The Methyl Group:
What It Can Do for You,
Plus 3 Mistakes Not to Make with MTHFR+

NANCY MULLAN MD

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Introduction

Thank you for attending to this material. You do well to take the time. This information is central to your staying well as you get older, or to your recovering from any significant illness without avoidable backslides.

You need to move forward and start feeling hopeful right away...

I am a medical doctor who works with Dr. Amy Yasko. I treat people with chronic disease from MTHFR+, Chronic Fatigue Syndrome, Lyme Disease, Fibromyalgia, Autism Spectrum Disorders, Psychiatric Disorders, and a whole range of other problems that may be disabling. I treat lesser disorders too, like menopausal disorder, pre-menstrual syndrome and thyroid disorder, even though they don't feel lesser when you are going through them.

Even though I was educated at the best schools, the University of Pennsylvania for college, Tufts University School of Medicine for a medical degree, and the University of Chicago Hospitals and Clinics for further training in psychiatry and child psychiatry, nothing prepared me for what I found in the real world practice of medicine and psychiatry.

As students, we were never taught about the significant downside of pharmaceutical commercial interests and their dominance of medical education. Pharmaceutical firms dominate medical education, therapeutics, research, professional publications and the mainstream media. And I had no idea that the strangle hold giant corporations have on the Food and Drug Administration (FDA) is so often at odds with your well being.

I had not suspected that many useful therapeutic modalities were suppressed because they did not serve pharmaceutical commercial interests. I just believed my teachers. But the nature of the beast is that if my teachers had not bought into the existing system, they would not have been my teachers.

I never thought anything about the surgical treatment of medical illness and what that meant for the pharmaceutical industry's share of our country's economy until I got the instruction to use these modalities for myself. Then I balked. This was a very good thing for both of us. It catapulted me right out of academia and on to the street to learn what else was out there that I could use both to heal myself and to help you.

You may be well and be looking to stay well as the years go by. Or you may be one of the chronically ill, very sick, sometimes very young people who has been relegated to a backwater in mainstream medicine. You may be the parent of a youngster on the autism spectrum, or you may be an adult feeling the ravages of

time and advancing age. Whoever you are, the concepts described in this e book are both pertinent and essential for you to know.

Because of my intense curiosity about healing modalities, I come to you with a special knowledge of genetics and biochemistry. I have learned the most thoughtful, effective procedures to lay the foundation for your body to get it right. You need to set up the proper conditions for methyl group production and methylation so your body can regulate the expression of your genes and do the other important functions for which methylation is necessary. Next you balance your biochemical pathways, heal your gastrointestinal tract, deal with your inevitable chronic infections, and divest your body of heavy metals and other toxins. Along the way as you are doing these things, you turn from sick to well.

Many of you may know people who used to be really sick who are doing much better now. They followed their own modifications of Dr. Amy Yasko's protocol. With Dr. Amy's and my guidance for approximately 18 months, they came into well-being. Yasko has an extraordinary track record for pulling clinical rabbits out of hats. She has an incredibly detailed knowledge of molecular biology and genetics. She has great intuitive insight about lab results and persistence about getting to the reasons for symptoms.

Many clinicians with other ideas are there to seduce you. Anyone can throw out suggestions now, and follow with other suggestions later. Do they have an

overarching methodology that makes sense scientifically? Not always. Can you see ahead two years in their program? Usually not. It's just ideas now and more ideas later. It won't get you there.

Make the core of your program balancing pathways that produce methyl groups. Then service the needs of your gastrointestinal tract. Deal intelligently with whatever else may come up, like mold, hormonal problems, dental issues, heavy metal toxicity, electro magnetic frequency intolerance, and problems with your water supply. In the end, you get to well-being. It's a marathon, not a sprint, as Dr. Amy says so often. And like the turtle in its race with the hare, you get there first!

So, what is in it for if you read further? First, you learn the about the foundation that must be there if you want to heal. Methyl groups and methylation are indispensable to regulating genetic expression in your body. They are like the traffic lights of your genes and biochemical pathways. They need to function in an organized way to keep your body's systems mobilized and working. You must have proper methylation function in order to heal.

