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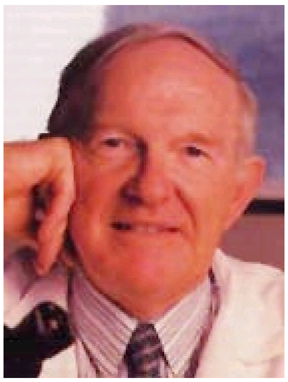
On The COVER

Resurrection of Kilmer McCully

By Terri Mitchell



Thirty years ago colleagues scoffed at his idea that homocysteine causes heart disease. New data proves McCully was right all along. This interview could change the way you view America's No. 1 killer disease.

In 1968, Kilmer McCully sat down to a meeting that would change his life. The newly-appointed Harvard pathologist would eventually prove a simple yet profound theory that is changing the way Americans think about heart attacks. At the time, McCully had no way of knowing that a single presentation would consume his interest for the next 30 years. On that hot day in August, it was just another lecture for the young scientist to attend.

The presentation was about a boy with a genetic disease called homocystinuria. Thirty-five years earlier, the boy had died in the very hospital where McCully now sat. The boy had died of a stroke-a curious death for an 8-year-old. Although the boy's death wasn't the focus of the lecture, McCully couldn't help but wonder about it.

McCully, who started out wanting to be a molecular biologist when such a thing was hardly on the map, ended up in human genetics after years of education that included medicine, pathology, chemistry and molecular biology. He had just come off a stint with the famous geneticist Guido Pontecorvo and James Watson of DNA fame when he heard the lecture. Fortunately, he had also just gotten a pathology degree and knew his way around the inside of an artery. As he sat listening to the talk, he began to wonder more about what the child's arteries looked like than what his DNA phenotype was.

There's a reason old, musty files are kept in hot attics: so people like McCully can scrounge around in them 30 years later. McCully located the boy's original autopsy report, and pulled out pieces of the boy's tissue embedded in paraffin blocks. Although the wax had melted together, technicians were able to salvage enough tissue to re-examine under a microscope. McCully was shocked, but not surprised at what he saw. The boy's arteries had undergone the same disastrous process he'd seen hundreds of times, only this time it was in an 8-year-old boy rather than an 80-year-old man. McCully knew that homocystinuria causes homocysteine to accumulate in the body. Could there be a link, he wondered, between homocystinuria and arteriosclerosis?

The link became more apparent after McCully reviewed the case of a 2-month-old baby with an even stranger form of homocystinuria. Not only was the baby unable to break down homocysteine, he couldn't convert another methionine by-product either. Unable to utilize vitamin B12, the baby was at the mercy of the two toxic by-products which eventually killed him. McCully realized that if this child also had arteriosclerosis, there was a good chance homocysteine itself had something to do with it. Sure enough, when McCully focused his microscope, what came into view was familiar. If the child hadn't died of a stroke, he would have soon succumbed to a heart attack.

McCully spent the next years proving that homocysteine causes heart disease and stroke. Yet despite undisputable evidence, he was told to leave Harvard. Where most people would have thrown in the towel, McCully was more determined than ever to prove his point. After leaving Harvard, he found a job at the Veterans Administration (VA) Medical Center in Providence, R.I., where he continued his homocysteine work. Still at the VA, McCully has accumulated 30 years of scientific findings on homocysteine. While he long ago moved on to other aspects of the molecule, he continues to have an abiding interest in homocysteine's role in heart disease. I talked to him recently at his home outside Boston, where his gracious wife, Annina, prepared a very civilized lunch.

Life Extension Magazine: In your new book, The Homocysteine Revolution, you mention a review of 200 studies on the relationship between homocysteine and arteriosclerosis. First of all, what is arteriosclerosis? Kilmer McCully: Hardening of the arteries. It comes from the Greek for "artery," which is a conduit, and "sclerosis," which means hardening.

LEM: And what are its effects?

McCully: What happens in arteriosclerosis is that the wall of the artery becomes replaced by fibrous tissue. The elastic tissue is partially or wholly destroyed, and the wall of the artery becomes encrusted with calcium and deposits of lipids. Blood thrombi and fibrin become incorporated into the wall of the artery. This process narrows the artery. In arteriosclerosis there is an increased tendency to form blood clots. When a clot forms at the site of this narrowing-depending on where it is in the body-heart attack, stroke or gangrene can occur.

LEM: What did the review of the 200 studies conclude?

