Methylation Overview for Professionals

Methyl groups are “CH3" groups that are utilized extensively in the body for transport of nutrients in fat soluble states and in epigenetic processes, turning genes on or off. In patients with decreased activity in the methylation pathway, there is a shortage of methyl groups in the body needed to execute a variety of important functions. Additionally, defects in methylation lay the appropriate groundwork for the further assault of environmental and infectious agents resulting in a wide range of conditions including diabetes, cardiovascular disease, thyroid dysfunction, neurological inflammation, diabetes, chronic viral infection, neurotransmitter imbalances, atherosclerosis, cancer, aging, schizophrenia, decreased repair of tissue damage, improper immune function, neural tube defects, Down’s syndrome, Multiple Sclerosis, ADD, ADHD, Huntington’s disease, Parkinson’s disease, Alzheimer’s, and autism. Appropriate supplementation with vitamins and nutrients will bypass these mutations to allow for restored function of the pathway.

The proper functioning of the methylation cycle is essential for a number of critical reactions in the body. Consequences of genetic weaknesses (mutations) in this pathway are increased risk factors leading to a number of serious health conditions. A central pathway in the body that is particularly amenable to bio-molecular genetic weaknesses is the methionine/folate pathway. There are several sites in this pathway where blocks can occur as a result of genetic differences. In general, single biomarkers are identified as indicators for specific disease states. However, it is possible that for a number of health conditions, including autism and other severe neurological syndromes, it may be necessary to look at the entire methylation pathway as “a biomarker” for underlying genetic susceptibility for a disease state. It may require expanding the view of a “biomarker” beyond the restriction of a mutation in a single gene to a mutation somewhere in an entire pathway of interconnected function.

This does not mean that every individual with mutations in this pathway will have one of the health conditions listed above. It may be a necessary element, but there may not be a sufficient environmental or infectious “trigger”. Most health conditions in society today are multifactorial in nature. In essence, there is an underlying genetically determined risk that requires a significant infectious or environmental “trigger” to initiate the process. A certain threshold or body burden needs to be met for each of these factors in order for multifactorial disease to occur. However, part of what makes the methylation cycle so unique and so critical for our health, is that mutations in this pathway have the capability to impair all three of these factors. This would suggest that if an individual has enough mutations or weaknesses in their methylation pathway, it may be sufficient to cause the multifactorial disease by itself, as methylation cycle mutations can lead to chronic infectious diseases, increased environmental toxin burdens and have secondary effects on genetic expression.

The Importance of the Methylation Pathway

New cell synthesis and repair
Mutations in the methylation pathway can cripple the ability of the body to make the building blocks (purines and pyrimidines) needed for new DNA and RNA synthesis. A reduced capacity for new DNA and RNA synthesis means that any new cell synthesis is impaired. For an organism to live, it must create new cells as fast as cells die. This requires that the body make millions of cells every minute, relying on DNA and RNA synthesis.

A reduced synthesis capacity due to methylation cycle mutations is a particular issue for cells that already have difficulties meeting their needs for DNA and RNA synthesis under normal conditions. Particularly susceptible cells include bone marrow, lymphocytes, erythrocytes and neural tissue. Adding a significant methylation issue to the cell synthesis makes it nearly impossible to recover from damage or stress on these tissues. Stress increases the need for nucleotides to overcome negative

effects of hormones released during stressful conditions. Cell repair after injury increases the need for nucleotides. In particular, the nervous system has the highest concentration of RNA in the body, and therefore has the highest requirement of methylation need.

Methylation and Heart Disease

Adequate levels of CoQ10 have been identified as necessary nutrients to help prevent congestive heart failure. Clinically CoQ10 has been used in the treatment of angina, heart failure prevention of reperfusion injury after coronary artery bypass and cardiomyopathy. The synthesis of CoQ10 in the body requires components of the methylation pathway; in particular it requires adequate levels of SAMe that is generated by the methylation cycle. Cholesterol lowering drugs (statin drugs) decrease the level of CoQ10 in the body. It may be particularly important for individuals taking statin drugs to be aware of the methylation status in their body and replenish CoQ10.

