



The Role of Methylation and Homocysteine in Aging and Age-Related Illnesses

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H heart disease, cancer, and stroke are the three big killers. Of course, heart disease and stroke are very strongly linked. They're basically both vascular diseases. Though homocysteine is a known risk factor for heart disease, what I'm going to expose is a biochemical link that links cancer and heart disease together. We'll also link it a little bit with Alzheimer's and other age-related disorders. These diseases are all age-related.

Once we have established a biochemical link between these diseases and we establish how we can affect that, what we really have put together then is an anti-aging program. And you'll see this is very simple. This program consists of dietary supplements you probably already use.

As you know, heart disease is the largest killer in the United States, killing more people than lung diseases, cancer, AIDS, and accidents combined.

Homocysteine is the single most important risk factor, not just statistically, but also because it's the easiest one to lower. It can be normalized 95 percent of the time with simple nutritional intervention.

Homocysteine rapidly induces the initial states of arteriosclerosis, and cholesterol's effects are not apparent.

Homocysteine. What is it? Well, it's just an amino acid. It's a nonessential amino acid. Everybody has it. You can't have zero homocysteine in your blood. It happens to be a very reactive amino acid.

Of the critical studies on homocysteine, the first came in 1969, and that was done by Dr. Kirner McCauley. He noticed that young children who had genetic problems that caused an elevation in homocysteine had vascular lesions very similar to older people. In fact, he went ahead and tried giving homocysteine to rabbits.

First of all, he found that the rabbits became huge, just as homocysteine in homocystinuria causes human children to become long and lanky. The rabbits got large but they also developed vascular lesions very similar to what you'd expect in a pathological situation. It was a model for heart disease.

These homocystinurians are very rare, but when they are placed on nutritional therapies to lower their homocysteine rate, their vascular diseases drop considerably. In a population where you would normally expect 20 vascular events, it drops down to two. And of the two vascular events they had in this population, they had some problems with compliance. So again, it dropped from 20 to two in the homocystinurians just with nutritional intervention alone.

In 1981, two researchers at MIT published a book reviewing all the different studies on homocysteine. So, 1981 was the book from MIT, then in 1992 the Physicians Health Study was done. That's a nice little jump of time where nothing really was done of any substance. Well, what they showed in the study of 15,000 physicians was that, yes, indeed, homocysteine was a risk factor for vascular disease.

Dr. Rene Mallana went ahead and reviewed a variety of other studies, some with 47 patients, another with 131 patients, and several others. Every single one of these studies confirmed the same thing: Homocysteine was a significant risk factor for vascular disease.

In 1996, five thousand subjects out of Tufts University established that two-thirds of the cases are simply due to inadequate nutrition.

The American Heart Association came out with an article showing that elevated levels of homocysteine seem to occur before the disease, and this supports the idea that this parameter plays a role in the disease and is not just altered by the disease itself. In addition, we do know that it is altered by the disease itself. It's a double whammy.

An interesting study published in the *New England Journal of Medicine* said that if the homocysteine levels were greater than 20 nanomoles per milliliter, the five-year survival for people with similar values of heart disease was 65 percent. If their homocysteine levels were less than nine nanomoles per milliliter, they had almost a 95 percent five-year survival. And this is with patients that had roughly the same baseline, with everything else controlled for. It's a statistical measure of eliminating all the other variables so these people are thought to be exactly the same. What you've got there is a jump from 60-some-odd percent to almost 95 percent, if you can get the people to go from a high level of homocysteine to a low level of homocysteine. So, a patient walks in and has a high level of homocysteine; it's an easy blood test, and most labs are able to do that.

If the patient does have a very high level or even an intermediate level, what are you going to do? Well, you're going to see if you can lower their level of homocysteine. It's very easy to do.

When you're talking about something like methylation metabolism, you're talking about antioxidants or oxidative stress, and it's extremely complicated. The way homocysteine is metabolized can either be through B6, where it's converted to cystathionine, or a methyl group to be transferred to homocysteine. This is the process called methylation. And it can be a methyl group that's put on to homocysteine and now it's called methionine. With a little bit of energy, the methionine can become S-Adenosyl-Methionine (SAM). Now, S-Adenosyl-Methionine is the ubiquitous methyl donor; this is very important in terms of maintaining DNA integrity.

So how does methylation metabolism occur? There are two pathways.

One pathway is through folic acid and B12, and there are a variety of enzymes that are zinc dependent. Another independent pathway is through a product called trimethyl-glycine or betaine; these are all commonly found in foods. Trimethylglycine donates the methyl group; it becomes dimethylglycine, and in that process it converts homocysteine to methionine. There is another name for trimethylglycine, it's called betaine, and the enzyme that allows this to happen-everything has to have an enzyme-is called betaine homocysteine methyltransferase.