McCully: A meta-analysis was done on homocysteine studies done up to that point which, I believe, was 1994. It was concluded that the vast majority of these studies were able to relate elevated homocysteine levels to increased risk of cardiovascular disease, especially cerebrovascular disease (stroke) and peripheral vascular disease (gangrene), and, less clearly, coronary vascular disease (heart attack).

LEM: And the studies on homocysteine and arteriosclerosis date back to when?

McCully: The first human study was done in 1976 by the Wilckens in Australia-small-scale clinical studies. The first large-scale epidemiological studies began in 1984, when Brattstrom showed that about 40 percent of patients with cerebral vascular disease and stroke have an elevated homocysteine level. And then, starting in 1985-1986, studies were published from the Netherlands, the United States, Japan, and other countries, showing that the risk of vascular disease correlates with the level of homocysteine.

LEM: Why are we just now hearing about these studies?

McCully: That's a very good question. I think that one of the main reasons is that it's been only within the last five to six years that we have population-based studies that are applicable to wide segments of the population. Prior to that, most of the studies were either basic science in animals or cell culture. There were a few early clinical studies, but no population studies.

LEM: What studies finally put homocysteine on the map?

McCully: The population study from the Harvard School of Public Health that showed increased heart attack risk with high homocysteine levels involved approximately 14,000 U.S. physicians. The Framingham Heart study showed that as vitamin B6 and folic acid decline, homocysteine levels rise. In their subsequent publication, they showed that this was correlated with thickening of the wall of the artery. So with these landmark studies, it begins to be proven that abnormal homocysteine metabolism is applicable to the population as a whole, rather than just to the rare genetic disease of homocystinuria by which this whole field was discovered.

LEM: Were we all led down the primrose path with cholesterol?

McCully: Cholesterol is only part of the story. And I think that looking at the long history of the cholesterol theory, there were some misinterpretations along the way, and there was an inadequate understanding of the total scope of the disease.

LEM: How did cholesterol theory start anyway?

McCully: Originally it arose from the discovery of cholesterol in atherosclerotic plaques at the turn of the century by chemists and pathologists, including Ludwig Aschoff. Another investigator, Nicolai Anitschkov, did experiments in St. Petersburg in 1913 showing that feeding cholesterol to animals produced a condition known as cholesterolosis-one of the aspects of which is vascular lesions. Unfortunately, these vascular lesions only generally resemble human lesions. They have much too much cholesterol and fat. Typical human lesions are fibrous, have a lot of calcification, and contain some cholesterol lipid deposits. But I think over the years the emphasis has been so heavily on the lipid deposition that the connective tissue changes have been overlooked. Actually, the pathologist Rudolph Virchow pointed out in the 19th century that the connective tissue changes tend to precede lipid deposition. Osborn did a beautiful study in England in the mid '60s, showing that in heart attack victims, connective tissue changes generally precede lipid deposition.

LEM: Could a person die without having lipid deposition?

McCully: Absolutely. As a practicing pathologist, I can assure you that I see many cases where the predominant arteriosclerotic lesion is fibrous and fibro-calcific. Especially in the lower extremities. It's really only in the larger arteries, such as the carotid arteries and coronary, the renal and the cerebral arteries, and the aorta where you see these prominent lipid depositions called "atheromas" in advanced cases of atherosclerosis.

LEM: So it seems that what has happened is there's been a huge emphasis on one aspect of heart disease.

McCully: Yes, although an important aspect. And the other reason I think that the homocysteine approach has been delayed is that until recently it has not been clear exactly how homocysteine relates to LDL cholesterol. It's becoming clear that LDL is a carrier of homocysteine in the form of small dense aggregates. These LDL aggregates have been shown to correlate with atherogenesis.

LEM: If cholesterol is not the big villain it's been made out to be, then how do you explain the "French paradox" and the phenomenon relating to a Mediterranean diet rich in olive oil?

McCully: Well, the French paradox is the following: the French eat a relatively high-fat diet containing high levels of cholesterol, and the paradox is that they have a very low rate of heart disease compared with other populations. One of the popular explanations is that red wine contains polyphenol antioxidant compounds-and this may well contribute. But in addition to that, I want to point out that the French diet is generally excellent in that it contains abundant fruits and vegetables-freshly prepared. They are also very fond of p'tÈ de foie gras and other p'tÈs, which are rich sources of folic acid and vitamin B6.