In addition, the relationship between elevated homocysteine levels, an increased risk of heart disease and the genetic risk associated with MTHFR C677T mutations in the methylation pathway has been recognized for quite some time. Appropriate supplementation of the methylation pathway should be able to help compensate for this mutation.

Methylation and Energy Production

The mitochondria are the energy producing organelles within each cell. Decreased mitochondrial energy has been implicated in chronic fatigue, fibromyalgia and mitochondrial disease. Coenzyme Q10 is also important for its role in ATP production in the mitochondrial respiratory chain. Again, as mentioned above, methylation pathway function is necessary for the synthesis of CoQ10 in the body. Carnitine is another nutrient produced by the body that is involved in mitochondrial energy production. Mitochondria fatty acid oxidation is the main energy source for heart and skeletal muscle. Carnitine is also involved in the transport of these fatty acids into the mitochondrial matrix. As with CoQ10, the synthesis of carnitine by the body requires methylation pathway function. Synthesis of carnitine begins with the methylation of the amino acid L-lysine by SAM, so once again we have a connection to the methionine/homocysteine pathways.

Another connection between carnitine and the methylation cycle is that an enzyme that is needed for carnitine synthesis is also utilized as part of a secondary route to form methionine from homocysteine. When there are methylation cycle mutations that impair the primary route of synthesis for methionine, this secondary route will be used more heavily.

Methylation and Mood

Folic acid is converted to monoglutamate entites by the enzyme alpha-L-glutamyl transferase in the intestinal wall as they are absorbed. Once absorbed, monoglutamate entities are converted to methylenetetrahydrofolate (MTHF), the fat soluble form of folate that passes into the brain and is utilized by trimonoamine neurons to facilitate neurotransmitter synthesis or dopamine, epinephrine and norepinephrine. Normally, ingesting folate from dihydrofolate in the diet or from folic acid in synthetic supplements will result in adequate delivery of MTHF levels to the brain, especially in those individuals with the more efficient methylation genotype (C677C) producing up to 100% of the enzyme methylene tetrahydrofolate reductase and who do not have depression.

However, in patients with methylation deficiencies, the level of MTHF produced is limited, therefore limiting dopamine production. Thus, administration of folinic acid, has significant advantages over administration of folic acid as a trimonoamine modulator to depressed or anxious patients or depressed patients who do not respond adequately to their antidepressant treatment. These patients may not be folate deficient on standard blood work.

Methylation and ADD

A Methylation Deficiency appears to be the primary abnormality in patients suffering from ADD/ADHD. The methylated form of folic acid (ie methylfolate) is essential in the conversion of tyrosine to dopamine. By genetically limiting the production of methylfolate, the patient secondarily limits the production of dopamine. Low dopamine levels affect focus, concentration, organization, short term memory, vestibulo-visual interaction, sleep patterns, emotional stability and even hormonal regulation. Altered levels of dopamine additionally affect the levels of epinephrine and norepinephrine. Imbalances in this biochemical region, dopamine, epinephrine and norepinephrine are implicated in ADD/ADHD. One can envision that methylation cycle function is needed to produce SAMe as a methyl donor for the dopamine/ norepinephrine / epinephrine pathways to help to recover ADD/ADHD.

Methylation and Myelin

Myelin coating on nerves is important for proper function of those nerves. Methylation of amino acids in myelin basic protein helps to stabilize it against degradation. In animal studies the developmental increase in methylation capacity is correlated with parameters of myelination. Decreased levels of methylation activity in these animal models are related to conditions of demyelination.