So, how are you going to lower homocysteine? Now that you know its metabolism, how

to lower it is going to be pretty easy. What you're going to want to do is give B6, folic acid, B12 and trimethylglycine.

Let's look at what *JAMA* said in 1992 from Harvard University. They wrote: "Because high levels can be easily treated with vitamin supplements, homocysteine may be an independent modifiable risk factor."

With that in mind, we went ahead and formulated a product. My partner in this holds a Ph.D. in animal nutrition and physiology. He's the one who figured out how to get elephants to breed in captivity by using natural vitamin E.

This is for people with fairly normal levels of homocysteine that simply want to bring them down. This is a dietary supplement that does not need to go through a physician's office. A physician, of course, has more ability to give higher doses of folic acid and work with it a little bit more than you could do just through a dietary supplement over the counter.

When you lower homocysteine through methylation, you also increase SAM, which is important in methylating DNA.

Now, how many nucleotides run your DNA? Most people think it's four. But actually the cytosine can be methylated or not, so really there's five. If you have the methylcytosine and you start losing those methyl groups, that is essentially DNA mutation. You can measure this mutation, this loss of methyl groups, by seeing how many methyl groups the DNA would take up.

After putting people on a low or moderately low folate diet not uncommon to what you see in some hospitals, what you find is that the DNA methyl acceptance-this is the rate at which the DNA will pick up methyl groups-went from 800 to 1,800, which means on a moderately low-folate diet, the methyl groups got lost on the DNA. At the exact same time, the oxidative stress increased. Of course, homocysteine was increased, but it's very interesting: you've also got the DNA methyl acceptance, which means DNA damage, and oxidative stress increases right away. The reason is that if you are not able to properly methylate, you can't make the most of your antioxidants. Most antioxidants are enzymes and proteins, and the body needs proper methylation metabolism to make them.

To affect DNA, you'd expect it to be related to cancer. So let's consider some cancer situations. The deadliest adult cancers, the ones that kill the most, are lung cancer and colorectal cancer. The deadliest child cancer is brain cancer. Well, if we're saying these are related to methylation metabolism and DNA damage, what happens when we start seeing what cancers are related to DNA methylation, and what do we get? The same cancers.

Let's go to lung cancer so I can give you some data on that. Of course, you realize that lung cancer, smoking, and heart disease are all related, so there's an indication that there's a link there. Let's see what happens if we go a little further.

Smokers taking folic acid, 10 milligrams of course a physician must prescribe this and B12, 500 micrograms, showed a decrease in precancerous cells after four months in 1988.

In 1994, researchers showed that the premalignant changes in smokers dropped from a score of 1.7 to .4, with the normal being 1.4. In other words, for cancer transformation-from a cell being normal to cancerous-they scored it in terms of its degree of metaplasia, and they found that this treatment decreased the score from 1.7 to .4.

In 1998, vitamin use, in particular serum folate, was associated with longer survival after surgical removal of cancer of the lung, and it was a difference of 41 months versus 11 months. Nearly a fourfold increase in survival was achieved simply with the use of nutritional supplements. That was published in the *Journal of Surgical Oncology* this year.

Regarding colorectal cancer: A study on 88,000 nurses found if people were taking large doses of folic acid over 15 years, they had a 75 percent drop in the rate of colon cancer.

Colon cancer rates have been decreasing since the fortification of cereals with folate. There are studies that show that excess methionine is related to cancer. Well, if you have excess methionine, you're also going to increase homocysteine. You need to have those cofactors to convert the homocysteine to methionine, otherwise the methionine can back-react into the homocysteine.

If it back-reacts, it goes around a cycle but nevertheless becomes elevated homocysteine. It's called the methionine-loading test.

Immigration studies have shown, of course, there was a relationship between diet and colon cancer. In fact, a diet high in folate causes a 40 percent drop in colon cancer, and other studies have shown there is double the risk for a typical Western diet.

Brain cancer is an interesting one. Brain cancer in children we're not going to relate to the diet of the children; we're going to relate it to the diet of the mother. It turns out that 15 years ago it was noted that women who took a prenatal supplement had a 40 percent decrease in the brain tumors of their children. There was a recent study in 1998 that confirmed this, and now they've found that another analysis shows that the longer the use of vitamins by the mother, the lower the risk of children with tumors, a reduction approaching 50 percent. The study did, of course, mention folic acid.

Now, people are saying, "Well, folic acid is involved with other things," but let's do a little experiment.

When they did the study, they found that serum folate levels in women whose fetuses had neural tube defects were exactly the same, or not distinguishable, from the serum folate levels in women who had normal fetuses. It was exactly the same. Actually, I think it was even a little higher, but it was statistically insignificant.

