



Each Tablet Contains: Niacin (as niacinamide) 20 mg, Folate (as L-5-Methyltetrahydrofolate) 500 mcg, Vitamin B-12 (as methylcobalamin) 500 mcg, Biotin 2000 mcg. Proprietary blend 415 mg* of: Sulforaphane (as broccoli sprout ext.), N-Acetyl Cysteine, Phosphatidyl Choline, Green Tea Catechin, S-Adenosyl Methionine (SAME), Curcumin, Intrinsic Factor, Pyridoxal-5-Phosphate.

Supportive Function: One of the most important reactions in the body for producing bioactive compounds is methylation. At least half of the population carries a gene polymorphism that impairs the ability to methylate. Methyl Renew contains active folate (5 MTHF) and other synergistic nutrients that optimize the methylation process.

When is Methyl Renew helpful? Methylation is important for maintaining and accelerating many pathways, especially brain neurotransmitters, hormones, detoxification, DNA synthesis, immune system activity and joint health. Also promotes healthy cells and is necessary for gene expression, gene repair, chromosome stability and embryonic development.

Clinical Applications/Research: **Methylation** is one of the most important biochemical reactions in the entire body. Methyl groups (one-carbon molecules) can be added to inactive compounds and thereby biologically activate them. This process, called methylation, is extremely important for maintaining and accelerating many pathways, especially brain neurotransmitters, hormones, detoxification, DNA synthesis, immune system activity and joint health. Methylation promotes healthy cells and regulates the expression of genes.

An alarming fact is that the majority of people are lacking in optimal methylation, and this could be putting them at a disadvantage for coping with daily insults to the body. At least 50% of people carry what's called a gene polymorphism (variant) that predisposes them to insufficient methylation. This gene polymorphism is a mutation of MTHFR and if present (and activated), it will result in the decreased ability to methylate and an "increased risk for the development of cardiovascular disease, Alzheimers, depression in adults, and of neural tube defects in the fetus [and more]" (Trimmer EE. Methylenetetrahydrofolate Reductase: Biochemical Characterization and Medical Significance, *Curr Pharm Des* 2012 Oct 31). This polymorphism is associated with elevated homocysteine (linked to over 100 medical conditions).

DNA Methylation is necessary for many essential functions, including gene expression, gene repair, chromosome stability and embryonic development. Inability to methylate DNA will create a host of problems. DNA methylation research has exposed the fascinating potential we possess for potential modification to the sequence of DNA we inherited. "Specifically, there is new evidence to suggest that the balance between growth promoting (oncogenes) and growth suppressor (tumor suppressor) genes is altered by inappropriate methylation (www.methylation.net Jan 2013).

Epigenetic regulation, which includes changes in DNA methylation and alteration in microRNA expression without any change in the DNA sequence, "constitutes an important mechanism by which **dietary components can selectively activate or inactivate gene expression**" (Simone Reuter et al. Epigenetic changes induced by curcumin and other natural compounds *Genes Nutr.* 2011 May; 6(2): 93-108.)

The Astounding Field of Epigenetics and how Methylation is Key:

Epigenetics refers to functionally relevant environmental modifications to DNA that do not involve a change in the sequence. Epi- comes from the Greek, meaning over or above, so epigenetics is above genetics. In other words, epigenetics describes a way to look at potential changes to our genomic function. There are changes to DNA that happen differently to each individual. Therefore, knowing what is unique about each person is crucial for any protocol. This is known as **“bio-individual medicine.”**