Methylation and the Immune System

New T cell synthesis is needed in order for T cell clones to expand and respond properly to an immune assault. T cells are needed to help to control the B cells and to balance TH1 and TH2 responses. If there are methylation cycle problems or mutations, you may have trouble making the bases that are needed for new DNA synthesis. If you cannot make new DNA, then you cannot make new T cells and as a result you may lack immune system regulatory cells.
The immune system has the B cell "arm" that makes antibodies, known as humoral immunity and the T cell "arm" known as cellular immunity. If you are having trouble making new T cells, in particular, T suppressor cells, then the immune response may become more heavily weighted in the direction of B cells. B cell skewed individual has the ability to respond by making antibodies (or autoantibodies) in high numbers to attempt to overcome the T cell deficiency that fights infection. B cell clones expand to be available for the future. This scenario creates a somewhat greater need for new DNA synthesis.

Methylation also plays a role in the ability of the immune system to recognize foreign bodies or antigens that it needs to respond to. Research has shown that methylation is decreased in humans with auto immune conditions. Impaired methylation of T cells may be involved in the production of auto antibodies. Studies from patients with systemic lupus erythrematosis (SLE) have shown that their T cells are undermethylated. As proper methylation function is restored, immune system regulation should slowly recover.

Methylation and Cancer

Undermethylation of the entire genome is referred to as global hypo-methylation. Global hypomethylation when it is paired with over methylation of highly select repeated regions of the gene is associated with both aging and cancer.

Both undermethylation of tumor causing genes (no turn OFF) and overmethylaiton of tumor suppressing genes (turned OFF) have been well characterized as contributing factors to cancer. Methylation is used to inactivate excess levels of endogenous products that may be harmful to the body. For instance, excess estrogen is inactivated by methylation, with SAMe donating a methyl group for this process. The inability to inactivate excess estrogen has been linked to an increased susceptibility to hormone sensitive cancers. Epidemiologic and mechanistic evidence suggests mutations in the methylation pathway are involved in colorectal neoplasia. Specifically the role of the MTHFR C677T and MTHFR A1298C, methionine synthase (MTR A2756G), methionine synthase reductase (MTRR A66G), cystathionine beta synthase (CBS exon 8, 68-base-pair insertion), and thymidylate synthase (TS enhancer region and 3′untranslated region)—have been implicated in colorectal cancer.

Methylation also plays a role in the ability of the immune system to recognize cancer cells or abnormal cell surface antigens in pre-cancerous lesions. Research has shown that methylation is decreased in many patients with cancer. Impaired methylation of the NK T cells may be involved poor recognition and function of these vital cancer killing cells. As proper methylation function is restored, immune system regulation should slowly recover and lead to decreased potential of recurrence or second primary lesions.

Methylation and Allergic Reactions

When methylation is impaired it can lead to abnormally high levels of histamine. In addition to the effect of methylation on histamine levels, the effect of methyl groups on the TH1/TH2 balance may be a second mechanism by which decreased methylation may increase allergies. There are two sets of T helper cells in the immune system, TH1 and TH2 cells. While TH1 cells are involved in cell mediated immune responses and toning down or regulating TH2 activity, the TH2 cells have been associated with humoral or B cell mediated responses and allergic responses. TH2 cells trigger the activation and recruitment of IgE antibody producing B cells, mast cells and eosinophils that are involved in allergic inflammation. Studies show that decreased methylation of CpG regions in these genes may influence the balance of TH1 and TH2 cells.

Methylation and Anesthesia

The levels of various metabolites of the methylation pathway are important for protection from side effects of anesthesia. As early as 1942 it was recognized that the addition of methionine is preventative for side effects from the use of chloroform. Methionine affords protection from liver injury as a result of chloroform anesthesia. Methionine also protects against effects of nitrous oxide anesthesia. Nitrous oxide disrupts the activity of methionine synthase, a central enzyme in the methylation cycle. Again, preloading with methionine appears to accelerate recover and reduce side effects associated with this form of anesthesia.

Methylation and Environmental Toxins

Methylation is also required to clear environmental toxins from the body. This process involves conjugating methyl groups to the toxins prior to removal, as well as, supporting the production of glutathione and metalloproteins.

