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## REPORT

### METHYLATION A LITTLE-KNOWN BUT ESSENTIAL PROCESS

Most people never heard of methylation, but without it we'd all be dead. Why is this little-known process causing such a stir?  
By Terri Mitchell

The 1980s were the decade of the antioxidant. Put on the map by Durk Pearson and Sandy Shaw in their book *Life Extension*, antioxidants became the darlings of science. Durk and Sandy used images of Jell-O and windshield wipers to convey the health risks associated with free radicals. It worked. America listened, and 16 years later vitamin E is as common as table salt in many homes.

Durk and Sandy didn't go far to unearth the antioxidant craze. It came straight from the pages of a chemistry book. Most people don't understand the ins and outs of free radicals, but they do understand the antidote: antioxidants.

The latest health breakthrough (methylation) also comes from chemistry. Like oxidation, methylation is a biochemical process best known to editors of 400-page textbooks. But methylation has potential for health and longevity that far exceeds its chemistry beginnings.

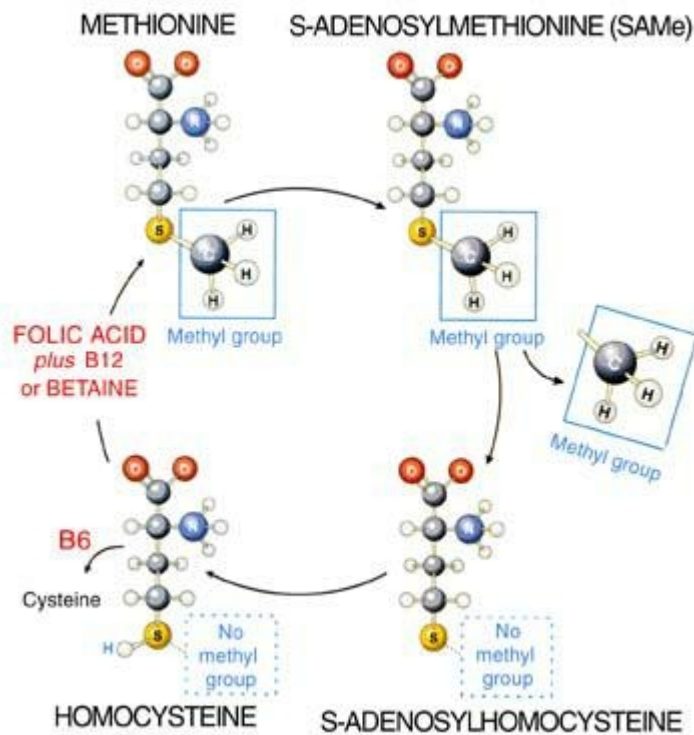
It is apparent that methylation enhancement plus antioxidants are going to give far greater benefits than antioxidants alone. Not surprisingly, methylation is blazing through scientific journals like wildfire.

In a general sense, methylation is a biochemical event that provokes changes in the body. Technically, methylation is the transfer of a "methyl group" composed of one atom of carbon and three atoms of hydrogen (CH<sub>3</sub>) to another molecule. While this doesn't sound exciting, the end result can be. Carbon is in every organic substance on earth, and when carbon atoms hop around, things happen. To understand methylation, think of the human body as a car. Methylation is the spark plug. Without it, everything stops. Methylation is a mover and shaker. It causes guanidinoacetic acid, for example, to become creatine (high energy). It makes adrenaline from norepinephrine, and melatonin from serotonin. It is crucial for the transcription of DNA, and other entities.

All methylation reactions in the body (except one) require an active form of the amino acid methionine called S-adenosylmethionine (SAME or AdoMet). The only methylation reaction that doesn't require SAME is the conversion of its own by-product back to methionine. SAME is created in the body from the interaction of methionine with ATP. Once SAME is created, important things happen.

- For years we've been hearing that free radicals damage DNA and cause cancer; now we know why.

Scientists are aware that chemicals create free radicals that cause cancer. Scientists also know that cancer cells have abnormal methylation. The connection between abnormal methylation and free radicals was put together when researchers at Northwestern University showed that if you oxidize a little section of DNA, it causes abnormal methylation. Free radicals attach themselves to nucleic acids and alter methylation.



Methylation is a biochemical process that starts with methionine. When methionine reacts with ATP, SAME is formed. SAME contains the "methyl groups" (CH<sub>3</sub>) necessary for methylation. In methylation, these groups break off from SAME to catalyze other reactions. The leftover product eventually becomes homocysteine, which can be toxic if not converted. B vitamins are necessary for the conversion of homocysteine. Homocysteine can also be converted by betaine, a product of choline.

