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LETTERS TO THE EDITOR

The Fleming Unified Theory of Vascular Disease: A Link Between Atherosclerosis, Inflammation, and Bacterially Aggravated Atherosclerosis (BAA)

To the Editor:

At the 72nd annual meeting of the American Heart Association recently held in Atlanta, GA, I was impressed with three major themes that rang out through many of the plenary sessions. First, the incidence of coronary artery disease and deaths resulting from it are not decreasing but actually appear to be increasing, with more women dying from heart disease than men. Second, approximately 70% of all heart attacks occur in coronary arteries that are viewed to be relatively disease free (< 50% diameter stenosis) by angiography (cardiac catheterization). This means that the detection of disease requires the use of more sophisticated and accurate tests including nuclear cardiac imaging (PET, SPECT), endothelial function, and electron beam (calcium) testing. Finally, despite our understanding of coronary artery disease, our evaluation and treatment of risk factors is sad. Patients and physicians alike are more confused about what constitutes an elevated cholesterol concentration and how to treat it than ever before. Not only are physicians uncertain about when to treat elevated cholesterol and what the best approach is, but also they are even less clear about what constitutes an elevated triglyceride concentration or what importance homocysteine, lipoprotein (a), C-reactive protein, bacterial infection of coronary arteries, and interleukins have.

I must admit that my focus on cholesterol during the first 15 years of my research resulted in my missing what I now consider to be very important issues in both the diagnosis and treatment of vascular (heart) disease. Two and one half years ago it occurred to me that I was missing the point. Research that I had been involved with was not yielding the results we thought it might. People going on vegetarian diets and modifying their lifestyles were showing regression of heart disease in only one third of the cases, no change in one third, and progression of disease in the other third. As a result of this insight, I forced myself to sit back and redevelop my working hypothesis of heart disease. From this evolved the Fleming Unified Theory of Vascular Disease, which connects eight groups of factors that interact to produce vascular disease including heart attacks, strokes, and claudication. These eight groups include (1) dietary factors. Since the beginning of the 20th century scientists have postulated that cholesterol and calcium (atherosclerosis) played an important role in the development of heart disease. While this was discussed in the 1920s–1930s, it was rapidly dropped, at least partially because the number one cause of death was infectious disease. With the discovery of penicillin by Sir Alexander Fleming in 1928, the old era of bacterial infection was ushered out and the new era of heart disease ushered in. Soldiers autopsied after their deaths in World Wars I and II showed little if any coronary artery disease (CAD) despite an average age of 25–35 years. Shortly after WW II and a change in the American diet, the incidence of CAD began to rise. Despite many popular misconceptions, this diet was not a problem because of greater cholesterol intake but rather because of an increase in "saturated" fats and excess calories. These excess calories can be from protein, carbohydrates, or fat, and while insulin levels increase to handle carbohydrate foods, insulin also increases with consumption of protein and fat—a fact frequently forgotten by people who would

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have you believe that a high protein diet will somehow mysteriously make you better. This is much like magic; despite our intellect telling us this cannot be so, we still like to be fooled. We have become very good at wanting to be fooled and have even included medications like Aminorex, fenfluramine-phentermine, and most recently, Triax in an effort to reduce weight while living sedentary lifestyles.

During the decades since WW II, evidence has been mounting that these dietary problems and fad-type diets have been harmful to all of us, except those selling us these diets. Today one fourth to one third of our youth are overweight, or have diabetes, or have high cholesterol concentrations, or have high blood pressure. Coupled with smoking and lack of exercise, their lives may be plagued with worsening health problems than generations before them.