LEM: Pate de foie gras is made from liver. Doesn't liver contain a lot of B12?

McCully: Yes. Liver is an excellent source of B12, but, of course, fish is, too, and they also consume a fair amount of fish. The overall French diet is of quite high quality from the point of view of vitamins, micronutrients and the antioxidants in red wine. I think that these are some explanations of the French paradox.

LEM: Would fish explain the Mediterranean diet that appears to be heart-protective?

McCully: Exactly. The omega-3 unsaturated oils in the fish, the antioxidants, folic acid and B6 in the tomatoes and other vegetables. Fish is also rich in B6.

LEM: How do these nutrients relate to heart disease?

McCully: The lack of certain nutrients precipitates high homocysteine levels, which lead to adverse changes in arteries.

LEM: Is this why homocysteine is a theory of deficiency, as compared with the cholesterol theory, which is a theory of excess?

McCully: Right. This is why I call it The Homocysteine Revolution. Because it's a revolution in thinking about the origin of heart disease. The cholesterol hypothesis has been that eating an excess of either cholesterol or high fat in the diet somehow causes the elevation of blood cholesterol and somehow damages the arteries. The homocysteine approach attributes the process of arteriosclerosis to a deficiency of B vitamins.

LEM: In that regard couldn't it also be a theory of excess? Methionine comes from meat, and an excess of meat protein can create the deficiency of B vitamins. Isn't that right?

McCully: In a sense. I think it is true that if you look at populations worldwide that vegetarian populations tend to be protected against arteriosclerosis, and the carnivores are more susceptible. However, as the French show, if one consumes large quantities of certain B vitamins in addition to meat, homocysteine and vascular disease can be kept at a low level. The indigenous Eskimos of Greenland-the Inuit, for example, who eat their traditional diet which is very high in fat and cholesterol-nonetheless have a very low incidence of heart disease. This paradox has been correlated with the intake of omega-3 unsaturated oils that are abundant in fish products, which they consume. The B6 in fish eliminates homocysteine from the body.

LEM: Does fish oil lower homocysteine?

McCully: Yes. My colleagues and I showed this effect in men with high blood lipid levels. Olive oil, on the other hand, has no effect on homocysteine levels.

LEM: How does aging affect homocysteine?

McCully: Aging slowly elevates the homocysteine levels. This is a complex subject that needs more study. But we are beginning to understand that in aging there is a progressive abnormality of methionine metabolism. Studies have shown that at the same time S-adenosylmethionine (SAMe) declines, homocysteine increases. Over the age of 65 there is a risk of elevated homocysteine levels that is attributable to the aging process as shown by several different epidemiological studies.

LEM: I've read several studies that also indicate that the levels of folic acid and B6 are low in people over 65.

McCully: Yes. Especially if you compare them with young children. There's a classic study by Hultberg from Sweden in which they measured vitamin B6 in fetuses, infants, young children, teenagers and adults. It showed a very dramatic decline of vitamin B6 with aging. The same is true of folic acid.

LEM: Is there any theory for why this occurs? Is it diet? Metabolism?

McCully: I don't think anyone really knows. In my opinion, it's multifactorial. I think that on the one hand there are factors that lead to poor intake of vitamins in the aging population-such as poor dentition, depression, and other factors which lead to poor and decreased food intake. In addition, I think that the aging process itself may also be involved.

LEM: You haven't said anything about trimethylglycine (also called "TMG" or "betaine"). Does the betaine pathway not also contribute to the breakdown of homocysteine?

McCully: Yes. Recent studies in children with enzyme deficiencies suggest that betaine can increase adenosylmethionine in the brain. Another factor that you haven't mentioned is choline. Choline is the precursor of betaine. It is, I think, another alternative that should be explored in relation to elevated homocysteine. Choline has beneficial effects on brain function, such as learning and memory.

LEM: You mention in your book that as much as 38 percent of the French-Canadian population has a genetic mutation that increases their need for folic acid. Could there be other genetic mutations that we don't know about that might increase a person's need for one of these vitamins?

McCully: Yes, the molecular biologists are busy hunting for them as we speak.

LEM: Is there evidence that these genetic factors exist?