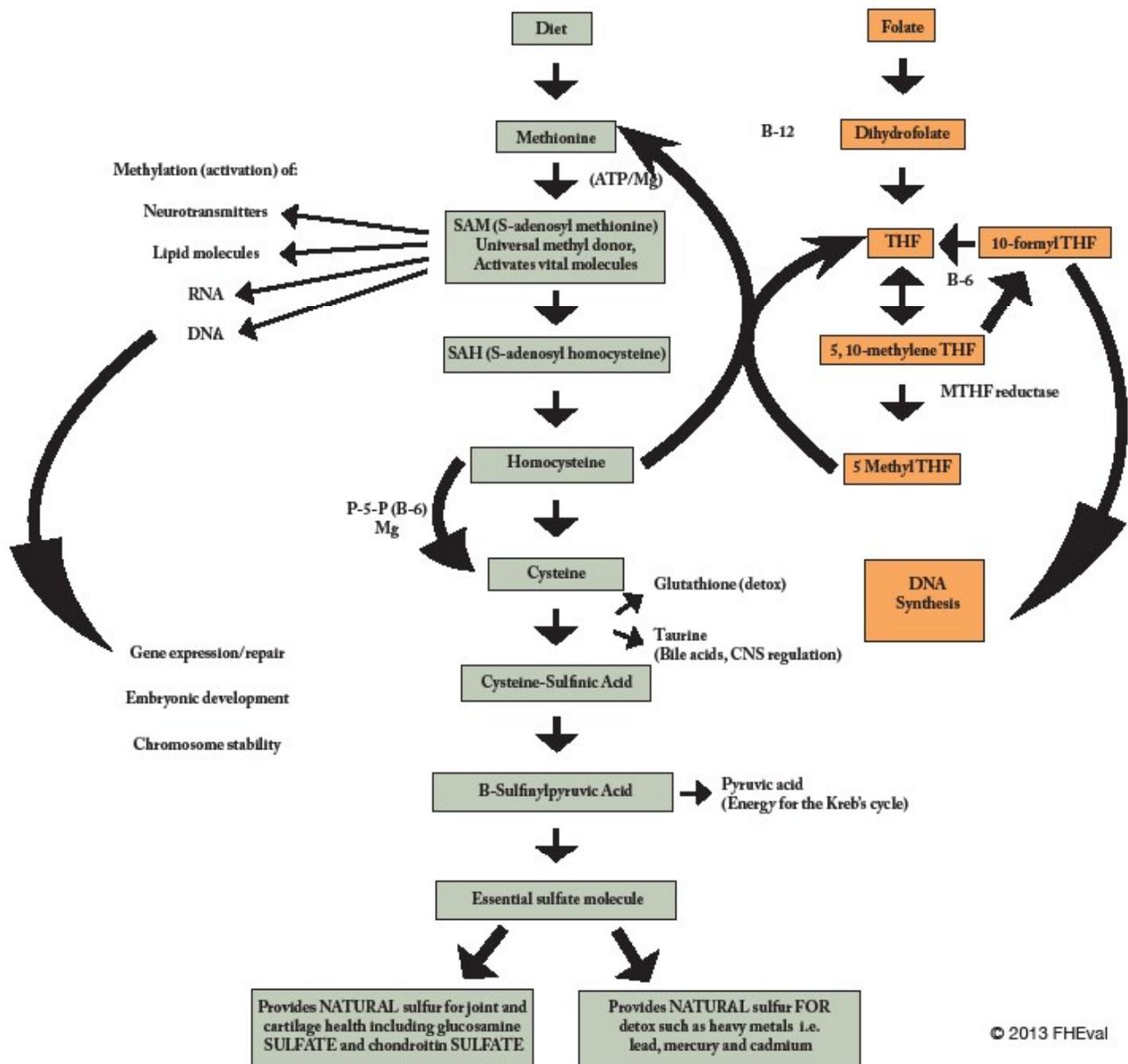
Most disease results from interplay between genetic and environmental factors; some conditions are due more in part to genetics, and some more in part to environmental, while for the vast majority, it is unclear where one comes in the other does not. It is likely that epigenetic factors, i.e., heritable, but often reversible changes to genomic function that are independent of DNA sequence, are also important. It is known that epigenetic processes can be induced following exposure to a range of external factors, and thus provide a mechanism by which the environment can lead to long-term alterations in phenotype. A genotype is the genetic material we inherit from our parents. The phenotype is what we express on a daily basis, and the two are not the same. **“Genotype”** is an organism's full hereditary information. **“Phenotype”** comes from the Greek word “show”, and it refers to an organism's actual observed properties, such as structural features, development, or behavior. But even though genotype can determine phenotype, the relatively new and exciting field of **Epigenetics is demonstrating that environmental factors can change genetic expression.** The best example of an epigenetic relevant modification to DNA is **DNA methylation.**

Synergy is crucial for optimal methylation; the right amounts and the right co-factors of certain nutrients (described below) are extremely important in the equation, especially in terms of facilitating methylation for those in the population suffering from the inability to methylate due to the common gene polymorphism.

