

# Homocysteine: The Key To Heart Attack, Stroke, & Cancer

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A series of brilliant research achievements in the past 30 years has confirmed the importance of homocysteine as a PREVENTABLE and TREATABLE factor in blood vessel disease. In fact over 200 research studies already provide a consensus that identifies this molecule as THE strategic factor in heart attacks and strokes, far more powerful than cholesterol and fat. In the first place, cholesterol has vital structural functions in every cell membrane in your body and very low toxicity; whereas homocysteine is a transitory metabolic intermediate. If the chemical pathways to its useful end-products are impaired, homocysteine build-up causes more mischief than any other physiologic "ortho"molecule.

The possibility of homocysteine toxicity has been known since 1962, when a rare genetic disease of infancy was linked to high levels of this substance. It has taken over 30 years to verify that homocysteine can and frequently does build up to dangerous levels in many normal people also, especially if they are deficient in vitamins, such as B6, B12 and folic acid and betaine. Because these vitamins are frequently deficient in large-scale health and nutrition surveys, it is now believed that homocysteine is the cause of at least 10 percent of all deaths from heart attack. That amounts to over 50,000 deaths per year in the United States!

An important new research, published in the prestigious New England Journal of Medicine, shows that by fortifying a breakfast cereal with folic acid, homocysteine disappears from the blood of patients with coronary heart disease<sup>1</sup>. The researchers found that it requires at least 400 mcg of supplemental folic acid plus the usual dietary intake in order to remove the risk of homocysteine toxicity and damage. This is a direct challenge to the previous governmental RDA of 200 mcg, which was expected to be entirely available from food.

The editorial commentary that accompanied this research carries the headline "Eat Right and Take A Multivitamin." That is an historic first in American medicine. Up until now such research findings have ended with an admonition against vitamin supplementation, and calling for more research instead. This time the editorial calls for raising the RDA for folic acid. Such a bold about-face is based not only on this research but also another recent study of folic acid levels and birth defects,<sup>2</sup> which showed that at least 400 mcg of folic acid plus the usual diet is required to achieve maximum prevention of neural tube birth defects, e.g. spina bifida.

The Nurse's Health Study found a roughly 50 percent reduction in coronary artery disease in women with diets rich in B6, folic acid, whether from supplements or diets high in fruits and grains. This was a large study of 80,000 participants and it was published in the Journal of the American Medical Association in February of 1998. It is the largest study so far that links heart disease and these two nutrients, vitamin B6 and folic acid, which are especially available in orange juice, spinach, bananas, and whole grains--but also in calves liver, 'pate', red meat (rare), and fish. The researchers found that the greatest protection was at twice the RDA, i.e. a dose of 400 mcg of folic acid and 3 milligrams of vitamin B6.

The fact that homocysteine can damage blood vessels was very evident in the original reports of deficient cystathionine synthase enzyme activity in babies who developed brain damage and seizures due to blood vessel damage resembling atherosclerosis. After much research we know that not all such cases die in infancy but about half do suffer blood clots before age 30. That means about half of these genetic cases can go unrecognized into adulthood.

Dr. Kilmer McCully, then a research fellow at Harvard, was fascinated by the fact that the arterial damage in these infants closely resembles hardening of the arteries in adults. The infants had premature "aging" of their arteries! However this type of arteriosclerosis was NOT caused by cholesterol and had no evident connection to dietary fat. Instead, it was caused by deficiency of the enzyme, cystathionine beta synthase, and the damage could be prevented by providing megadoses of vitamin B6, to compensate for the genetic enzyme weakness.

Dr. McCully wrote a landmark research paper in 1969 in which he suggested that homocysteine might be implicated in coronary heart disease and that research should be conducted to determine if coronary arteriosclerosis could be responsive to vitamin therapy.<sup>3</sup> That was about the time Linus Pauling introduced the idea of orthomolecular medicine, which promoted the idea that nutrients are the "right molecules" for prevention and treatment of disease. Both men were ridiculed for advocating vitamin therapy but McCully has lived long enough to enjoy vindication. Homocysteine is a classic example of orthomolecular medicine because most cases can be effectively treated with vitamins.