McCully: Yes. It has been shown that a so-called thermo-labile defect in an enzyme that relates to the breakdown of homocysteine is widespread in the population [Note: the enzyme is methylene tetrahydrofolate reductase]. Studies are currently being done to see how that defect affects a person's requirement for folic acid. Another area of research is the search for cystathionine synthase mutants. When a person inherits two of these genes, they end up with homocystinuria. When they inherit only one, we don't know what happens. Some of the older studies have suggested that having only one of the genes that creates cystathionine synthase deficiency can lead to elevated homocysteine levels, but more recent studies using molecular markers have sometimes failed to corroborate these earlier studies. It is an active area of research. The conversion of choline to betaine may also be affected by genetic abnormalities which have not as yet been looked at either.

LEM: What you're saying is that you can inherit a gene from your mother or father and have an extra need for one of these vitamins. Is that right?

McCully: Exactly. Another important point is that it's been known for years that vascular disease is closely related to family history. In some cases, it may be the dietary tradition of a family. But in other cases, it appears to relate to a genetic deficiency. We're now beginning to understand the molecular basis for these genetic deficiencies. The homocysteine approach is really expanding the genetic concept to a different area of metabolism-to methionine-to explain cases of familial susceptibility that cannot be explained by lipid and cholesterol.

LEM: And, in general, the homocysteine theory does not negate the cholesterol theory. Is that correct?

McCully: Absolutely. They actually work together. When atherogenesis is understood in its totality, the two theories cooperate.

LEM: But even aside from the hidden genetic problems that people could have, heart disease is the number-one killer in America and the problem doesn't seem to be getting any better. What's going on?

McCully: It is getting better. There has been a very significant decline in death from myocardial infarctions since about 1968. The peak incidence in the United States was between 1965 and 1968, when it reached a maximum, but since then there has been a dramatic decline in risk.

LEM: What accounts for the decline?

McCully: There was a very interesting conference held at the National Institutes of Health in 1979. Experts gathered from all over the country to try to explain why there was this decline in heart disease. And they found that it wasn't due to changes in blood cholesterol levels or dietary fats and cholesterol. The exercise fad had not hit at that point. There was discussion about the effect of coronary care units, bypass grafting and other medical intervention, but none of these appeared to really explain the dramatic decline. In my first monograph in 1983, I point out that the production of synthetic vitamin B6 began to be significant for the population as a whole around 1968. So one factor may be the increased availability of synthetic vitamin B6. But in addition to this, I think another factor that has to be considered is the year-long availability of fresh fruit and vegetables that has been brought about by improved transportation and food distribution methods.

LEM: Speaking of vitamins, the Food and Drug Administration recently decided to allow the fortification of processed foods with folic acid. It seems as if this is a slow and tortuous process to return each vitamin back to the food it was taken out of during processing. Must we sit and wait for fortification to save us from heart disease, or should we take action?

McCully: You're right. One of the reasons for the decline in heart disease since 1968 is the fortification of breakfast cereals with B6 and increased B6 in multi-vitamins. Fortification of grains and cereals with folic acid may reduce the rate even further when it begins in 1998. Let's look at food processing. Food processing goes back centuries. For example, the production of flour from wheat. This is an ancient process that goes back at least a thousand years. The Romans knew how to do it.

LEM: "Roman Meal," huh?

McCully: Right, but it's only within the last few decades that we've realized that the process of milling results in the loss of many essential vitamins, minerals, antioxidants and other micronutrients. I think that the whole concept of food processing has to be reexamined from the point of view of preserving the micronutrients.

LEM: Yes, all these wonderful fruits and vegetables are available, but we're still dying of heart disease.

McCully: They are available, but try to get your children to eat them. The junk food/fast food industries relentlessly promote products which are profitable to them but deleterious to our children and young adults. What we need in this country is an improved attitude toward eating a high-quality diet. Somehow the message has to get out to the young people that if they engage in nutritional abuse of their bodies they will pay the price when they get to be older in terms of increased susceptibility to arteriosclerosis.

LEM: You said in your book that a healthy diet would include six to 10 servings of fruits and vegetables, and two to three servings of grains/starch a day. Most people are so busy they don't have time to prepare all that. Aren't supplements a reasonable alternative in some cases?

McCully: I think that supplements should be used with care and caution because the best source of these essential nutrients is from whole foods. We should never forget this, because when one eats a whole vegetable or fruit or grain one is eating thousands of compounds-only some of which we understand. When one consumes a supplement, one is consuming a single compound, or very few compounds that, while they may be helpful in some instances, do not have the broad range of benefit of the whole food.