If the folate levels were the same, what was different? The homocysteine was high. The women who had fetuses with neural tube defects had high levels of homocysteine and relatively normal levels of folic acid. Since folic acid does work to lower homocysteine, they recommend extra folic acid to lower the homocysteine in those individuals.

So we're talking about very simple nutritional supplements, but who's going to fund the study? It's very hard. You're looking at a lot of animal studies and very few human studies, almost all of them are federally done. Animal studies, done in mice, now suggest a role for methylation and T-cell lymphoma. These are animal studies because, again, for the lower-incidence cancers, it's harder to get the studies funded.

There was a sevenfold increase in life expectancies for the animals supplemented with extra methyl groups. Liver cancer and fatty infiltration under alcohol stress was reduced with betaine and that was done at the University of Nebraska. Human studies are underway now.

Other cancers are awaiting study. There are a lot of cancers out there that have not been studied with regard to methylation. It has been noticed that in almost all cancers, the DNA methylation pattern is abnormal. Normally speaking, the DNA methylation pattern is actually decreased in general, and there is a lower methylation in the DNA and almost always it's aberrant. It's an altered DNA methylation pattern.

Maybe we could say this: You've got heart disease, cancer, and stroke, but since each of these is so strongly related to folic acid and methylation metabolism, perhaps if we were to statistically take care of those imbalances, we could actually find out that maybe the most popular way to die was simply poor methylation.

Let's talk about Alzheimer's. If we're talking about an age-related biochemical link between cancer and heart disease, and we're talking about it in terms of DNA degradation over time, let's see if we can link it to Alzheimer's.

It turns out that homocysteine is a risk factor for Alzheimer's. The risk of Alzheimer's for people with high homocysteine is higher than the risk of heart disease. In other words, it's a more statistically significant risk factor for Alzheimer's than for heart disease.

Folate and B12 status are critical. SAM levels are reduced in Alzheimer's patients. The prognosis for Alzheimer's patients is worse if they have high homocysteine levels, which means they have poor methylation metabolism.

Now, of course, Alzheimer's is also difficult to do clinical studies on because diagnosis is very poor. In a general clinician setting, it's about a 75 percent accurate diagnosis if the doctor thinks it's Alzheimer's, 50 percent accurate if they think it's not.

Now, there's a new test called the AD7C test, which might make diagnosis easier. Once it becomes easier to diagnose, you can start getting your clinical studies to make a little bit more sense. After all, if you're studying something that is actually not Alzheimer's, it makes it very difficult to make sense out of it.

Other diseases related to methylation metabolism are multiple sclerosis as described in 1992. Alzheimer's disease was first discussed in 1993, HIV in 1990, and dementia in 1991. They have a very strange homocysteine and methylation metabolism. It's just being worked out.

Let's take a look now at what happens if you start using some of these dietary supplements to raise SAM levels. There is a ubiquitous methyl donor that we've been talking about.

There was a study done on a 16-year-old Japanese girl. She couldn't walk. She had convulsions. She was mentally retarded. At first she just needed help walking and then eventually she couldn't walk. They tried every medication. They tried folic acid, but she wasn't responsive. There are certain people that don't respond to folic acid no matter what the dose; they don't have the gene products to process the folic acid. She had a methylene tetrahydrofolate reductase deficiency.

So what they gave her was betaine, the other pathway, and they jacked it up to several grams a day like they do for the homocystinurias. They found that the SAM levels went from not detectable at 17 months to 38.5 at 24 months to 85.3 - this is near normal, not quite normal but close. And guess what? She was able to walk again, her seizures stopped, she was doing much better. That was the last report. It was in the *Journal of Inherited Metabolic Diseases* by an author by the name of Tikishi out of Japan.

Beginning with S-Adenosyl-Methionine, that's created through proper metabolism of homocysteine to methionine to SAM. And then it takes a methyl group from SAM and sticks it on the DNA. And there's an enzyme for that. It's called DNA methyltransferase.

Sometimes a mistake is made and in Chemical Society meetings they talk about methyl this and methyl that. Usually when there's a word "methyl" in front of a chemical name that they're working with, it's not necessarily good because it really alters the structure of the molecule and you need to be dealing with biology here.

The methyl transferase is an enzyme that works with the methylation very well, if you'd taken a product that just says methyltestosterone, for example, an abnormal form of testosterone, the body doesn't quite know how to handle it, there are no enzymes for it, and the body has a hard time detoxifying it.

If we just take a methyl group from SAM, and stick it onto the DNA, really what you want to do is maintain the same DNA pattern over time. That would be a very strong anti-aging approach.

Methylation metabolism is inherently deficient. Nutritional support is necessary to keep it even close to what it used to be, because inherently we're not going to be able to perfectly reproduce the methylation pattern on our DNA.

Methylation metabolism can be manipulated through diet and provides possible intervention in aging.