L 5-MTHF (methyl tetrahydrofolate):

This is the active form of MTHF and the most biologically active form of folate. As you can see from the diagram, MTHF is responsible for promoting DNA synthesis and for recycling toxic homocysteine back to methionine. This recycling of homocysteine alone facilitates a pathway responsible for: reduction of a toxic substance (homocysteine), provision of sulfur for joint health, production of detoxification enzymes, formation of pyruvate for energy, and the activation of neurotransmitters, some hormones, and gene expression (DNA methylation).

MTHF-R, or MTHF reductase, is an enzyme that plays a key role in folate metabolism and in the homeostasis of the homocysteine pathway. As previously mentioned, MTHF keeps homocysteine cycled back to methionine, and the reaction by which MTHF-R creates MTHF is the only source for MTHF in the body. Mutations in the MTHF-R enzyme are common (at least 50% of the population) and lead to high levels of the toxic homocysteine. High levels of homocysteine are associated with multiple disorders.



Many practitioners encourage all of their patients to test for the MTHFR polymorphisms to know if a greater risk for improper methylation exists, establishing the need for preventive therapeutics to include greater amounts of pre-methylated folate (L-5 MTHF) and other methylation co-factors included in **Methyl Renew**. It is a fairly simple test that can be done through many labs. It is important that the test include both forms of MTHFR alleles C677T and A1298C.

Compared with other forms of folates, 5-methyl tetrahydrofolate is more highly recommended due to the exceptional bioavailability. For instance, researchers noted that it “may represent a preferable treatment option for Major Depressive Disorder (MDD) given its greater bioavailability in patients with the genetic polymorphism” (Papakostas GI. Folates and s-adenosylmethionine for major depressive disorder. *Can J Psychiatry*. 2012 Jul;57(7):406-13.)

According to the report from the Shanghai Breast Cancer Study (n > 2700), since folate is involved in DNA synthesis, repair, and methylation, it is hypothesized that “high intake of folate may reduce the risk of human cancers, including cancer of the breast” (Shrubsole MJ. Et al. Dietary folate intake and breast cancer risk: results from the Shanghai Breast Cancer Study. *Cancer Res*. 2001 Oct 1;61(19):7136-41.) Additionally, they reported that their study “adds additional support to the protective role of dietary folate in breast carcinogenesis and suggests further that the effect of folate may be modified by dietary intake of methionine, vitamin B(12), and vitamin B(6)”, which further supports the idea of synergy with methylating nutrients.

The importance of potential environmental modification of the aberrant gene polymorphism to optimize methylation becomes very apparent in studies such as the one published in the *Journal of Molecular Neuroscience*. Researchers established that both genetic and inflammatory factors are suspected in the etiology of multiple sclerosis (MS), and they also established that of genetic factors, the MTHF-R polymorphism is associated with increased levels of plasma homocysteine, which is toxic to neurons. The researchers recruited 230 healthy and 194 MS patients to test the association between MS and the MTHF-R polymorphism (MS patients have elevated levels of homocysteine). Their conclusion was that the polymorphism was indeed most likely associated with higher levels of inflammatory markers and a vulnerability to an earlier age of onset (Alatab S. et al. Inflammatory profile, age of onset, and the MTHFR polymorphism in patients with multiple sclerosis. *J Mol Neurosci*. 2011 May;44(1):6-11.)