Beyond that, you learn the 3 mistakes that you must not make with chronic illness and MTHFR+ in order to get well. These are like sand traps on a golf course. They cost you time and create more hardship in your journey.

Finally, you get authentic hope for your future. The systems I describe are the ones that got people whom you may know back on their feet. These are people who were on their last hope. Some of them were desperate. They had been suffering the whole range of health dysfunctions, fatigue, weakness, dizziness, depression, anxiety, and inability to work or function. Some had left their homes and their families looking for help. They had been in mental hospitals and had been given shock treatments. They were on their last idea about what to do.

They had been called severely autistic. Their parents had been told that there was nothing more to be done. They were in diapers at 14 years old. They were prescribed behavioral therapies and pharmaceuticals that promised only minimal improvement.

These people may not be strangers to you. They may be your friends on Face book. You find them on Dr. Amy's forum or on her Facebook page. You do well to find out their stories, because their stories can give you hope. What they did is not impossible. In fact, things like specially compounded supplements have since been developed that make it even easier for you than it was for them.

Plus, you can get a **Complimentary 15 Minute Conversation** with me to help you find out what more you can do to optimize methyl group formation and methylation in your body. But for now, just continue reading...

Genetics and Epigenetics

Genes contain codes for the various proteins that your body needs to function. You have approximately 25,000 genes. Darwin taught us that it takes many generations to rewrite this basic genetic code because genes are constant from generation to generation. But there are mysteries in the way your genes function that are not explained by classical genetics. Your body has trillions of cells, each one with a nucleus, its command center. In each nucleus, the DNA is tightly coiled around proteins called histones that work as support structures for your genes. DNA is wound around histones the way you would wind yarn into a ball. It helps to compress your DNA and to regulate your body's ability to work with it.

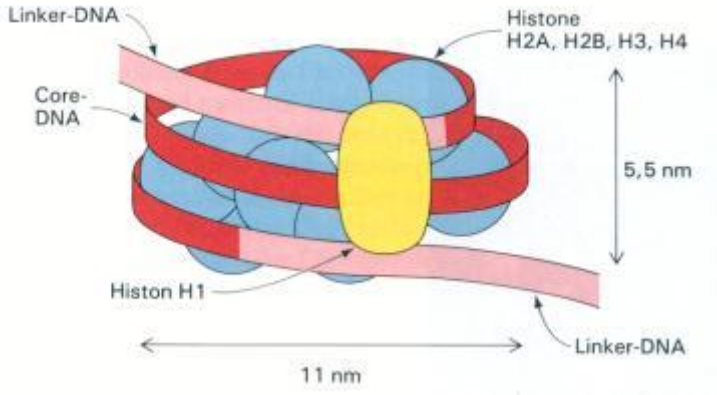


Figure 1: The DNA in the nucleus of the cell is stored around structures called histones.

With the completion of the Human Genome Project, there now exists a nearly complete list of the genes needed to produce a human. However, the situation is far more complex than a simple catalogue of genes. Since the 1970s, researchers have known that the tightly wound spools of DNA inside each cell's nucleus require something extra to tell them exactly which genes to transcribe to make a heart cell, a liver cell, or a brain cell, for example. These cell types are obviously different, yet they all have exactly the same inherited genetic code.

Beyond that, according to classical genetics, identical twins should have many of the same problem conditions, such as diabetes, schizophrenia, major depression, alcoholism, and obesity. But they don't. It became increasingly evident that genetics alone could not explain the complexity of physical characteristics observable in the living world.

For example, why does one member of a pair of identical twins develop bipolar disorder or asthma, while the other is fine? Or why does autism strike boys four times as often as girls? Or why do extreme changes in diet over a short period of time lead to extreme changes in longevity? In these cases, the genes may be the same, but the patterns of expression have clearly been tweaked.

Enter ***epigenetics***. Epigenetics can help to explain phenomena that traditional genetics never could. If the genome is the hardware, then the epigenome is the software. These patterns of gene expression are governed by the cellular

material that surrounds your genes, that sits on top of the genes themselves. Various chemicals called epigenetic marks, sit on your genes and offer basic instructions to them, telling them to switch on or off. The objects of epigenetic study are observable characteristic changes in living organisms that are not caused by DNA sequence alterations, ***yet they are inheritable***.

