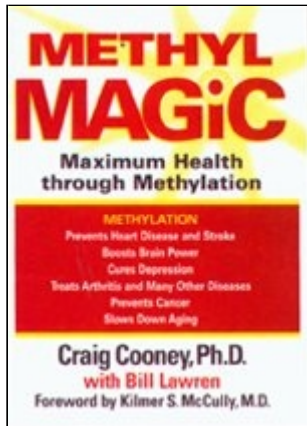


LE Magazine September 1999

REVIEW



Methylation
Equals Life

A review of Methyl Magic:
Maximum Health Through Methylation
by Craig Cooney, PhD with Bill Lawren
by Ivy Greenwell

Methylation is a major and fundamental determinant of health and sickness, or life and death. Like a car out of gas, life without methyl power comes to a screeching halt," Craig Cooney asserts. It is indeed awesome to ponder how the seemingly simple process of methylation-the transfer of methyl groups (CH₃) among various compounds in our bodies-is critical for our health, longevity, and our sense of well-being. Cooney's book is the long-awaited popular source that explains how methylation works, how we gradually run out of "methyl power" as we age, and how

we can enhance methylation and thus enjoy better health and possibly even extend our life span.

S-adenosylmethionine (SAME), a metabolite of the sulfur-bearing amino acid methionine, is the chief donor of methyl groups. The book calls SAME "the philanthropist in the methylation process, the Daddy Warbucks of methylation." Every cell in the body uses SAME. But if you feel you can't afford SAME, do not despair. There are plenty of inexpensive methyl supplements that effectively raise the levels of SAME. It is in fact those supplements that are the focus of Cooney's book.

The importance of supplementation

Cooney strongly believes that we cannot maintain sufficient methylation without supplements. He states that "diet alone won't supply enough methyl groups to prevent declines in DNA methylation and thus slow aging and prevent or at least postpone age-related diseases."

Why do we lose methyl groups as we age? No one knows the definitive answer, but it may have to do with built-in metabolic defects. We could produce a car engine that would last much longer than current engines, but it would also cost a lot more to produce. Likewise, nature too could no doubt provide for more efficient methylation that would promote longer survival-but at a cost in resources that could instead be used for successful early reproduction.

The mechanism of evolution tends to select for reproductive success rather than longevity, per se. Thus we have evolved sufficient rather than optimal methylation. Our methylation works well enough for reproductive success when we are young, but not for a life span much beyond 100 years. One of the "cruel" principles in biology is "When reproduction is finished, the animal is finished." Being human, however, we have other values, and dream of the fulfillment that could come with true "golden years" in the second half of life. Those are the years that seem ideally suited for greater creativity, productivity and enjoyment, providing we stay healthy and vigorous.

Besides the built-in genetic methylation deficiency, part of the problem lies in the fact that the diet we have evolved to eat does not indeed supply sufficient methyl groups for long postreproductive survival. Fortunately we have also evolved a marvelous brain that allows us to come up with solutions designed to bypass these genetic and dietary limitations. Cooney's book is a primer showing us how it can be done.

Cardiovascular health

According to Cooney, "high homocysteine is now widely recognized by scientists to be the greatest single biochemical risk factor for heart disease." Cooney estimates that homocysteine may be responsible for as much as 90% of cardiovascular disease. Cholesterol does not correlate with the risk of heart disease until it reaches levels above 240. In Cooney's view, however, even so-called "normal" homocysteine levels cause heart disease. In order to obtain protection against cardiovascular disorders, we need to keep homocysteine as low as possible, probably in the 4 - 6 micromolar range.

One of the most interesting findings discussed in the book is that in animal studies, "methyl-deficient/ methionine-excessive diets were more likely to produce vascular disease than high-fat diets." Low homocysteine, on the other hand, correlates with clean arteries. People with Down's syndrome, for instance, have very low homocysteine and also much less cardiovascular disease.