P-5-P, Methyl B-12, Niacin, and Biotin are all synergistic B vitamins that contribute to methylation processes. P-5-P is the activated form of vitamin B-6. B-6 is necessary to bring homocysteine down the pathway to produce glutathione, taurine for bile acids, pyruvate for energy, and sulfur for joint health. It is also necessary in the folate pathway responsible for DNA synthesis and also for recycling homocysteine back to methionine. Methyl B-12 recycles homocysteine to methionine. The power of B-12 to methylate in many areas, including DNA synthesis and immune activity, has been confirmed (Paula Dominguez-Salas Maternal nutritional status, C₁ metabolism and offspring DNA methylation: a review of current evidence in human subjects. *Proc Nutr Soc*. 2012 February.) All of these B vitamins work together in different stages of the methylation processes to optimize the results, which include methylation of neurotransmitters, lipids, DNA, and some hormones. Methylation is needed for many biochemical reactions, including activating DNA for gene expression and repair.

N-Acetyl Cysteine (NAC): NAC is the main precursor to glutathione, the major antioxidant of the body. Administration of N-acetyl cysteine is utilized to raise glutathione levels. As shown in the diagram, B-12 and MTHF methylate homocysteine and recycle it back to methionine; it has been proposed that glutathione is necessary for the synthesis of methyl B-12 and that glutathione is also necessary for the enzyme activity involved in the recycling process. When researchers studied alcohol-induced decreases in that methylation cycle, they discovered that the deleterious effect of the alcohol was secondary to the effects on methylation from decreased glutathione levels and a decreased ability to synthesize glutathione. This greatly emphasizes the importance of glutathione to optimize methylation processes. When glutathione was added, the enzyme (methionine synthase) and thereby the methylation process, was restored to control levels (Waly MI et al. Ethanol lowers glutathione in rat liver and brain and inhibits methionine synthase in a cobalamin-dependent manner. *Alcohol Clin Exp Res*. 2011 Feb;35(2):277-83.)

NAC, Glutathione and Autism/ADHD: Diagnostic criteria for these conditions have traditionally relied solely on behavioral criteria without consideration for a potential biomedical foundation, however, “newer evidence reveals that autism spectrum disorders (ASDs) are associated with: oxidative stress, decreased methylation capacity, **limited production of glutathione**, and mitochondrial dysfunction” (Bradstreet JJ. et al. Biomarker-guided

interventions of clinically relevant conditions associated with autism spectrum disorders and attention deficit hyperactivity disorder. *Altern Med Rev.* 2010 Apr;15(1):15-32.) Bradstreet et al. also note that glutathione is a biomarker that provides “useful guides for selection, efficacy, and sufficiency of biomedical interventions. The use of these biomarkers is of great importance in young children with ADHD or individuals of any age with ASD, because typically they cannot adequately communicate regarding their symptoms”. It is interesting that intestinal dysbiosis, increased toxic metal burden, immune dysregulation (characterized by a unique inflammatory bowel disease and immune activation of neuroglial cells), and ongoing brain hypoperfusion were other suggested biomarkers.

Phosphatidylcholine is an important bioactive lipid. Besides being a bioactive lipid with health benefits in its own right, phosphatidylcholine additionally helps to preserve the status of the main methyl donor, namely SAM-e.

Green Tea Catechins exert their effects on major metabolic pathways that explain some of their health benefits, and those pathways include methylation, glucuronidation, and sulfation (Sang S, et al. The chemistry and biotransformation of tea constituents. *Pharmacol Res.* 2011 Aug;64(2):87-99.) “Cancer-preventive effects of tea polyphenols, especially epigallocatechin-3-gallate (EGCG), have been demonstrated by epidemiological, preclinical, and clinical studies. Green tea polyphenols such as EGCG have the potential to affect multiple biological pathways, including gene expression and growth factor-mediated pathways” (Chen D, et al. EGCG, green tea polyphenols and their synthetic analogs and prodrugs for human cancer prevention and treatment. *Adv Clin Chem.* 2011;53:155-77.)

Accumulating data, such as that published in the journal *Carcinogenesis*, “suggest that dietary phytochemicals may alter cancer risk by modifications of epigenetic processes in the cells”. They investigated whether tea catechins would modify epigenetic events to regulate DNA methylation, and they found that administration of the catechins “resulted in re-expression of the mRNA and proteins of silenced tumor suppressor genes”. In other words they were able to re-activate the suppressor genes. “Together, our study provides new insight into the epigenetic mechanism of action of EGCG (tea catechin) that may contribute to the chemoprevention of skin cancer and may have important implications for epigenetic therapy 4 (Nandakumar V, et al. EGCG reactivates silenced tumor suppressor genes. *Carcinogenesis.* 2011 Apr;32(4):537-44.)