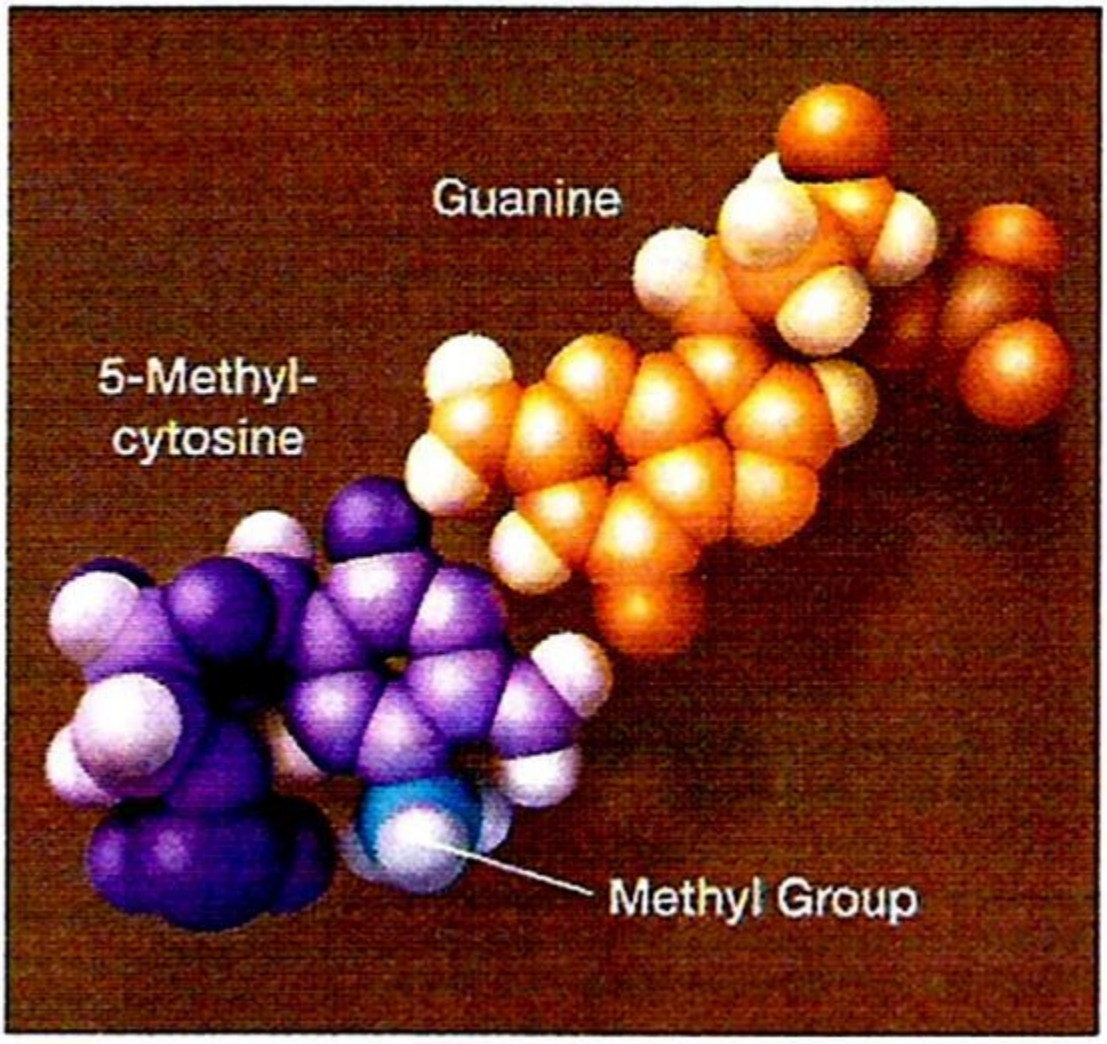


Figure 2: Epigenetic modification of the cytosine base in DNA by a methyl group.

