

Jeffrey Bland Video Blog Transcript
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You all know about the Dr. Kilmer McCully story related to homocysteine and atherosclerosis. His observation that he published in the 1960s as a pathologist at Harvard really ignited a whole new field in the etiology of cardiovascular disease. The interesting thing about this is that it was recognized that lowering of homocysteine could be accomplished by giving supplemental doses of B vitamins (folic acid, vitamin B12, vitamin B6). And so it was recognized that here was an example of how a nutrient (or a family of nutrients) could be very useful in the protection against cardiovascular disease in that subset of individuals who had cardiovascular disease associated with elevated homocysteine.

All sounds good. All is consistent with many studies published over many years. Everybody was on the bandwagon that the marker (the surrogate marker) homocysteine was a very good way of evaluating the relative need for these B vitamins to reduce the risk of cardiovascular disease. And then lo and behold, May 8, 2008, in the *Journal of the American Medical Association*, we find a new intervention trial has been published out of Brigham and Women's and Harvard that raises questions as to whether we understand everything we need to understand about this homocysteine theory.

What was this intervention trial? This intervention trial was to take physicians who are part of the Physicians' Health Study who had existing evidence of cardiovascular disease and supplement them for 7.1 years with supplemental doses of folic acid, vitamin B12, and vitamin B6 far in excess of the recommended dietary allowances, and to evaluate over time (7.1. years) the relative difference between the incidence of cardiovascular accident in the group getting the folic acid, B12, B6 supplements versus those who got a placebo that were stratified and randomized in this trial.

The outcomes did not show any statistical difference between the two groups in terms of incidence of cardiovascular disease or mean disease for years. There was, however, an 18.1% reduction in homocysteine blood levels in the group that got the folic acid, B12, and B6 versus that of the placebo group. Here is the question: why is it that the

levels of homocysteine were reduced but there was no incident increase (or change) in cardiovascular appearance in the supplemented versus unsupplemented group?

Of course, this once again comes back to our previous discussions we've been having over the last several months about the role these various nutrients play and how they modulate function. What is a biomarker? Is it possible that homocysteine is really a surrogate biomarker for more than just vascular disease? That it is a surrogate marker for methylation defects, only some of which then trigger or relate to vascular disease and others which may relate to other chronic age-related dysfunctions? What this really signals to us is that this whole concept that a single nutrient against a single marker may be somewhat limited in its understanding of how it influences health. And, in fact, it may also raise some questions and things about the nature of other biomarkers like cholesterol and heart disease. We've made the assumption that these biomarkers have a one-to-one connection with the etiology of a disease, but in a polymorphic population with complex variables that are now being recognized that translate differences in functional outcome from genetic potential, we are starting to see the story is much more complicated than we originally thought.

I think this is a disturbing outcome, but it is also very enlightening. The enlightening part of the story is there is no such thing as a simple answer to a complex chronic disease. To assume that one biomarker is the regulatory feature that ultimately determines the presence or absence of that disease any more than cholesterol (HDL or LDL) are in and of themselves singular markers for the etiology of this disease. It is a web of understanding how diet, lifestyle, and environment are connected to the etiology of these diseases. For the moment, I think our takeaway is supplemental doses of B6, B12, and folic acid (at that which was used in this trial) did not appear to produce any measurable reduction of cardiovascular incidence in a group at risk with elevated homocysteine.