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Dialogue with the Experts

Kilmer McCully, M.D., Connects Homocysteine and Heart Disease

By Gloria Bucco

Thirty years ago, Kilmer McCully, M.D., discovered that cholesterol and clogged arteries are not the causes but rather the symptoms of heart disease. McCully's pioneering 1969 theory that linked homocysteine—an amino acid that accumulates in the blood—and heart disease was not embraced by the medical community. In fact, he was banished from Harvard University and Massachusetts General Hospital and denied a new position for more than two years because of his research.

Times have changed for McCully. The cum laude graduate of Harvard Medical School has received numerous awards for his research including the 1998 Linus Pauling Functional Medicine Award. This month he receives the Burton Kallman Science Award from the National Nutritional Foods Association, Newport Beach, Calif., in honor of his scientific achievements relevant to the natural products industry. He is currently a clinical associate professor of pathology at Brown University and a pathologist at the Veterans Affairs Medical Center, both in Providence, R.I. His latest book, *The Heart Revolution* (HarperCollins, 1999), outlines how vitamin B6, B12 and folic acid deficiencies can elevate homocysteine levels and lead to arteriosclerosis.

Bucco:
What were you working on when you made the connection between homocysteine and heart disease?

McCully:
After completing a residency in pathology at Massachusetts General Hospital, I began looking around for a project where I could use my background to investigate the causes of genetic diseases. At a human genetics conference I learned about the case of a 9-year-old girl who was mentally retarded and had dislocated lenses [in the eyes]. She had what was a new disease at that time [1968] called homocystinuria, which had been discovered in Belfast, Northern Ireland, in 1962.

The girl's uncle had died of a similar disease in the 1930s and a review of the case had been published in the *New England Journal of Medicine* in 1933. The uncle was an 8-year-old boy who came to the hospital with mild mental retardation and dislocated lenses [a characteristic finding in homocystinuria]. At the time the physicians had no idea what was causing the boy's problems. He developed complications and died of a massive stroke. Doctors later found a blood clot in the carotid artery that caused the child's death. In the case discussion, a pathologist commented that the boy's carotid arteries had hardening or arteriosclerosis, commonly seen in the elderly.

I believed this boy most likely had homocystinuria and died of arteriosclerosis—I was fascinated by this. I was able to look at the original protocol, six of the original slides and a small amount of tissue that had been preserved. I made new slides and restudied the tissue, finding scattered arteriosclerotic plaques in arteries throughout the boy's body. I wondered about the relationship between homocysteine and these plaques.

Four months later I heard of a second case of what was thought to be homocystinuria. A 2-month-old boy was admitted to the hospital for pneumonia and failure to grow properly. He not only had homocysteine in the urine but also another amino acid—cystathionine. This meant it was a different disease, a new disease. It turned out that this disease, now called cobalamin C, is caused by deficiency of an enzyme requiring vitamin B12 and folic acid. As a result of this enzyme deficiency, the child produced excess cystathionine and had a low concentration of methionine in the blood and the urine.

Bucco:
What was the significance of this new condition?

McCully:
I realized immediately that this was a critical case because if this boy had arteriosclerosis, it would prove that no matter what the enzyme defect and no matter what the metabolic pattern, patients with inherited diseases causing homocystinuria also developed arteriosclerosis. Because of this I could attribute formation of the plaques to elevated homocysteine levels. On the other hand, if there were no plaques in the arteries, it would show that an individual could have high homocysteine in the blood and yet have no arteriosclerosis.

Knowing this was a crucial case, I rushed back to the lab, went to the archives, and found the case of the 2-month-old boy that had been filed and forgotten several months before. The original slides and tissue specimens allowed me to restudy this second case in great detail. The baby had rapidly progressive arteriosclerosis at the age of 2 months. I concluded from this observation that elevated homocysteine levels damage the cells and tissues of the arteries as a direct result of the amino acid in the cells.