The second (2) group consists of homocysteine. Elevations of homocysteine can lead to blood clotting, narrowing of blood vessels (vasoconstriction), and abnormal function of the cells that make the blood vessels (endothelial dysfunction) react abnormally. Homocysteine is associated with increased oxidation of LDL cholesterol, which can cause more damage and buildup of cholesterol in the arteries of our body. A third (3) group of factors includes fibrinogen and lipoprotein (a), which can increase the clotting tendency of blood, stopping blood flow in already narrowed or inadequately supplied arteries. This process can be worsened when arteries are damaged by cholesterol plaque rupture, angioplasty, or other invasive procedures that can result in the release of proteins from the arteries, which, when released in small amounts, cause new blood vessel growth (gene therapy) but, when released in larger quantities, can actually cause blood vessels to close off, resulting in heart attacks, strokes, and perhaps death. This leads us into the fourth (4) group of factors, which are released from the blood vessel walls themselves in an effort to stop the loss of blood from damaged arteries. However, once released, these chemicals (platelet-derived growth factor, tissue growth factor β, and others) are designed to limit blood loss and lead to further narrowing of coronary arteries. A fifth (5) group of factors includes chemicals released in the body that cause damage to the arteries. These are called oxidants (oxidative free radicals/OFRs), and we now know that many vitamins, minerals, and medications can help to reduce these free radicals, thereby limiting the damage. Elevated homocysteine levels are one way in which these OFRs can increase. A sixth (6) group includes the leukotrienes (interleukins). This proved to be the link between the other groups of factors, and 6 months after I presented the theory, researchers in England showed that diseased coronary arteries vasoconstricted in the presence of interleukins. Six months later these were shown to be associated with CVAs (strokes) and 6 months later claudication (peripheral vascular disease). These inflammatory and infectious mediators once thought to be associated only with asthma are now known to be involved with vascular disease. The seventh (7) group includes the complement cascade, which is involved with both inflammatory and infectious problems. The eighth (8) and final group in the theory involved bacterial infections. While several different bacteria have been implicated, we have seen bacterially aggravated atherosclerosis (BAA) in 24% of the people we have studied. These individuals are initially diagnosed with elevated C-reactive protein levels, followed by acute phase antibodies. Each of the individuals so diagnosed has shown improvement in coronary blood flow following antibiotic treatment. Additionally, we have detected the thymus glands in these individuals on nuclear imaging during the acute phase of infection. The thymus gland is undetectable following treatment and improvement in coronary blood flow.

While only a theory 2½ years ago, we have just completed work on an 8-month project looking at 19 people without a history of heart disease. Each of these individuals (50% men and 50% women) had a series of blood tests analyzed for the above-listed eight groups of factors in addition to myocardial (nuclear) perfusion imaging and echocardiographic studies. Sixteen people improved their coronary artery blood flow (both extent and severity of disease improved), and 44% showed improvement in wall motion. Twenty-five percent had BAA, and responded favorably within 2 weeks of antibiotic therapy. Each of the three people who did not improve consumed a high-protein diet throughout part of their 8 months of study. While the 16 people who improved showed improvement in their eight groups of factors, in addition to wall motion and coronary blood flow, the three people who went on high-protein diets demonstrated poorer blood flow and worsening of blood tests (cholesterol,

triglycerides, homocysteine, lipoprotein (a), C-reactive protein, and even fibrinogen).

Although the performance of these above-listed blood tests and the treatment of each in connection with the others appear to be formidable tasks, they are less expensive both economically and personally to the patient and to the healthcare system. Not only does our current work support the Unified Theory of Vascular Disease, but also it demonstrates the treatability of this epidemic of health problems. The change in dietary habits and sedentary lifestyles may have set up this scenario, but it does not explain or totally treat it. At the beginning of the 20th century, infectious disease was the number one cause of death. As we leave the 20th century, we have a new infectious and immunologically mediated cause of death that we have created by diet, lifestyle, indiscriminate use of antibiotics, and failure to adequately diagnose and treat until late in the disease. The disease that once plagued only a few is no longer the disease of white males of the United States. It is now the number one cause of death in the world, of women, and, if not taken more seriously, of our children.

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