When this occurs, abnormal activation and deactivation of genes occur. The result is turned-on cancer genes and turned-off normal genes. This finding has major implications for aging as well as cancer since DNA damage occurs naturally with age.

- Free radicals do most of their damage by inhibiting methylation. Maintaining and enhancing methylation is the next therapy for aging and disease, including cancer and heart disease.

Researchers from all over the world met last summer in closed-door sessions to discuss methylation and cancer. Since then, several articles have been published on "CpG islands," areas in DNA that are abnormally methylated in cancer. We're going to be hearing a lot about CpG islands in the future. Methylation acts as a check on cancer genes. When methylation is deficient, good genes get turned off and bad genes in these islands turn on.

Researchers recently reported that a gene associated with breast cancer is turned off due to abnormal methylation in CpG. Another group reported that the gene activates the tumor suppressor p53. The result? Cancer. And earlier this year, researchers at Sloan-Kettering reported that one of the gene functions is to repair DNA.

Free radical damage can be reversed with methylating factors. "SAME is not an antioxidant, but its role as the primary methylating substance in the body gives it unique power to reverse damage to methylation patterns caused by free radicals. member: free radicals alter methylation patterns, and it's those alterations that turn on cancer genes.

The process has been well-documented in liver cancer. Free radical damage occurs first, then cirrhosis, then cancer. SAME, or methylating factors that increase SAME, can reverse the process. SAME's ability to reverse cancer in animals has been shown. According to a study published in *Cancer Letters*, "SAM...caused inhibition of enzyme altered foci growth (early cancer), recovery of SAM/SAH (homocysteine) ratio and DNA methylation, and decreased protooncogene (cancer gene) expression proportional to the dose and length of treatment."

Caveat: Do not take SAME or methylating factors if you already have cancer. The above study was done on animals, and pertains only to liver cancer. While it appears certain that methylation-enhancement will prevent cancer from starting, and while it looks very promising in liver cancer, not enough research has been done to show what happens when methylation-enhancing factors are taken during cancer. Most cancers are methionine-dependent. Patients with cancer should never take supplemental methionine.

## Methylation and Homocysteine

SAMe is created in the body from methionine and ATP. When SAMe is used for methylation, a chemical reaction occurs where a methyl group is lost, and a by-product is created. This by-product is homocysteine. Homocysteine has gotten a lot of press recently as a culprit in heart attack and stroke. But homocysteine is not a bad thing in and of itself. Only when it's allowed to accumulate does it start trouble.

If things are going as they're supposed to, homocysteine is converted to glutathione, a natural antioxidant, or back to methionine. If not converted, homocysteine can inhibit methylation.

Elevated homocysteine causes lipid peroxidation and sticky platelets, both of which are associated with oxidation. It has been recently discovered that pigs with elevated homocysteine have abnormally high iron levels in heart muscle. Iron promotes free radical formation.

Free radicals are not all bad. The body generates them for certain things. Surprising new research shows that homocysteine may help the immune system create the free radicals it uses to fight off invaders. Apparently, a gene that provokes the death of defective cells (apoptosis) begins the "destruct" process by increasing levels of homocysteine.

There is some evidence that oxidative stress may impede methylation, and anything that reduces oxidative stress may enhance methylation. Researchers in Italy found that free radicals greatly reduce the synthesis of proteins, including lipoproteins. They attribute the decreased synthesis to under-methylation. Methylation is critical for protein synthesis, including the synthesis of lipoproteins such as cholesterol.

## Vitamins Lower Homocysteine

The natural detoxification of homocysteine can happen only if enough B-vitamins are present. In order to convert homocysteine to glutathione, sufficient vitamin B6 must be present. In order to convert it to methionine, there must be enough folate and vitamin B12. These vitamins, along with TMG (trimethylglycine) which can also lower homocysteine, are called "methylating factors" because they increase SAMe and enhance methylation.

Unfortunately, the American fast-food, meat-based diet is rich in methionine (meat) and poor in B vitamins (vegetables). The best sources of vitamin B6 and folate are unfrozen, uncanned vegetables and grains. Without the crucial B vitamins, homocysteine becomes a problem. High doses of certain vitamins decrease homocysteine by as much as 55 percent, according to a recent study published in *Arteriosclerosis, Thrombosis and Vascular Biology*.

## Methylation Deficiencies

A person can't go out and have his or her methylation measured. But the effects of under-methylation can be seen as premature aging, cancer, heart disease, liver disease and other chronic illness, depression and birth defects.