One important mechanism for epigenetic control operates on the DNA by way of DNA methylation. A methyl group attaches to the appropriate mark and gives the gene an instruction. The human genome contains roughly 25,000 genes, but the number of patterns of epigenetic marks is likely to be 50 to 100 times as large. The influence of the epigenome is tremendous, especially when you consider that it is inheritable.

Certain diseases are known to be genetically predisposed, such as systemic lupus erythematosis, in which the immune system attacks your body's own cells. Early studies indicated that there is a genetic contribution involved with the development of this disease, but it could not be proved until a study was done on identical twins that helped to elucidate the matter.

Identical twins have identical DNA. If genes alone were responsible for determining whether a person gets a particular disease, every time one identical twin got the disease, the other would too. But that doesn't actually happen with systemic lupus. Between 40 and 76% of the time, when one twin developed lupus, the other stayed healthy, indicating that some other factor must be involved.

The lupus identical twin study showed that the twin sick with lupus had lower levels of methylated DNA on at least 49 different genes than his healthy sibling. These methylation differences do not appear to be random. The researchers

found that other people with lupus shared the same methylation pattern as the sick twins, a pattern not found in healthy people. Fewer DNA methylation marks may leave one twin vulnerable to the inflammatory autoimmune disease while the other remains healthy.

Subsequent to this, scientists found that people with lupus and rheumatoid arthritis have lower levels of methylated DNA than healthy people do. Methylation places a chemical mark on the DNA that reduces gene activity without changing the genes themselves. Lower levels of methylated DNA could lead to over activity of genes, including over activity of the genes that control immune responses and the body's tendency to attack its own cells.

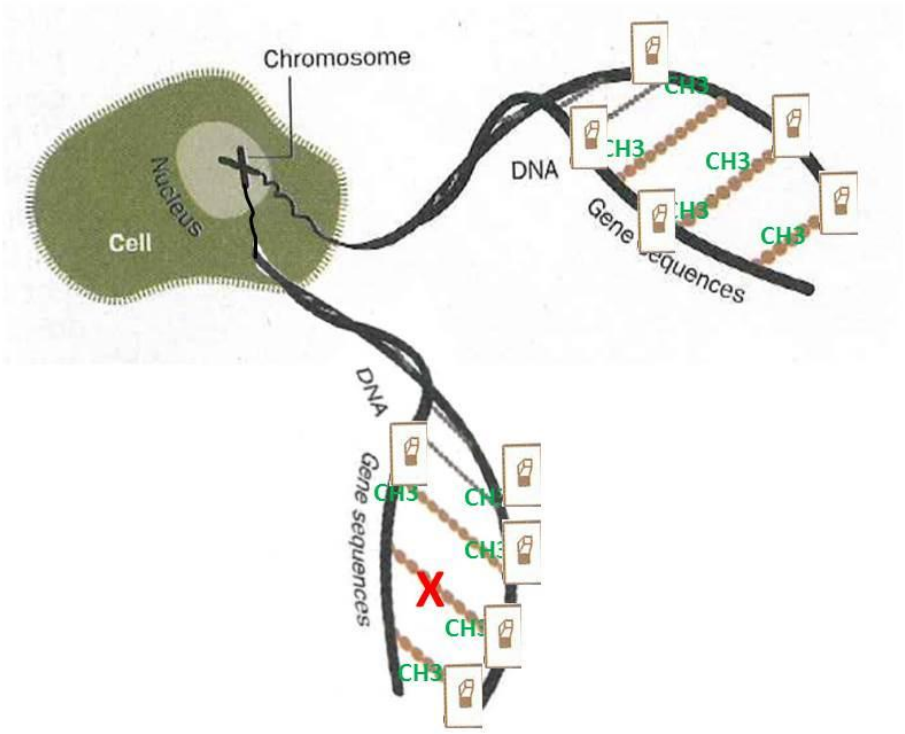


Figure 3: Epigenetic marks sit on your genes telling them to switch on or off.