SAM-e supplementation benefits are widespread; methylation affects so many pathways it is not surprising that the research holds so many diverse reports of favorable effects. More than 40 metabolic reactions involve the methyl transfer from SAM-e, a natural substance, to various substrates, such as nucleic acids, proteins, lipids and secondary metabolites. SAM-e supplementation is recommended in addition to 5 MTHF especially for those exhibiting the gene polymorphism that impedes methylation processes. Please see the fact sheet on SAM-e for more detailed info on this powerful nutrient.

Curcumin (diferuloylmethane) is a component of the spice turmeric and has recently been determined to induce epigenetic changes (epigenetic changes include DNA methylation changes without any change in DNA sequence). Scientists claim that this can be an important mechanism “by which dietary components can selectively activate or inactivate gene expression” and furthermore, “The development of curcumin for clinical use as a regulator of epigenetic changes, however, needs further investigation to determine novel and effective chemopreventive strategies, either alone or in combination with other anticancer agents, for improving cancer treatment” (Simone Reuter et al. Epigenetic changes induced by curcumin and other natural compounds *Genes Nutr.* 2011 May; 6(2): 93–108.)

Intrinsic Factor is manufactured in the parietal cells of the stomach and forms a complex with B-12 that allows the B-12 to be absorbed in the small intestine. Vitamin B-12 is not easily absorbed in people with gastrointestinal problems. People with GI problems are at higher risk for B-12 insufficiency and deficiency. There are many types of anemia, but pernicious anemia is an autoimmune condition resulting in a lack of intrinsic factor. That in turn causes a deficiency of B-12 (needed for the DNA synthesis of new red blood cells), and without enough red blood cells to carry oxygen to the body, weakness and fatigue can result. Supplying intrinsic factor can increase the probability of forming the B-12 – intrinsic factor complex so that the B-12 gets absorbed. Many people have intrinsic factor antibodies which make it less likely for B-12 to be absorbed. It may also take decades for B-12 deficiencies to show up as pernicious anemia, making it that much more difficult to detect early and avoid neurological problems. Furthermore, as one ages intrinsic factor production slows, perhaps explaining why many elderly people show signs of B-12 deficiency.

Sulforaphane (SFN), an isothiocyanate derived from cruciferous vegetables, “induces potent anti-proliferative effects in prostate cancer cells. One mechanism that may contribute to the anti-proliferative effects of SFN is the modulation of epigenetic marks, ... the effects of SFN on other common epigenetic marks such as DNA methylation are understudied”. In this study appearing in *Clinical Epigenetics*, scientists investigated the effects of SFN on DNA methylation status because of the role SFN plays in impacting epigenetic pathways. Their results demonstrated the ability of SFN to epigenetically modulate important gene expression, “and provide novel insights into the mechanisms by which SFN may regulate gene expression as a prostate cancer chemopreventive agent” (Hsu A, et al. Promoter de-methylation of cyclin D2 by sulforaphane in prostate cancer cells. *Clin Epigenetics*. 2011;3:3).

Suggested Dosage: 1 tablet daily or as directed

Size: 60 tablets

Vegetarian: Yes

Contraindication: Side effects are uncommon for SAM-e, but occasionally gastrointestinal upset and anxiety can occur (*Can Fam Physician*. 2011 June; 57(6): 659–663.) There are no confirmed drug interactions with SAM-e, but caution is advised with the use of antidepressants, including serotonin re-uptake inhibitors and MAO inhibitors due to potentially enhanced serotonin. Some recommend avoiding SAM-e for individuals with bipolar disorder or manic depression (this is controversial and at least one trial studied those with MDD (manic depressive disorder) (Levkovitz Y, et al. *J Affect Disord*. 2012 Feb;136(3):1174-8.)

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