Likewise, homocysteine is a risk factor for high blood pressure and stroke. It also plays a role in osteoporosis, and may be involved in diabetes and kidney failure. It seems likely that it is involved in all major degenerative disorders. But we are in luck. As Cooney states, "the fortunate truth is that homocysteine levels are easy to control."

It is interesting that in countries with "heart-healthy" diets, such as Spain, France and Japan, homocysteine levels tend to be much lower (7 - 8 micromolar) than in countries such as Finland or the U.S., where homocysteine averages above 10. In fact, the U.S. average is already close to 10 in people still in their 20s, and much higher in older populations.

Interestingly, pregnant women have the lowest homocysteine levels, followed by non-pregnant premenopausal women. Homocysteine goes up after menopause. This implies a strong relationship between the so-called female hormones and methylation. It appears that both estrogens and progesterone lower homocysteine. Recently, it has been discovered that raloxifene lowers homocysteine as well. There are also indications that methylation becomes less efficient during the premenstrual week, when both estradiol and progesterone drop sharply. Hence methyl supplements hold out a promise of improving PMS symptoms.

Above all, the evidence that hormone replacement therapy lowers homocysteine and thus improves women's methylation status is another important reason for encouraging postmenopausal women to use hormones. Cooney warns, however, that women should take methyl supplements together with their supplemental hormones. For one thing, safe estrogen metabolism depends on efficient methylation, and diet alone does not supply enough methyl groups. Women taking oral contraceptives likewise need more methyl supplements, particularly vitamin B6.

Cancer

In a fascinating chapter, Cooney shows just how complex the process of methylation can really be. What we see in cancer is both hypomethylation and hypermethylation.

Methylation regulates gene expression. It "silences" those genes that are not needed by a particular cell. An enzyme called DNA methyltransferase detaches methyl groups from SAMe and transfers them to various parts of DNA. This enzyme also preserves the methylation pattern from one cell generation to the next.

Cancer is chiefly a disease of aging, so it is not surprising that the decreased methylation and higher homocysteine seen in the elderly correlate with increased incidence of cancer. Animal studies showed that low methylation is associated with more breakage in DNA strands, including the area bearing the cancer-suppressing gene known as p53. Also, as cancer progresses, methylation decreases at each stage, switching on more of the cancer-promoting "oncogenes." At the same time, some DNA sequences (the tumor-suppressor genes) in the cancer cells become hypermethylated and thus silenced. Consequently, it is more correct to speak of abnormal methylation in cancer, rather than low methylation.

Can methyl supplements prevent cancer? So far we know that supplementation with SAMe helps protect rats from liver cancer. In humans, folic acid appears to offer a high degree of protection against colon cancer and cervical cancer (the folate has to come from supplements rather than diet in order to be effective). An eye-opening study by Bruce Ames showed that when people who were folate-deficient were supplemented with 5mg of folic acid for eight weeks, they showed 20 times less DNA damage. Those who had normal folate levels at the start of the study showed three times less DNA damage in response to high folate supplementation.

The high dose of folate used in this study makes one wonder about the RDA. How much cancer, heart disease and Alzheimer's disease could be prevented if it were easy for people to take a few milligrams of folic acid, without the current restriction to 800 mcg per capsule?

Can folic acid be used in the treatment of cancer? The issue is unfortunately complicated. There is more to the metabolism of folic acid than improving methylation and lowering homocysteine and DNA damage. But more knowledge should bring us closer to victory over cancer, which according to predictions will soon become the number one killer, ahead of heart disease. "If one could control the folate cycles that the body uses both to make methyl groups and to manufacture the 'building blocks' for DNA, then control of cell growth should follow," Cooney asserts.

Cooney is of course cautious enough to warn that we do not have enough knowledge to recommend methyl supplements to those who already have cancer. We need a lot more research into this area. One promising supplement is choline. Besides its function in methylation, it also regulates chemical signaling in cell membranes. In animal studies, folic acid has already been shown to enhance the effectiveness of chemotherapy while reducing its side effects. Ultimately, Cooney foresees cancer treatment that consists of severe modification of the diet and selective chemotherapy combined with methylating agents.