LEM: I'm sure that's true, but isn't it also true that supplements have been used in some of the homocysteine studies and they were found to be very effective at lowering homocysteine? And isn't it better to have a less-than-healthy diet with supplements than a less-than-healthy diet without supplements?

McCully: Supplements of vitamins B6, folic acid and vitamin B12 are useful to control homocysteine levels in persons who consume suboptimal diets. It's true that studies have shown that these vitamins taken as supplements are as effective as an improved diet in reducing homocysteine levels.

LEM: Are the recommended daily allowances for B6 and folic acid sufficient to inhibit homocysteine?

McCully: No. The RDAs for vitamin B6 were arrived at without consideration of the possibility that homocysteine can cause vascular disease. The Food and Nutrition Board neglected to cite the important experiments of Rinehart, who showed in his vitamin B6-deficient monkeys that an equivalent of 31/2 to 4 milligrams a day of vitamin B6 is required to prevent arteriosclerotic lesions. And yet the human RDA is set at 2 milligrams a day. And as shown by the Tufts study, the majority of the elderly population consumes less than the RDA. The RDA is insufficient. It should be higher, and the same is true for folic acid. In 1989 the National Research Council lowered the RDA of folic acid from 400 to 200 micrograms. The main reason for this is that the vast majority of the population only consumes 200 micrograms a day. The Tufts-Framingham study shows clearly that one requires 350 to 400 micrograms a day to prevent accumulation of homocysteine.

LEM: You've talked about some of the things that people should eat. What about some of the things they shouldn't eat?

McCully: Most people really know what they shouldn't eat-sugary desserts, fried foods-I go into this somewhat in the book.

LEM: What about meat? Haven't you referred to arteriosclerosis as "protein intoxication," and doesn't most methionine-where homocysteine originates- come from meat?

McCully:I think meat should be consumed in moderate to modest quantities, with an emphasis on light meats. But also moderate quantities of liver, which can be in the form of liver or pate. I think that highly preserved meats should be avoided. The main reliance for methionine in the diet should be on vegetable protein from grains or legumes, which contain less methionine than meat and dairy foods.

LEM: What about canned vegetables?

McCully: Studies from the Department of Agriculture and the studies of Schroeder show that the canning process results in major losses of both folic acid and vitamin B6-up to 40 to 50 percent. In terms of these vitamins, canned vegetables are only half as nutritious as the fresh product.

LEM: What about frozen vegetables?

McCully: They're first blanched. This is a process where the vegetable is immersed in boiling water or heated to a high temperature for a minute or so to inactivate certain enzymes. If the blanching process is not included, frozen food slowly deteriorates because of enzymes which are active even in the frozen state. Blanching destroys about 10 to 15 percent of vitamin B6 and folic acid-and other sensitive nutrients. Again, there is loss. But not as large as what occurs in the canning process.

LEM: You mentioned in your book that powdered egg yolks are particularly bad to eat because they have oxidized cholesterol. Where would a person encounter a powdered egg yolk?

McCully: Powdered egg yolks are widely used in commercial boxed cake mixes and by commercial bakeries. A lot of the prepared and preserved foods use dried egg yolks as a source of egg protein. And the studies have shown clearly that the drying process-the exposure of egg yolks to oxygen and air-causes high levels of oxycholesterols, which are very damaging to arteries. They may be involved, for example, in the production of arteriosclerosis in young people in the military service. It has been shown that the young men who were killed in Korea and Vietnam had significant atherosclerosis. Powdered eggs are a standard in the military diet. The other thing is french fries.

LEM: What's wrong with french fries? I thought they were one of the major food groups.

McCully: They contain a lot of oxycholesterols and oxidized oils. And the reason is that when they produce french fries, they use the same heated oil day after day. Oxidized lipids build up in heated oil.

LEM: That sounds ugly. And oxycholesterol is what, exactly?

McCully: Oxidized cholesterol, which is cholesterol that contains extra oxygen atoms.

LEM: You say in your book that smoking and blood pressure drugs elevate homocysteine. Why is that?

McCully: In the case of smoking, it's been shown by studies from South Africa that a component of cigarette smoke-probably carbon monoxide-inactivates vitamin B6. B6 levels are lower in smokers. Homocysteine levels are higher in smokers. In addition to carbon monoxide, cigarette smoke and other forms of tobacco smoke contain over 600 toxic compounds. Some of these compounds are carcinogenic; others have toxic actions we don't fully understand, but which may contribute to the elevation of homocysteine levels. In the case of the antihypertensive drugs, these are relatively recent observations that show minor effects on homocysteine levels. Whether this is reflected in increased risk of vascular disease is not known.