Glutathione is a highly sulfated protein involved in inflammatory control and reduction reactions, catalyzed by glutathione S-transferase in cytosol, microsomes and mitochondria. It is intimately involved in producing and controlling leukotrienes.

• It is the major endogenous antioxidant produced by the cells, participating directly in the neutralization of free radicals and reactive oxygen compounds, as well as maintaining exogenous antioxidants such as vitamins C and E in their reduced (active) forms.
• Regulation of the nitric oxide cycle, which is critical for life but can be problematic if unregulated
• Through direct conjugation, it detoxifies many xenobiotics (foreign compounds) and carcinogens, both organic and inorganic. This includes heavy metals, such as mercury, lead, and arsenic.
• It is essential for the immune system to exert its full potential, e.g., (1) modulating antigen presentation to lymphocytes, thereby influencing cytokine production and type of response (cellular or humoral) that develops, (2) enhancing proliferation of lymphocytes, thereby increasing magnitude of response, (3) enhancing killing activity of cytotoxic T cells and NK cells, and (4) regulating apoptosis, thereby maintaining control of the immune response.
• It plays a fundamental role in numerous metabolic and biochemical reactions such as DNA synthesis and repair, protein synthesis, prostaglandin synthesis, amino acid transport, and enzyme activation. Thus, every system in the body can be affected by the state of the glutathione system, especially the immune system, the nervous system, the gastrointestinal system and the lungs.

Methylation and Aging

Intermediates of the methylation pathway are known to decrease with age along with a decline in methylation pathway function. DNA methylation is also known to decrease with aging. Age related decreases in methylation can lead to decreased methylation of T cells which may in part explain changes in immune function with age. Age related decreases in methylation can result in increased levels of homocysteine, increasing the risk of arthritis, cancer depression and heart disease. This would suggest that increasing the body’s level of methylation through supplementation may extend healthy life span.

Methylation and Viral DNA

DNA methylation helps to maintain the large amount of non-coding DNA in an inert state. This is applicable to the DNA or genome of the organism, as well as any viral genes that are harbored within the cell. The methylation process prevents the transcription (the reading) of inserted viral sequences. One of the consequences of loss of methylation function is that it could cause the potentially harmful expression of these inserted viral genes. Under-methylation in normally silent regions of the DNA can cause the expression of inserted viral genes and may lead to autoimmunity or cancer.

Methylation and Host Organism DNA

Methylation is important for turning on and off mammalian DNA. This is true for silencing viral DNA in the body as well as cellular DNA. There are sections of the DNA prior to the information or coding portion that contain regulatory sequences or sections. When these regulatory regions are methylated properly they turn on and off the information portions as they should. During development, DNA methylation patterns are established and are essential for normal development. During new cell synthesis these patterns are then replicated. When these regions do not have the correct amount of methyl groups bound to them it can prevent the information from being turned off, resulting in autoimmunity, aging and cancer.

Methylation and Trinucleotide Repeat Disorders

Certain disease states occur as a result of increases in the length of specific three base repeat sections in the genome. These special “repeat regions” are prior to the information or coding region of the DNA. These trinucleotide repeats are involved in certain disorders such as Friedreich’s ataxia, Fragile X and Huntington's disease. We also see a role for trinucleotide repeats in particular regions of genes that serve regulatory purposes, such as the reelin gene that is involved in myelination.
When there is insufficient methylation capacity (mutations in the pathway) there is often not enough methyl groups to bind to these repeat regions, so they are able to multiply. This results in very long repeat sections, much longer than they should be. Studies have shown that inhibition of DNA methylation resulted in a 1000 fold increase in these three base repeat sections. Therefore, decreased DNA methylation results in increases in trinucleotide repeats and increases the risks for particular neurological disorders.