Methylation and the Brain

The brain seems almost insatiable in its demand for both SAMe and choline. Whether it's the production of neurotransmitters or the maintenance of the myelin sheath around nerves fibers, SAMe plays a crucial role.

The best-known therapeutic role of SAMe is as an effective antidepressant. SAMe has been found to be more effective than imipramine, for instance. The fascinating finding was that those patients on imipramine who showed the greatest improvement also showed a rise in SAMe levels.

Folic acid (more often referred to as "folate") has also been found to be an effective antidepressant. Interestingly, lack of response to Prozac seems to go hand in hand with low folate levels. TMG likewise seems promising as an antidepressant. Altogether it is high time for more research into the connection between depression and deficient methylation, and the effectiveness of various methyl supplements as antidepressants (though one can easily imagine the dismay of drug companies if people started using something as cheap as folic acid, B12, and TMG instead of Prozac).

Because SAMe is also involved in the clearance of excess serotonin and dopamine, two chief mood regulators, it is likely to be involved in schizophrenia and the manic-depressive disorder. While we do not yet have data on SAMe as a possible adjuvant treatment for schizophrenia, we know that schizophrenics have elevated homocysteine, and that their symptoms significantly improve when they are treated with methylfolate (an active form of folic acid). It is also interesting that schizophrenia has a male prevalence, since estradiol is known to activate certain methylating enzymes in the brain, and also to alleviate schizophrenic symptoms.

The manic depressive disorder presents a more complicated case, since the use of SAMe may shift the balance toward manic elation. Hence SAMe is recommended only for unipolar melancholic depression, and not for the bipolar disorders.

Alzheimer's disease is also associated with high homocysteine and low levels of folate and B12, as well as low levels of SAMe in the brain. Improved methylation is probably one crucial way we can protect ourselves against devastating brain diseases. In view of the brain's insatiable appetite for both SAMe and choline, it would be fascinating to see if the combined treatment with these two nutrients (perhaps substitute CDP-choline for ordinary choline) could prevent, delay or at least slow down the progression of Alzheimer's disease.

Cooney also points out that multiple sclerosis (MS) has symptoms that resemble those of folate or B12 deficiency. Since methylation is essential for the formation of the myelin sheath that insulates nerve fibers, he suggests that a combination of methyl supplements and anti-inflammatory fatty acids be used for the treatment of this disease. (Again, we know that steroid hormones are also very important. The recent findings on the role of progesterone are particularly encouraging.)

How about arthritis?

The discovery of the benefits of increased methylation for osteoarthritis was due to a happy accident. SAMe was being tested in an Italian study of its usefulness against depression. Some of the depressed patients also happened to have arthritis. These patients experienced an improvement not only in their mood, but also in their joint pain. SAMe was found to be as effective as NSAIDs (non-steroidal anti-inflammatory drugs) such as ibuprofen, without ibuprofen's disastrous side effects. It's not only that nonselective NSAIDs such as ibuprofen and indomethacin can cause ulcers and the leaky gut syndrome. They actually inhibit the formation of new cartilage. Ultimately they make arthritis worse, and the pain less responsive to painkillers. The current mainstream treatment of osteoarthritis is a devil's bargain: in the end the cure is worse than the disease.

One of the pathological aspects of arthritis is the shrinking in the molecular size of proteoglycans-the building blocks of cartilage-and hence a deterioration in the capacity of cartilage to act as a shock absorber. We now know that SAMe improves the quality of cartilage by increasing the size of proteoglycans.

Since glucosamine sulfate has also been found helpful in arthritis, Cooney suggests that the treatment of arthritis should include either SAMe or SAMe-increasing methylating agents in combination with glucosamine sulfate.