LEM: According to your book, the FDA withdrew the drug azaribine from the market in 1977. Azaribine is used to treat psoriasis, and the agency found that it was elevating homocysteine and causing heart attack and stroke. In light of the large amount of data that's accumulated about the relationship between homocysteine and heart disease since that time, is the FDA evaluating any other drugs for this potential effect?

McCully: Not to my knowledge.

LEM: Shouldn't it?

McCully: I think so. I think that another example of a drug that is well-documented to elevate homocysteine levels is methotrexate. This is a drug that's widely used in cancer chemotherapy. Of course, in this setting one is attempting to obtain benefit from the chemotherapeutic action of the drug, regardless of its potentially toxic side effects.

LEM: You published your first animal studies on homocysteine and heart disease in 1970, yet the medical establishment is just now beginning to accept this evidence. Why is that?

McCully: One of the things that happened is that when I first presented this work at a national meeting, some of the cholesterol people were listening. And after my talk I was met by stony silence.

LEM: Why?

McCully: There was a refusal to acknowledge the significance of this work-which I cannot explain to this day. I think part of it is misinterpretation, tradition-professional preferences-let's put it that way. And another curious thing happened which didn't help matters. A group contacted me about repeating some of my experiments, and I agreed. After they did this, they sent me slides, and I clearly identified lesions in the arteries. Yet they published a photograph of a normal artery, and claimed that no lesions were observed that could be attributed to homocysteine. In a footnote they said that the few lesions that were found were attributed to spontaneous origin. I felt-as I say in the book-totally betrayed by this. Because of what they did, the whole idea of homocysteine causing vascular disease was called into question-by this one paper. In retrospect, I realize what I should have done was to photograph the lesions and publish an illustrated rebuttal. But I was too busy doing other things, and I was too naÔve to think they would pull a trick like that.

LEM: But weren't your studies confirmed?

McCully: Absolutely. Absolutely they had been confirmed. I still remember the day when I was called from the hospital saying that some of my rabbits had died. I remember examining the rabbits and finding that they had died of pulmonary embolism-which is what some of the children with homocystinuria died of. These effects were duplicated by Kuzuya of Japan. Unfortunately, he published all his findings in Japanese, and I only found out about it relatively recently. About five or six years ago, he sent me a review in English, saying he had repeated all my experiments from 1974 and got the same results. It was one of those unfortunate circumstances where important data was not available to the English-speaking scientific world.

LEM: To what extent do drug companies drive scientific research?

McCully: The drug companies are highly oriented to the evaluation and promotion of their own products.

They don't contribute to a basic knowledge of disease processes in most cases. So, new ideas that involve unpatentable vitamin preparations or basic disease processes are not really supported by the drug industry because they have no commercial reason to do so. Quite the contrary. The drug companies are very busy making a tremendous fortune out of cholesterol-lowering drugs with limited demonstrable benefit-only questionable benefit in highly selected populations-with the unspoken knowledge that these drugs are carcinogenic in animals and highly toxic in certain individuals, causing liver damage and muscle damage, and other questionable effects. I'm talking about the statin drugs.

LEM: You have written that homocysteine may have a connection to cancer. Can you briefly explain that?

McCully: Homocysteine has been known for some years to be involved in the metabolism of malignant cells. This is not well-understood at the present time. However, our work on synthetic homocysteine derivatives may, in the future, help explain some of the abnormalities found in cancer cells and their dependence on methionine.

LEM: Can you explain a little more about cancer cells being dependent on methionine?

McCully: Yes. Methionine makes malignant cells grow actively. Malignant cells cannot convert homocysteine to sulfate (for utilization) because of a loss of a chemo-preventive substance containing homocysteine from cellular membranes. This is part of our theory. We have found two forms of homocysteine which are likely precursors to what we believe is a chemo-preventive substance.

LEM: And you have also hinted that homocysteine may relate to aging. What is that about?

McCully: It's well demonstrated by several large epidemiological studies that homocysteine levels do rise with aging. In my recent monograph, I have suggested that a basic process in aging may involve loss of thioretinaco ozonide from the cellular membranes of aging individuals. This remains to be proven from an experimental or demonstrable point of view, but I think it is a possibility that must be explored.

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