Here's an interesting thing. Take a cell that is considered immortal. What happens to its DNA methylation pattern? The DNA methylation pattern stays roughly the same over time with an immortalized cell. If you look at cells from animals, what you find is they're decreasing with time and actually the short-lived animals lose their DNA methylation pattern faster. The longer-lived animals take longer to lose their DNA methylation pattern.

Methylation is lost with a methyl-deficient diet. That's clear and has been done in human studies now. As of this year, we have the data in humans.

Do you know methylation can be largely regained by feeding deficient animals a controlled diet? Again, that was shown in 1992. It's now been verified in humans.

So what we've connected it to is human age-related disease, including vascular disease, cancer, and neurological disorders.

The idea is to increase methylation and decrease homocysteine. The first thing you need to do is "wash hands often." Immunological stress is going to impede your ability to properly have methylation metabolism. And one of the most important things is good sanitation.

So from there, of course, you need more moderate exercise. Interestingly enough, when you talk about all the risk factors for vascular disease, it turns out that none of them can explain why exercise is good. It turns out that homocysteine can. This is the first risk factor that seems to go down with exercise. So this is one of the first explanations of the exercise missing link, if you will.

If the person is a vegetarian, one of the questions that's going to come up is are they getting adequate B12? This can be determined by a test. There are some studies that show you can get B12 from seaweed and some other nonanimal products, but generally speaking, a lot of vegetarians are B12 deficient. So if they're vegetarians, you might want them to take a little extra B12. If they're not, then the question is about protein intake.

Excess protein intake is going to be a problem because you're going to have higher levels of methionine, and you're going to have higher levels of other amino acids that you need to detoxify. What you need to do is simply try to instruct people to eat the protein according to their needs. There's some standard RDAs for that. Typically, in the United States, there are a lot of people who eat more protein than they need.

A good model for a proper diet in terms of protein is when you sit on an airplane. It's hard to believe, but if you sit on an airplane and look at the serving that they give you, that is a single serving. If you eat according to that amount of protein, you should be okay. Most people are not happy with airplane meals, and they'd like to get that second tray of food, but if people will eat that amount of protein, it will help their methylation metabolism. If they're eating more than that, especially if it's processed, they're going to need to get extra B6, which is necessary to help process that extra protein.

If they're eating deficient protein, which is rare, the obvious thing is to have them eat more protein. Again, if their protein level is proper, then the question is, do they consume enough vegetables? Are they eating a good diet with a variety of vegetables? The answer is yes or no.

If the answer is no, then they need to be placed on a program with folic acid. You could try to tell them to change their diet, but I have found that to be very difficult. I have found it easier to get people to take a pill than change their diets. Typically this involves a fairly

low-level trimethylglycine, folic acid, B12, B6, vitamin E, some antioxidants, and a multi-vitamin. The vitamin E's very important because it actually protects the B12. Once you've taken care of that, are you getting beans and legumes and other things? Because you need the minerals to activate the enzymes. If you're not getting the minerals, you need zinc and magnesium. If you have a high intake of meat, you don't need so much because you're probably getting it that way.

All right. So now your patient seems to have a reasonable pattern. They've got

adequate protein, but not too much. You've given them supplements to offset their dietary inadequacies, so what are you going to do? You test them. There's a simple test for homocysteine. Probably within the next 12 months, there's going to be a test for S-Adenosyl-Methionine.

If it's a bad result, if you get high homocysteine levels, then of course you can increase the level of trimethylglycine. Folic acid increases the dose and then you can discuss other things you want to try. Then you can just retest.

Of course, wait to see that it goes down. My colleague found that he was able to get his level down to five nanomoles. So, if you remember the highest survival was at less than nine, he was able to get it down to five.

Once you test your homocysteine levels and everything's good, you still want to go ahead and test your iron stores. If you have extra iron, then that's going to create oxidative stress, which has been shown to decrease DNA methylation. It's been shown to decrease methylation in general. It's going to put a tremendous strain on methylation metabolism, and so what you want to do is to make sure your patients have low-normal levels of iron. Not high. Not too low. Hopefully, on the lower side of the normal range.

Now, if their levels are too high, what are you going to do? Well, I understand from my friends in the animal industry who have been studying this that it's very hard to get rid of high iron. Most of the researchers who study iron metabolism have taken to donating blood. Donating blood seems to be one of the best ways of lowering iron stores. Of course, it helps a lot of people at the same time.

If their iron is low, then they can take an iron supplement. Typically, men are going to be more of a concern with high iron than women, especially premenopausal women.

So, now you've got iron stores under control. You've got homocysteine down, you're washing your hands a lot, and you've got immunological stress down. You're taking supplements and protein, eating better, and everything's fine. That is when you're doing the best job possible.

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