At that point, I recalled a series of studies, published by a pathologist in the late 1940s, showing that intermittent severe deficiency of vitamin B6 in the diet causes arteriosclerosis in monkeys. I realized the monkeys must have had elevated homocysteine. This has proven true in animal models. I also found another classic animal model of rats deprived of the compound choline. These rats also developed arteriosclerosis and cancer. I concluded the rats must have had elevated homocysteine because of failure to convert homocysteine to methionine by folic acid and vitamin B12. This has also proven true. With this observation I was able to explain two of the most interesting and important animal models in the medical literature.

Bucco:
So you put these findings into a paper that was published in the *American Journal of Pathology* in 1969.

McCully:
Yes, in that first paper I described these findings and suggested that elevated homocysteine was likely important for people even without genetic defects but who might have dietary deficiencies of the B vitamins. I still remember mailing the manuscript and thinking something would probably come of it. I wasn't sure what, but I thought this was a very significant observation. I had no idea I would spend the rest of my career working on this problem.

Three weeks later the paper was accepted without changes, which is remarkable. After publication I was astounded that research scientists all around the world were asking me for reprints because they were looking for another explanation for the cause of arteriosclerosis.

Bucco:
What led to you being denied tenure at Harvard?

McCully:
For about six or seven years I continued work on this project. I made a number of observations and discoveries in homocysteine metabolism. Every experiment I conducted showed something new. It was an exciting time. In the early and mid-1970s I published quite a number of papers presenting evidence that supported the observation that homocysteine had something to do with vascular disease.

Then in 1976, the chairman of my department at Harvard retired and the new chairman told me the elders at Harvard felt I had not proved my theory, and unless I could support my salary from grant money I would be cut off and have no position. They moved my lab into the basement where I had no contact with other people. They made the situation so unpleasant I decided I couldn't work there.

I left in January 1979 and tried to find another position. For the next 27 months I was unable to find a position anywhere in North America that would allow me to continue this work.

Bucco:
Why do you think the medical community became so resistant to your work nearly 10 years after you published that first paper?

McCully: During the first two or three years, my work was presented to the scientific advisory board of Massachusetts General Hospital as a great example of a new observation made by someone who had the correct background. They knew exactly what I was doing. I had been publishing papers and giving conferences.

They told me later they didn't want to have Harvard or Massachusetts General Hospital associated with my theory because it appeared to contradict the conventional wisdom that cholesterol and fats were the causes of heart disease. I guess some people assumed I

knew nothing about cholesterol, when in fact I had studied cholesterol metabolism with some of the masters including Konrad Bloch, the Nobel Prize winner for cholesterol biosynthesis.

I had a background in this area, and I knew what I was proposing was significantly different from what was accepted in the literature. It was so different the establishment reacted against me. My suggestion was that the cause of arteriosclerosis in the general population was an underlying deficiency of certain B vitamins—B6, B12 and folic acid. The role of cholesterol and fats was secondary. This was too much for the establishment to take.

Bucco:
Do you think the initial skepticism about your theory has changed in light of all the supporting evidence collected in the last 30 years?

McCully:
Yes. For the first 20 years or so there were few if any clinical studies. The ones that were done were mainly in the area of rare and inherited children's diseases, or with animals and cell cultures. The theory was not based on human observation. Then in the mid-1970s, a human study was published. By 1985, additional clinical studies were published. During the last 10 years quite a number of clinical and epidemiological studies have supported and proven the underlying validity of the homocysteine theory. I think the climate has totally changed and now there is wide acceptance of this concept. Every day a new article about homocysteine is published. There's an explosion of interest. Many of these articles cite my original data from 1969. People have really given me the credit for pioneering this concept.

Bucco:
Let's talk a little about homocysteine. What is its normal function in the body?