Methylation and the X Chromosome

Females contain two copies of the X chromosome. Silencing one of these two copies is essential for normal development. Methylation of the DNA is the mechanism by which the second X chromosome is silenced. The normally nonmethylated “CpG islands” become methylated as part of this silencing process.
A similar strategy is utilized to silence one of two copies of genes other than those on the X chromosome. In these cases the inactivated (or imprinted) gene that is inactivated by methylation can be of either maternal or paternal origin. Loss of normal imprinting as a result of decreased methylation contributes to a number of inherited diseases including Beckwith-Wiedemann, Prader-Willi and Angelman syndromes, among others.

Methylation Affects Both Nature and Nurture

The overwhelming impact of methylation pathway mutations is exemplified by the July 9, 2005 article in Science News which reported that although identical twins have the identical DNA they often have differences in a number of traits including disease susceptibility. This study suggests that as twins go through life the environmental influences to which they are exposed affects which genes are actually

turned on or off. Methyl or acetyl groups can attach to the DNA in a similar way that charms attach to a charm bracelet. This modification of the DNA is known as epigenetic regulation. The combination of environmentally determined addition of these "charms" to the bracelet of DNA, combined with inherited DNA changes or mutations lead to an individuals susceptibility to disease. According to the scientist who headed this study, Dr. Manuel Estseller, "My belief is that people are 50 percent genetics and 50 percent environment."

This statement should give us some understanding as to why mutations in the methylation pathway can be so devastating. Mutations in the methylation pathway affect the 50% of the pure genetic susceptibility; this would be analogous to defects in the links of the chain of our charm bracelet. In addition, because methylation is also necessary for the epigenetic modification of the DNA, methylation also affects the environmental 50%. If we take the analogy a step further to really understand the global impact of defects in this pathway we can view genetically inherited mutations in the methylation pathway as causing problems in the links of the bracelet and environmental effects creating a problem with the ability to put charms on the bracelet of DNA. Problems in the methylation pathway therefore can affect 100% of our susceptibility to disease.

Methylation, Pregnancy and Neural Tube Defects

Pre-conceptional supplementation to support the methylation cycle helps to prevent miscarriages. Mutations in the MTHFR genes of the methylation pathway as well as mutations that lead to decreased B12 are risk factors for neural tube defects. Mutations in the methylation pathway, specifically methionine synthase, methionine synthase reductase as well as abnormal homocysteine levels are risk factors for having a child with Down's syndrome.

It is important to consider methylation pathway mutations when looking at supplementing folate during pregnancy. One way to understand this more easily is to think about the studies on folate and neural tube defects. Using folate during pregnancy helps to decrease the risk of neural tube defects. This is not changing the DNA but having a regulatory effect on the ability of the DNA to be expressed, known as epigenetics. Now, if folate can make a difference in DNA expression, but you have a mutation so that you cannot use folate appropriately, then taking folate may not do any good; it is almost as if you never supplemented at all. Running a nutrigenomic test to determine the form of folate that will bypass mutations in your folate pathway will enable you to supplement with the appropriate form of folate and should help to reduce the risk of neural tube defects in a similar way to the use of plain folate in the absence of mutations in this pathway.

The genetics of the parent are reflected in the child. So that if a pregnant mother has mutations that make her unable to utilize plain folate, you should consider testing the infant for similar weaknesses in this pathway. The sooner that you know if and where a newborn's genetic weaknesses reside in the methylation pathway the sooner you can start to supplement to bypass these mutations. Remember by supplementing properly you should have the potential to bypass and compensate for the mutations. If this is commenced from day one you do not allow time for virus to build up (remember that methylation is necessary to silence virus). In addition, some of the mutations in the methylation cycle make it difficult to make new T cells which are a critical part of your immune system. If chronic virus is not building then it cannot hang onto and store heavy metals. This should help to prevent huge stores of metals in the chronic virus in the system. If as suspected, virus and metal loads from vaccines are related to the autism epidemic and if a newborn does have some weakness in their methylation pathway, you have the option of supplementing with the appropriate nutrients prior to vaccination. This may make it easier for the immune system of infants to react to vaccines in the correct fashion. If the methylation cycle is working properly from day one it should help with myelination, immune regulation, the ability to make new DNA and RNA that is needed for growing cells.