Epigenetics is being heralded as arguably the most important discovery in the science of genetics since the gene. The great hope for ongoing epigenetic research is that with the flick of a biochemical switch, doctors could tell genes that play a role in many diseases -- including cancer, schizophrenia, autism, Alzheimer's, and diabetes, among others -- to lie dormant.

DNA methylation is a crucial modification of the genome that is involved in regulating cellular processes. These include embryonic development, transcription of DNA, chromatin structure, X chromosome inactivation, genomic imprinting, and chromosomal stability. Consistent with these important roles, a growing number of human diseases have been found to involve aberrant DNA methylation. The study of these diseases has provided new and fundamental insights into the roles that DNA methylation and other epigenetic modifications have in development and normal cellular homeostasis.

Methylation also regulates proteins, histones and stem cells. This is not simply methyl group regulation at a DNA level. It is global regulation.

A methyl group is a basic unit in organic chemistry; one carbon atom attached to three hydrogen atoms with an open chemical bond that can attach to another molecule. When a methyl group attaches to a specific spot on a gene, it can change the gene's expression, turning it off or on, dampening it or making it louder.

Lifestyle choices like smoking or overeating can imprint the environment around your DNA with epigenetic marks in important ways. These marks can trigger the genes for obesity to express themselves too strongly, and the genes for longevity to express themselves too weakly. It is common knowledge that you can shorten your own life if you smoke or overeat. But now it appears that your behavior can actually predispose your unborn children to the same problems before they are even conceived.

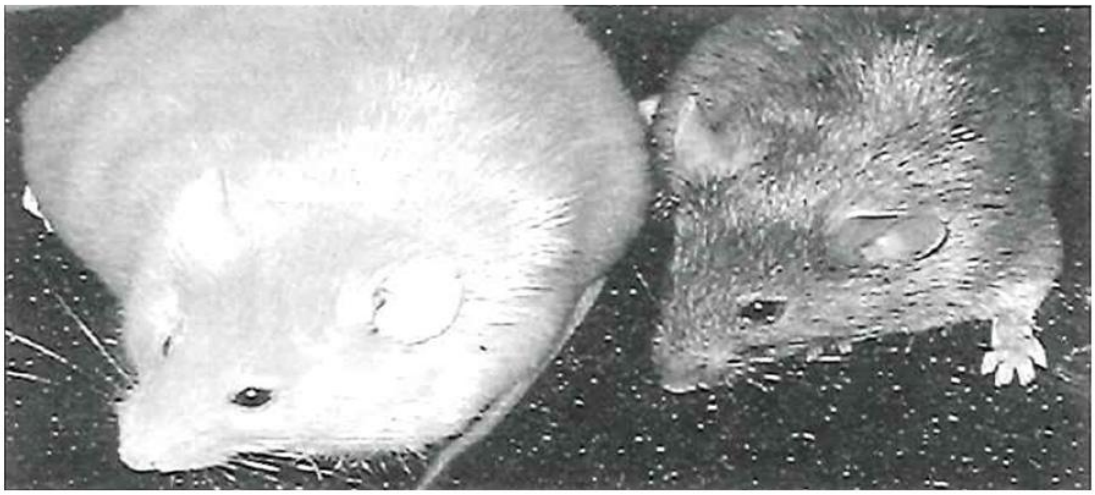
Epigenetic marks are passed down to your children, and their genes for obesity or longevity may be switched on or off. Environmental factors, like your diet, your level of stress, or your particular prenatal nutrition, make an epigenetic imprint on your genes, which then gets passed down to your children.

Geneticists were initially surprised to find that epigenetic change could be passed down from parent to child. Darwin taught us that it takes many generations for a genome to evolve, but researchers have found that it takes only the addition of methyl groups.

In 2003 at Duke University, experiments were done which demonstrated the potency of DNA methylation for altering the physical characteristics of an organism. Agouti mice have a gene that gives them yellow coats and a propensity for obesity and diabetes when it is expressed. One group of pregnant

agouti mice got a diet rich in methyl donors, folic acid, and B12. Another group of genetically identical pregnant agouti mice did not get enhanced prenatal nutrition.