McCully:
Homocysteine is an amino acid that's normally produced in the body in small amounts from the amino acid methionine. We know now that the normal role of homocysteine in the body is to control growth and support bone and tissue formation. When I began to study this question, homocysteine's medical and nutritional implications were almost totally unknown. It was only known that homocysteine supported growth in animals. My colleagues and I showed that homocysteine is also involved in the normal human growth process. Homocysteine stimulates formation of insulin like a growth factor and acts like growth hormone. In fact, some of the children with homocystinuria have accelerated growth in childhood.

Bucco:
What elevates homocysteine levels?

McCully:
Homocysteine becomes elevated in the blood when there is a deficiency of the B

vitamins—B6, B12 and folic acid. Other factors also play a role. For example, normal aging causes homocysteine levels to rise. So do female hormones. Women have a lower level of homocysteine than men until menopause. After menopause a woman's homocysteine levels begin to approach those of men. Thyroid hormone controls the level of homocysteine in the blood as well. The kidneys are also crucial. High levels of homocysteine in the blood are characteristic of kidney failure and lead to a high incidence of vascular disease.

Genetics also plays a role. There's a fascinating genetic defect called thermolabile reductase deficiency. About 12 percent of the population has this hidden defect. It increases the amount of folic acid needed to keep homocysteine levels in the normal range. Toxic factors such as cigarette smoking are important. Also a number of different drugs and certain industrial toxins can increase homocysteine.

Bucco:
How are elevated homocysteine levels related to heart disease?

McCully:
When homocysteine levels rise, they begin to damage the cells and tissues of arteries and stimulate growth of arteriosclerotic plaques, which lead to heart disease.

Bucco:
So how can we prevent homocysteine from reaching these dangerous levels?

McCully:
I'm a strong believer in dietary improvement, and I believe the high incidence of arteriosclerosis and heart disease in our population can be traced to diet. This new theory allows us to understand what we can do to improve our diet.

Both folic acid and vitamin B6 are chemically unstable vitamins that are often lost during food processing. It's been shown that the population is not getting enough of these vitamins, and this in turn leads to elevated homocysteine levels.

The way to get these vitamins is to eat fresh whole foods—fresh vegetables, fruits, meat, fish and dairy products. We should also eliminate foods that contain highly processed ingredients such as white flour, sugar and oils. If we do this, we can vastly improve the quality of our diet and increase the intake of these important vitamins.

If a person has been eating a nutritionally depleted diet his whole life, it may be difficult to correct this abnormality just by improving diet. Supplemental vitamins may also be needed. Anyone who has a high risk for heart disease, either from family history or poor nutritional background, or who has early signs of heart disease, probably should take vitamin supplements to control homocysteine levels and stop the arteriosclerotic process.

Bucco:
What are you working on now?

McCully:
Homocysteine is involved in more than arteriosclerosis. It's involved in the aging process, cancer and degenerative diseases. Right now I'm trying to pursue a theory I've developed about how homocysteine works in normal metabolism. In 1994 I published a detailed biochemical explanation of how homocysteine acts in the body. Basically the idea is that homocysteine combines with vitamins A and B12 to produce a new compound that I discovered called thioretinaco. Thioretinaco controls the use of oxygen and energy metabolism in the body. My theory is that this substance is lost from the cancer cell, which causes an abnormality in the metabolism of homocysteine in cancer cells.

I'm also interested in the role of this compound in aging. During aging, thioretinaco is lost from the cell membranes and as a result, free radical compounds build up and produce free radical damage.

Bucco:
Are homocysteine levels being routinely tested today?

McCully:
Oh yes. You can request a homocysteine test from a simple blood sample. Last year several new tests were introduced that bring the cost of homocysteine testing down and make it available to any hospital. So testing will be more widespread in the future. Many people in the field believe it's going to be at least as important, if not more so, than cholesterol testing.

Bucco:
Is there anything you'd like to say about being this year's recipient of NNFA's Burton Kallman Science Award?

McCully:
I'm very pleased and honored to be given this important award. I think the most powerful aspect of this award is that it recognizes the importance of nutrition in the genesis of heart disease. It also recognizes the role of proper nutrition, whole foods and supplying adequate nutrients in the prevention of disease.

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