Homocysteine is formed when the essential amino acid, methionine, loses a carbon atom, one of its physiological actions. The carbon atom also carries 3 hydrogen atoms, and it is quickly transferred to other molecules in a process called methylation. Methylation thus refers to the transfer of a carbon atom from methionine to other molecules. This is a vital process in biochemistry and requires co-factors, such as folic acid, cobalamin (B12), choline, betaine, and possibly dimethylglycine, all of which can transfer methyl groups. For example, methylation is required in order to form creatine for muscle energy, carnitine for cell energy throughout the body, taurine for cell membrane stability and cholesterol excretion, glucosamine for maintaining connective tissues and joint surfaces, phospholipids for cell regulation (PS) and cell structure (PC), and spermine for cell growth.

The methyl group is one of the smallest units of organic biochemistry, a single carbon atom with three hydrogens in attendance, but it has the ability to form electronic bonds with other atoms of carbon, hydrogen, nitrogen, and sulfur as well as oxygen. Methyl is one of the the most active players in the chemistry of life and homocysteine is one of the transport factors that carries the methyl carbons to their appropriate reaction sites. In the process homocysteine is transmuted into methionine, cystathionine, and adenosyl homocysteine, but only if the co-factor vitamins, amino acids, minerals and enzymes are in balance.

For example, in order to become cystathionine, homocysteine must join with the amino acid, serine, in a reaction that requires a synthase enzyme and adequate amounts of activated vitamin B6, i.e. pyridoxal phosphate. The enzyme, cystathionine synthase, was at first believed to be the whole story, and that excess homocysteine was due only to a genetic defect in this enzyme. Now we know that it is also a dietary problem, related to vitamin B6, which acts as a co-enzyme. That is, cystathionine synthase enzyme requires vitamin B6 in order to reach full activity. Dr. McCully suggested that mild genetic damage, (heterozygous), might cause sub-clinical cases that could respond to treatment with vitamin B6 therapy. He theorized that this might explain the observation that vitamin B6 deficiency provokes arteriosclerosis.

Now we know that the synthase enzyme was only one of seven enzyme defects that can cause homocysteine to build up to toxic levels. In particular, blockade of methylene tetrahydrofolic reductase (MeTHF reductase) is now recognized as more common and therefore more important.

A remarkable research in support of the homocysteine-heart theory was published in 1976. Patients with premature atherosclerosis, confirmed by angiogram, showed high homocysteine levels after taking a loading dose of the amino acid, methionine. Healthy controls did not. This eye-catching study did not open the door to the homocysteine paradigm but it did encourage research and by 1995 there were enough studies for a meta-analysis, bringing together results of 27 studies. Boushey<sup>5</sup> concluded that homocysteine is an independent risk factor for coronary artery disease, cerebrovascular disease and peripheral vascular disease, i.e. heart attack, stroke, and blockage of arteries and veins of the legs. He estimates that it causes 10 percent of the risk of heart attack and that the risk is graded, i.e. the higher the homocysteine level, the greater the individual risk.

Statistical analysis shows 15 mM/L to be high risk (95 percentile), while 11 mM is the upper limit of the mean (75 percentile). Previous to this analysis, homocysteine data was misleading and was rated as moderate (15-30), intermediate (30-100) and severe (>100)<sup>6</sup>, which gave a false sense of security in interpreting results of testing. The reason for the discrepancy is simply that these numbers were intended for research into genetics, not clinical use. Full-blown enzyme deficiency (homozygous) causes blood homocysteine over 400 mM/L. 'Mild' cases (heterozygous) typically have blood levels of 20 to 40 mM, sufficient to be 'mildly fatal.'

This is especially important amongst French Canadians, who have recently been found at high risk, almost 40 percent bearing a mutant MeTHF reductase enzyme, which exaggerates the homocysteine level if they are folic acid deficient. In general it is now believed that vitamin inadequacies, especially low folic acid,

account for two thirds of all cases of high homocysteine. So far no conclusive study has been carried out to determine if correction of homocysteine will improve cardiovascular disease outcomes--but it is almost certain.

Other conditions that increase homocysteine levels are pernicious anemia, low thyroid, and kidney disease. Victims of end-stage renal disease typically develop accelerated atherosclerosis also. Since B12 is a co-factor with folic acid in the remethylation process that transforms homocysteine into methionine, it is logical to expect a similar increase in homocysteine in case of B12 deficiency. Thus it is no surprise to find that of 434 patients with B12 deficiency<sup>7</sup>, almost all had homocysteine above 95 percentile (15 mM/L). Excess homocysteine is associated with several types of cancer, including breast, ovary and pancreas, and I have noticed a tendency for bone metastases in patients with high homocysteine. It may be a good idea to treat all cancer patients with folic acid, vitamin B12 and vitamin B6. For the same reason, I am wary of treating with methotrexate as it blocks folic acid and thus increases homocysteine levels. This inevitably must provoke platelet clots, growth factors and metastases, though I have seen no research paper on this subject to date (1998).