The B vitamins and methyl donors caused methyl groups to attach more frequently to the agouti gene in the pregnant mice, thereby altering its expression. And so, without changing the genomic structure of the DNA of the mother mouse, the agouti mothers were able to produce healthy brown pups with a normal weight and not prone to diabetes, simply by enhancing her ability to methylate.



The mother of the mouse on the left received a normal diet, while the mother of the mouse on the right received a diet supplemented with methyl donors such as choline, betaine, folic acid and vitamin B12. Since the mice are genetically identical, phenotypic differences are the results of epigenetic, as opposed to genetic changes.

Figure 4: These two mice are genetically identical.

Their differences lie in what their mothers were fed.

While epigenetic changes are inheritable changes, they are also reversible. They depend on the make-up of the cellular fluid immediately surrounding the gene. When the constituents of that fluid changes, for better or for worse, the epigenetic imprint on the gene changes also.

Folate status is certainly important in methyl group formation. Low folate has been seen to be a causative factor in the formation of colorectal cancer in at least one study. Folate is essential for the synthesis of S-adenosylmethionine (SAMe), the main methyl donor required for methylation reactions in cells. Global hypomethylation appears to be an early and consistent molecular event in colorectal carcinogenesis, and can sometimes be reversed by folate administration. This suggests that optimal folate status may normalize DNA hypomethylation, offering potential protective effects against cancer.

Some of the impact of heavy metals is to impair your ability to make methyl groups. Hence, your ability to methylate other molecules is reduced. Conversely, reduced methylation diminishes your body's capacity to rid itself of heavy metals.

Toxins in your environment affect and work through epigenetic mechanisms also. So you are less able to deal with toxins if you can't methylate.

Epigenetics functions in neuronal plasticity, the change in neural pathways and synapses that comes from the new things you have learned, the changes that

your environment imposes upon you, and changes resulting from bodily injury. Epigenetic modification is necessary for learning in the adult nervous system. Methyl group modification of DNA helps to regulate memory formation. Additionally, the growth that repairs nerves and develops language involves epigenetic control.

Editing genetic expression is also a function of methyl group epigenetic modification. To use an analogy, if your computer has a broken "M" key, when you attempt to type a document, the letter "M" will always be missing from the words that include "M". But your computer also has an editing function, so that if you typed "_iss," your computer might ask you, "Did you mean 'miss ' ?" In this way, the editing function will catch the mistakes that occur because of the broken "M" key. While you still will not be able to type a letter "M", you will be able to spell the words correctly in your document because the editing function will find the mistakes and point them out to you. Methyl groups are the molecules that operate this gene repairing function. Editing works by adding methyl groups to the DNA, turning on and turning off certain areas.

By now, you ought to be understanding how important epigenetics is and how central the methyl group is in the operation of this function.

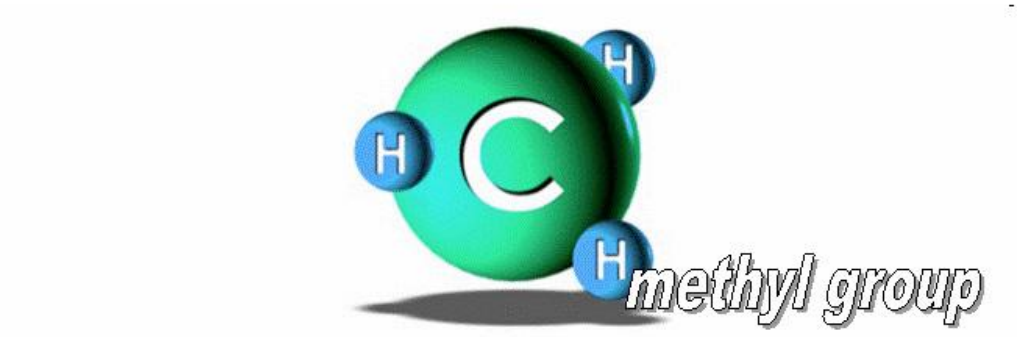


Figure 5: The small but mighty methyl group.

