteinemia. As mentioned previously in this chapter, the most serious form of hyperhomocysteinemia (homocystinuria) is caused by an extremely rare genetic disorder.
- Addressing the damage directly caused by homocysteine. This may mean supplementing with antioxidants and other nutrients to reduce damage caused by homocysteine.
- Managing underlying conditions—including high blood pressure, coronary artery disease, diabetes, and hypothyroidism—that are associated with a high homocysteine level.

Fortunately, homocysteine levels are responsive to dietary supplements, and it is possible for even moderate or high levels to be brought under control.

THE B VITAMINS: A POWERFUL WEAPON

Management of hyperhomocysteinemia begins with folic acid, vitamin B6, and vitamin B12. To varying degrees, folic acid and vitamin B12 increase the remethylation of homocysteine back into SAMe. Vitamin B6 is necessary for the conversion of homocysteine into glutathione along the transsulfuration pathway. (For safety information on vitamin B6, see the Safety Caveats section at the end of this chapter.)

The following studies have shown a rapid and dramatic decrease in homocysteine levels caused by folic acid and some B vitamins:

- In 1996, the Food and Drug Administration (FDA) mandated that cereal-grain flour products be fortified with folic acid. Modest but significant decreases in homocysteine levels followed (Jacques PF et al 1999; Anderson JL et al 2004).
- One set of patients with a history of myocardial infarction or unstable angina was given 2000 mcg of folic acid daily. Another group of patients with the same conditions received only 200 mcg. The higher dosage significantly reduced total homocysteine levels (Neal B et al 2002).
- Daily supplementation with 350 mcg of folic acid for 17 weeks reduced serum homocysteine levels by nearly 20 percent, enough to reduce the risk of vascular disease (Venn BJ et al 2002).
- Folic acid and vitamins B6 and B12 reduced homocysteine levels, restored endothelial function, and reduced arterial plaque (Spence JD et al 2001).
- Middle-aged to elderly men and women with initially modest to significantly elevated homocysteine levels (>8 µmol/L) who took a multivitamin and mineral supplement for 56 days had significantly higher vitamin B and lower homocysteine levels when retested. Plasma folic acid and vitamin B12 concentrations rose by 42 percent and 14 percent, respectively, while homocysteine concentrations fell 10 percent (McKay DL et al 2000).
- Another B vitamin, vitamin B2, is also involved in remethylation pathways in the body (Devlin TM 2001).

TMG AND ZINC: BRINGING HOMOCYSTEINE UNDER CONTROL

Other nutrients that encourage the remethylation of homocysteine include TMG and zinc, both of which enhance the action of B vitamins.

TMG operates along a different pathway than the B vitamins. In fact, some individuals who have a severely elevated homocysteine level respond only to TMG because its activity is limited to the liver and kidneys. To decrease a severely elevated homocysteine level, repeated high doses of TMG must be taken throughout the day. One small study found that TMG supplementation taken concurrently with vitamin B6 and folic acid significantly reduced homocysteine (Dudman NP et al 1996).

Zinc acts in concert with vitamin B6 to promote remethylation of homocysteine to methionine. Zinc is also needed for the conversion of homocysteine to cysteine and glutathione. (For safety information on zinc, see the Safety Caveats section at the end of this chapter.)

For More Information

To learn more about the conditions associated with hyperhomocysteinemia, see the following chapters:

- Congestive Heart Failure
- Atherosclerosis
- Managing High Blood Pressure
- Diabetes
- Thyroid Disorders

REMOVING EXCESS HOMOCYSTEINE

While the remethylation pathway recycles homocysteine back into methionine, the transsulfuration pathway removes it. In the transsulfuration pathway, homocysteine is condensed with serine to form cystathionine, which is converted into cysteine. In turn, cysteine is converted into glutathione, taurine, and sulfate waste products that are flushed from the body in urine. All of these reactions occur with the help of vitamin B6.

Besides vitamin B6, other nutrients that strengthen the transsulfuration of homocysteine include:

- **SAMe**—SAMe is derived directly from methionine. Its job is to provide methyl groups for reactions throughout the body, including the methylation of nucleic acids (RNA and DNA), proteins, and structures throughout the brain. SAMe is the precursor to such nutrients as creatine, glutathione, taurine, L-carnitine, and melatonin and can be found in almost every tissue in the body. It has been studied in the treatment of depression, schizophrenia, demyelination diseases, liver disease, dementia, arthritis, and other conditions. It is also necessary for normal circadian rhythms. High doses of SAMe, 1600 milligrams (mg) daily, increased phosphocreatine levels in the human brain (Silveri MM et al 2003), indicating that SAMe is important in forming creatine. Although SAMe is part of the methionine cycle, taking supplemental SAMe does not increase the production of homocysteine (Devlin TM 2001). It does, however, encourage the conversion of homocysteine to cysteine and glutathione (Devlin TM 2001), thus lowering homocysteine levels. (For safety information on SAMe, see the Safety Caveats section at the end of this chapter.)
- **Selenium**—The trace mineral selenium is necessary for the antioxidant activity of glutathione, which is converted from homocysteine. Selenium deficiency has been shown to increase oxidative damage in animals. By boosting selenium levels, you can raise your level of glutathione and help lower your homocysteine level (Devlin TM 2002).
- **N-acetyl-cysteine**—Consuming N-acetyl-cysteine may reduce homocysteine levels by encouraging the production of cysteine, which is critical to the conversion of homocysteine to glutathione. By increasing the production of cysteine, it may be possible to boost the amount of homocysteine converted into glutathione.
- **Cysteine**—Like N-acetyl-cysteine, cysteine supplementation may prevent the release of stored homocysteine into the bloodstream. The Life Extension Foundation favors maintaining an adequate level of cysteine to maintain normal glutathione levels.