Just as the body can become depleted of antioxidants, it can become methylation-depleted. Since SAMe is the number-one methylation substance, anything that depletes SAMe lowers methylation. Anything that interferes with the synthesis of ATP (such as alcohol) will deplete SAMe, as will aging. Lack of vitamins B6, B12 and folic acid will eventually deplete SAMe, and so will unusual demand.

Aging decreases SAMe. As with free radicals, once under-methylation begins, it can snowball into a monster. All sorts of bad things can happen, from broken DNA to cancer, which brings up an important point.

## Multiple Effects: Fact or Fiction?

One of the criticisms of the supplement industry is that it claims that some products can be used to treat multiple conditions. It doesn't make sense. How can something that's good for the liver also be good for the heart? It can. When a product affects a fundamental process of the body, that product can have different effects, depending on who is taking it and what they're taking it for.

Brain cells depend on methylation as surely as liver cells. A product that enhances methylation can be used to treat methylation-related diseases whether they occur in the brain or the liver.

In the pharmaceutical world this doesn't happen often. Drugs are pretty much disease-specific; it wouldn't make sense to take a liver medication to treat a heart attack. Americans are so steeped in the drug culture that they don't realize at first that the concept of "one substance, one cure" comes from the pharmaceutical industry, not science. One substance can be therapy for different diseases. Just as antioxidants are taken for everything from baldness to cataracts, methylation-enhancers provide multiple health benefits.

## How To Enhance Methylation

Restoring SAmE is the key to enhancing methylation. There are several ways of elevating SAmE. Taking SAmE itself will increase SAmE levels. Taking the vitamins known to convert homocysteine into SAmE (vitamin B12 and folate) will elevate SAmE. Or taking anhydrous betaine-TMG-will elevate SAmE.

The best strategy is to take all of the methyl-enhancers, since studies show that what works for one person may not work for another. Vitamin B6 should also be taken for the detoxification of homocysteine (but be careful; chronic doses over 500 mg a day can cause toxicity).

Science has only begun to uncover the potential of methylation in health and longevity. But it is already well established that methyl-enhanced diets provide health benefits, including the prevention of cancer. Methyl-enhancement reverses the effects of chemical carcinogens. People in modern society encounter numerous carcinogens throughout the day in food, water and air. A simple shower exposes one to significant amounts of cancer-causing chemicals that are readily absorbed through the skin. Environmental carcinogens inhibit methylation and increase one's cancer risk. Age decreases methylation and increases cancer risk.

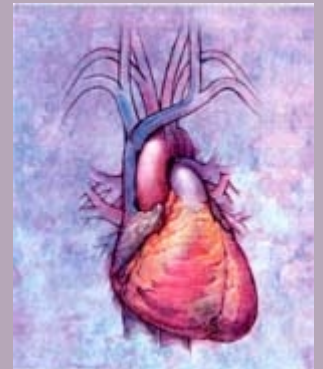
The health-conscious, longevity-minded person cannot ignore methylation. It is the next wave of health science. Methylation affects free radical status, and vice versa. Enhancing one without the other is like eating half the cake. Data show that methyl enhancers may take their place alongside antioxidants as important health and longevity enhancers.

For more information about methylation, see the book *Stop Homocysteine Through The Methylation Process*, by Paul Frankel, Ph.D. and Fred Madsen, Ph.D., \$10.95, available from the Life Extension Foundation. Call toll-free 1-800-544-4440.

### Increasing Methylation

The key to better methylation is SAmE. When SAmE is increased, methylation increases. The following supplements will elevate SAmE:

1. SAmE. Taking SAmE itself is a sure way of increasing SAmE. A good way to cut the expense of SAmE is to use the less-expensive supplements listed below to boost SAmE.
2. TMG (trimethylglycine), also known as betaine. This substance is manufactured from sugar beets. It is not the same as betaine HCL (betaine hydrochloride), which is too acidic to take in adequate doses to elevate SAmE.
3. Vitamins B6, B12 and folic acid (folate). While any one of these, or TMG, may increase SAmE by itself, it is not known which people will respond to which vitamin. In order to ensure that SAmE is increased, all of them should be taken.
4. In addition to the above, research in animals has shown that the following may enhance the body's ability to create SAmE: zinc, selenium, vitamin E and fish oil.



This information is not intended to replace the attention or advice of a physician or other health care professional. Anyone who wishes to embark on any dietary, drug, exercise, or other life style change intended to prevent or treat a specific disease or condition should first consult with and seek clearance from a qualified health care professional.

## Further Reading

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