Cooney, however, does not cite the study that found the effectiveness of folic acid and vitamin B6 in osteoarthritis. This confirms his hypothesis that methyl donors are indeed helpful against the most common type of arthritis. Animal studies have also shown greater thickness and density of cartilage in SAMe-supplemented animals, with higher concentration of proteoglycans (possibly thanks to a greater activation of the polyamine pathway, leading to more protein synthesis).

Other studies have shown that SAMe counteracts the effects of inflammatory cytokines such as the tumor necrosis factor (TNF), inhibits the enzymes that destroy cartilage, and probably increases glutathione levels in the damaged joint. In vitro (meaning in cell colonies outside the body), SAMe also increases the number of cartilage cells (chondrocytes). Finally, SAMe reduces

homocysteine, which results in better blood circulation and other anti-arthritis effects.

In sharp contrast to NSAIDs, the benefits of SAME for joint health increase over time. Also in contrast to NSAIDs, SAME protects the liver, kidneys and the gastrointestinal tract while it helps build healthier cartilage.

Rheumatoid arthritis (RA) is a more severe form of arthritis, with a much more pronounced auto-immune component. It has indeed been found that the T-cells of RA-sufferers have lower DNA methylation. Patients with rheumatoid arthritis also tend to have higher homocysteine, and lower levels of vitamin B6. The implications are clear, although studies on the efficacy of methylating agents in RA are yet to be done. We do, however, have one very promising Italian study showing the benefits of SAME in the treatment of fibromyalgia, which some experts regard as having an autoimmune component and being related to arthritis.

Millions of older people suffer from osteoarthritis and other arthritis-related conditions. The estimated yearly cost of these diseases is \$50 billion. According to various studies, it takes mega-doses of methylating agents such as folic acid, as well as mega-doses of glucosamine and chondroitin sulfate, to effectively combat osteoarthritis. It also helps enormously to be taking proven anti-inflammatories such as vitamin E, fish oil, and grape seed extract. Because of the urgent need to find a non-toxic treatment for these debilitating conditions, a lot more publicity should be given to the efficacy of SAME and SAME-raising methylating agents in improving joint health. Slowly, we're getting there.

Natural hormone replacement is also tremendously important for preserving youthful cartilage production. Here again it is too bad that Cooney does not discuss in more detail the role of methylation in estrogen metabolism. It turns out that one of the estrogen metabolites, methoxyestradiol, appears to protect cartilage, besides providing the wonderful bonus of breast cancer prevention. All arthritis-related disorders have a huge female predominance, with osteoarthritis being primarily postmenopausal. Women especially need to know about the joint-protective role of estrogen, when it is taken more safely, with sufficient antioxidants (to make sure estrogen is regenerated to its antioxidant form) and methylating agents, to ensure sufficient production of the methylated varieties.

The aging process

This is the most fascinating chapter in the whole book. There is strong evidence for the theory that impaired methylation is one of the key mechanisms of aging. Just as long-lived animals have strong antioxidant defenses, so too can they maintain methylation much better than short-lived animals. The big question of course is whether enhancing methylation and lowering homocysteine can extend life span.

Cooney presents a curve showing the inexorable rise in homocysteine with aging. The peripheral blood vessels start clogging up first, and eventually we seem doomed to end up with homocysteine-related damage to blood vessels, the nervous system, bone density and so forth-the very changes that define aging. "It could be that homocysteine is one thing that limits our life span to the often assumed limit of 120 years," Cooney states.

Even the development of cataracts is related to rising levels of homocysteine, and thus inadequate methylation. When the lens proteins are damaged, a special enzyme uses SAME to methylate them and repair them. Even hair graying seems to have something to do with deficient methylation! It would be fascinating to see if correct methyl supplementation (together with the avoidance of obesity; obesity goes hand in hand with higher homocysteine) would prevent such "inevitable" developments of aging as cataracts and gray hair. And if you are wondering if it is possible to lower homocysteine levels in the elderly, the answer is a resounding yes. Cooney quotes a study that showed elderly subjects supplemented with folic acid, B12 and B6 ended up with homocysteine levels lower than those usually seen in healthy 35-year-olds.