INHIBITING THE FORMATION OF HOMOCYSTEINE

Not all the homocysteine created is released directly into the bloodstream as free homocysteine. In fact, less than 1 percent of the homocysteine in the blood is free. The majority, about 98 to 99 percent, is bound to proteins in the blood and considered stored.

This store of homocysteine may be released in response to decreased methylation or oxidative damage, or in response to other influences. Nutrients that have been shown to inhibit the release of homocysteine include:

- **Creatine**—Somewhere between 50 and 90 percent of the SAMe required by the body goes into the production of creatine (Devlin TM 2001; Finkelstein JD et al 1984; Lee H et al 1998; Silveri MM et al 2003; Stead LM et al 2001). Supplementation with creatine diminishes the need for SAMe, reduces formation of homocysteine, and the need for homocysteine remethylation. In animal studies, supplementation with creatine for 2 weeks reduced homocysteine levels by 25 percent (Stead LM et al 2001).
- **Choline-producing nutrients**—SAMe is involved in the production of choline. By taking choline-producing nutrients, your body produces less SAMe, which reduces the amount of homocysteine needed. Choline-producing nutrients include cytidine diphosphate (CDP) choline, lecithin, alpha-glycerylphosphorylcholine, and choline chloride.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

It is important to begin your homocysteine-lowering program by working with a qualified physician and taking the necessary blood tests to evaluate your risk. To help lower your homocysteine level, the Life Extension Foundation suggests:

- **Folic acid**—4000 to 8000 mcg daily
- **Vitamin B12**—1 to 2 mg daily
- **Vitamin B6**—100 to 200 mg daily
- **SAMe**—400 mg two to four times daily
- **TMG**—2 to 4 grams daily
- **Zinc**—30 to 90 mg daily
- **CDP choline**—250 to 500 mg daily. Alternatively, you can use 1 to 3 teaspoons of liquid choline chloride daily mixed with 2 ounces of juice, 1 tablespoon of pure lecithin granules daily, or 250 mg of a-GPC daily.
- **Micronized creatine**—500 mg (in capsule form) four to eight times daily
- **N-acetyl-cysteine**—600 mg (in capsule form) one to two times daily on an empty stomach

If this protocol is not successful at lowering homocysteine level, a weekly 1-mg vitamin B12 injection may be necessary (this requires a prescription).

HYPERHOMOCYSTEINE SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

Creatine

- People with impaired kidney function should discuss creatine use with their doctor.
- Creatine can cause muscle cramping, muscle strains, and gastrointestinal symptoms such as nausea and diarrhea.

Folic acid

- Consult your doctor before taking folic acid if you have a vitamin B12 deficiency.
- Daily doses of more than 1 milligram of folic acid can precipitate or exacerbate the neurological damage caused by a vitamin B12 deficiency.

NAC

- NAC clearance is reduced in people who have chronic liver disease.
- Do not take NAC if you have a history of kidney stones (particularly cystine stones).
- NAC can produce a false-positive result in the nitroprusside test for ketone bodies used to detect diabetes.
- Consult your doctor before taking NAC if you have a history of peptic ulcer disease. Mucolytic agents may disrupt the gastric mucosal barrier.
- NAC can cause headache (especially when used along with nitrates) and gastrointestinal symptoms such as nausea and diarrhea.

Phosphatidylcholine

- Phosphatidylcholine can cause increased salivation, a metallic taste, headache, drowsiness, and gastrointestinal symptoms such as nausea and diarrhea

SAMe

- Consult your doctor before taking SAMe if you have bipolar disorder. See your doctor frequently if you take SAMe and you have bipolar disorder.
- Consult your doctor before taking SAMe if you take antidepressants. See your doctor frequently if you take SAMe in place of or in addition to antidepressants.
- Consult your doctor before taking SAMe if you have cancer. Nucleic acid methylation patterns may change in people who have cancer and take SAMe.
- Do not take SAMe if you are undergoing gene therapy.
  SAMe can cause anxiety, hyperactive muscle movement, insomnia, hypomania, and gastrointestinal symptoms such as nausea and diarrhea

Vitamin B6

- Individuals who are being treated with levodopa without taking carbidopa at the same time should avoid doses of 5 milligrams or greater daily of vitamin B6.

Vitamin B12 (cyanocobalamin)

- Do not take cyanocobalamin if you have Leber's optic atrophy.

Zinc

- High doses of zinc (above 30 milligrams daily) can cause adverse reactions.
- Zinc can cause a metallic taste, headache, drowsiness, and gastrointestinal symptoms such as nausea and diarrhea.
- High doses of zinc can lead to copper deficiency and hypochromic microcytic anemia secondary to zinc-induced copper deficiency.
- High doses of zinc may suppress the immune system.

For more information see the Safety Appendix