Other medications are also known to increase homocysteine levels. Anticonvulsants, particularly phenytoin (Dilantin™) are notorious folic acid inhibitors. Pancreatic enzyme supplements, also seem to interfere with folate absorption!<sup>8</sup> Theophylline is believed to inhibit activation of vitamin B6 (pyridoxal phosphate) and caffeine is also chemically similar and associated with high homocysteine. Cigarette smoke has also been implicated and cigarette smokers have lower B6 levels than non-smokers and therefore higher homocysteine levels.

In order to underscore the importance of homocysteine and the extent of the supporting research, the next few paragraphs are a brief summary of the most important studies that have reached mainstream acceptance by the medical community.

In 1985 Boers<sup>9</sup> tested 75 patients with vascular disease and found nearly a third of those with cerebral and peripheral vascular disease also had high homocysteine. In 1991 Clarke<sup>10</sup> measured homocysteine after loading doses of methionine in his patients with premature vascular disease. He found 42 percent of those with cerebral disease, 28 percent of those with peripheral vessel disease and 30 percent of those with heart attack had high homocysteine. The relative risk of coronary artery disease in these patients was over 20 times higher than in a comparison group with normal homocysteine.

In 1988 Boers tested 32 patients with high homocysteine after treating them with vitamin B6 250 mg, and 5 mg of folic acid if they were deficient. This normalized homocysteine in 81 percent. After adding 6000 mg of betaine, the results were 100 percent! This was an example of megavitamin therapy on all counts: B6 was given at 100 times RDA, folic acid at 50 times the then RDA, and betaine was given by the teaspoonful as there was no RDA. Before then one was likely to be called a quack for offering such treatment.

After Boers broke the ice, many other studies then succeeded in bracketing the required doses. Brattstrom found a 52% drop in homocysteine after 5 mg doses of folic acid in healthy subjects, also in 1988. Five years later a more definitive study was performed by Ubbink, who observed a similar 55 % drop in high homocysteine subjects (over 16.3 mM/L) when treated with only 1 mg folic but combined with 50 mcg of B12 and 10 mg of B6. A year later Ubbink fine-tuned his study by using a placebo group. The placebo had no effect on homocysteine, of course, but to a skeptical audience, it was a necessary demonstration.

Ubbink also tested folic acid at a lower dose, only 650 mcg, and found only 42 % lowering in high homocysteine subjects. This same dose of folic acid got better results when combined with B12 and B6. On the other hand a 10 mg dose of B6 by itself lowered homocysteine only 5%; and 400 mcg doses of B12 alone managed only 15% reductions. So it became clear that the key player in homocysteine therapy is folic acid and that doses as high as 650 mcg reach only 80 percent efficiency. Since the RDA is only 400 mg per day, it is likely that many people, otherwise well-informed, are still at unnecessarily increased risk for heart attack, stroke and cancer metastasis.

The Physicians' Health Study<sup>11</sup> followed 14, 916 men for over seven years during which there were 271 heart attacks, of which 19 were attributed to homocysteine (7 percent). When homocysteine scores were analyzed, those above 15 mM/L (95 percentile) were at three times greater risk than those below 14 mM (90 percentile). Thus, a 12 percent increase, the difference between 14 mM and 15 mM, was associated with a triple increase in risk of heart attack.

Other studies show that our norms for homocysteine are still too high and need to be lowered further. For example, Dr. Selhub<sup>12</sup> found the incidence of carotid artery narrowing is increased. between 11.4 and 14.3mM/L. Dr. Graham's large study in Europe takes it even lower. His study compared fasting levels of homocysteine in atherosclerosis patients and healthy controls. The 750 atherosclerosis patients averaged 11.3 mM/L; but 800 normal controls averaged only 9.7. A methionine challenge test revealed an additional 27 percent of patients with high homocysteine that otherwise would have been missed. That is a lot of possible error in testing for a disease as lethal as this and for which there is a cure.

In 1988 the National Research Council increased the official Recommended Dietary Allowances (RDA) for folate and B6. Will we see changes in the public health as a result? Certainly! The impact on cardiovascular disease will lead to better health and longevity of such magnitude as to make this the biggest public health event of the second half of the 20th Century.

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