Most important, however, might be the prevention of depression. Depression doesn't just lower the quality of life. It is also a major risk factor for heart disease and cancer, and even osteoporosis. Depression in the elderly is endemic, and one can certainly point to various social and cultural factors besides the deteriorating neurochemistry. While no one is suggesting that simply taking SAME or megadoses of folic acid and TMG would be the end of all depressive illness, methyl supplements could indeed make a terrific difference. If, in addition to preventing and alleviating depression, these supplements could also at least delay Alzheimer's disease, old age would look very different than now. Perhaps we could even speak about the "golden years" and mean it.

Our great good luck is that it is easy to lower homocysteine levels and enhance methylation. The ideal of aging as maturation rather than ever-accelerating mental and physical deterioration does seem within reach. Here, the phrase "methyl magic" certainly applies.

Actually the slowing down of aging might start already in the womb-with the mother's methylation status. Fertile women might be very interested in how maternal methyl supplements affect the health and longevity of their offspring. Cooney does try his best to provide guidance for pregnant women. The issue is obviously of prime importance. Let us hope that it receives more research emphasis.

The book's strengths, weaknesses

One of the disappointments of this book is that Cooney pays little attention to the role of hormones in methylation. He duly notes gender differences: premenopausal women and women on hormone replacement have lower levels of homocysteine-pregnant women have the lowest levels-than men, but men have higher levels of SAME. Yet he doesn't go on to discuss those fascinating findings. Some studies indicate that hormones have a considerable impact on methylation. Testosterone, for instance, appears to increase the activity of the enzyme SAME-synthase, thus raising the levels of SAME. In turn, it seems that SAME increases testosterone production. And all women need to know that efficient methylation is crucial for safe estrogen metabolism, and that elevated homocysteine inhibits this process.

But the book's greatest drawback is the lack of an extensive discussion of SAME. This supreme methylator, the biochemical superstar whose importance has been compared to that of ATP, our energy molecule, is quickly summarized in three pages, with cursory statements such as, "SAME is a major player in the synthesis of acetylcholine, one of the most important neurotransmitters," or, "SAME also plays an important part in the metabolism of estrogen." The fact that SAME may thus help prevent Alzheimer's disease and breast cancer is of tremendous interest to women readers. I think many women would be more motivated to take either SAME or other less expensive methyl supplements if they could learn in more detail about these matters, and would appreciate such information a lot more than the pages devoted to recipes. Educated women would likely prefer learning more about SAME.

Then there is the publisher's pressure to keep the book as popular as possible. Hence, the "magic" in the title and the constant use of the phrase "methyl magic supplements" rather than simply "methyl supplements." There are also the superfluous metaphors such as the Mickey Mouse cap that is supposed to make us visualize the methyl group (but wouldn't that require three ears?), and the strive toward a chatty style that maintains a precarious balance between solid factual writing and "biochemistry for dummies." But these are minor complaints, considering that when the book does discuss a topic in depth, it becomes fascinating.

Cooney's honesty in stating that we do not know the optimal doses for the various supplements is appreciated. (Editor's note: The Life Extension Foundation has discovered that individual testing of serum homocysteine is the only way of optimizing a supplement program.) Nor do we know how much folate, B12 and TMG to take for antidepressant effects that might be equivalent to those of taking an antidepressant dose of SAME. He is also careful to state precautions about taking methyl supplements in conditions such as Parkinson's disease or epilepsy.

The cover states: "Methylation prevents heart disease and stroke, boosts brain power, cures depression, treats arthritis and many other diseases, prevents cancer, slows down aging." Craig Cooney does a fine job of documenting these claims. He has expanded our knowledge of the aging process to include gradual loss of methylation. Even better, he also tells us how to enhance methylation. Altogether, the wealth of quality information in *Methyl Magic* is outstanding. It is an excellent book for anyone interested in health and longevity.

Continuation of Article Diet, Supplements, Exercise and Sauna

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