There are other critical roles that methyl groups and methylation play in your body's biochemical reactions that do not involve genetics or epigenetics. Aside from genetics, without an adequate supply of methyl groups, you cannot form certain base molecules that make DNA and RNA. Without these, the function of making new cells that your body needs to renew itself as the old ones die and slough off is impaired. You age more rapidly. Wound healing is impaired. You do not learn new tasks readily or have the ability to adapt to the changes in your environment easily. Your energy may sink to new lows. You may develop high homocysteine and the vascular inflammation and heart disease that come with this condition.

Without good methylation capacity, you are not likely to be able to form cells with fast turnover as quickly as you need them. Red blood cells are especially vulnerable to this problem. You may get a defect in red blood cell synthesis called megaloblastic anemia, an anemia in which red blood cells do not function normally and are larger than they should be. This condition results from impaired DNA synthesis during red blood cell formation. The defect in red cell synthesis is most often due to a deficiency of vitamin B12 and/or folic acid, both of these vitamins being critically important to methyl group production.

Other fast growing cells that are impacted by low methyl group availability are the white blood cells needed to mount an immune response. T cell clones cannot expand without adequate methyl groups available. In addition, the cells of your gastrointestinal mucosa, the lining of your gastrointestinal tract, normally turn over very rapidly. Both of these functions are impaired by low methyl group availability.

Allergic reactions cause the secretion of histamine as part of an immune response to foreign pathogens. Histamine is involved in the inflammatory response to an offending particle. It increases the permeability of your capillaries to white blood cells and some proteins, which allows them to engage pathogens in the infected tissues. It takes methyl groups and methylation to deactivate histamine and to reduce the inflammatory response to the allergen. In another important function, methyl groups are central to the recovery from anesthesia.

If you do not have adequate methyl groups and you are pregnant, you are at risk for having a child whose spinal cord does not fuse properly, a child with a neural tube defect, or spina bifida. Ostetricians now recommend folic acid, a methyl donor, for their patients.

A child's ability to grow may be impaired by insufficient methylation. In addition, one of the causes of Attention Deficit Disorder or Attention Deficit Hyperactivity Disorder is the inability to properly regulate the neurotransmitters dopamine and norepinephrine. These take methyl groups to deactivate. Also, the metabolism of tryptophan, the precursor to the neurotransmitter serotonin, and melatonin formation, both require methylation.

Insufficient methylation may lead to abnormal myelin formation, impaired nervous impulse transmission, and the improper pruning of nerve fibers as development progresses. Methylation is essential for neuronal cell survival, development, function, and longevity. It is necessary for neuronal plasticity as mentioned earlier. Nerve cell membranes need to be methylated in order to be sufficiently fluid for receptor site activity and the transmission of impulses and substrates.

It is hard to describe a more central process to your overall function than methylation. It takes its place in your body among processes such as oxygenation and energy production. Dr. Amy focuses her attention and her

genetic testing on the pathway that produces methyl groups specifically because of its massive impact, an impact that starts with genetic regulatory function, but does not end there by any means.

Dr. Amy's first clinical intervention is to support the production of methyl groups by using nutritional supplementation that bypasses whatever genetic mutations may be impairing the function of this pathway. So, of necessity, our attention turns to the processes that make methyl groups and the genes that impact them.

Making Methyl Groups

The methylation pathway is the pathway that makes methyl groups. It is a nutritional pathway and is well characterized. Its functions are known, and what nutritional supports are needed to bypass the genetic problems with its function are also known. Nutrigenomic testing focuses exclusively on this pathway.

Dr. Amy correctly intuited that producing methyl groups, supporting methylation, promoting the epigenetic regulation of genes, and enhancing the many other functions that methylation performs, would be key factors in the recovery from difficult to treat chronic disease. Using blood testing to determine genetic mutations is expensive, but Dr. Amy uses blood because her work in research requires accurate test results. There is no dispute that using a blood sample for genetic testing is more reliable than saliva or buccal smears.

The mutations in the Methylation Pathway, the pathway below in Figure 6, that most profoundly impact methyl group production are CBS, MTR, MTRR, MTHFR, SHMT, and BHMT. In this chapter, the overall function of this pathway is described, as well as the role of these genes in particular.

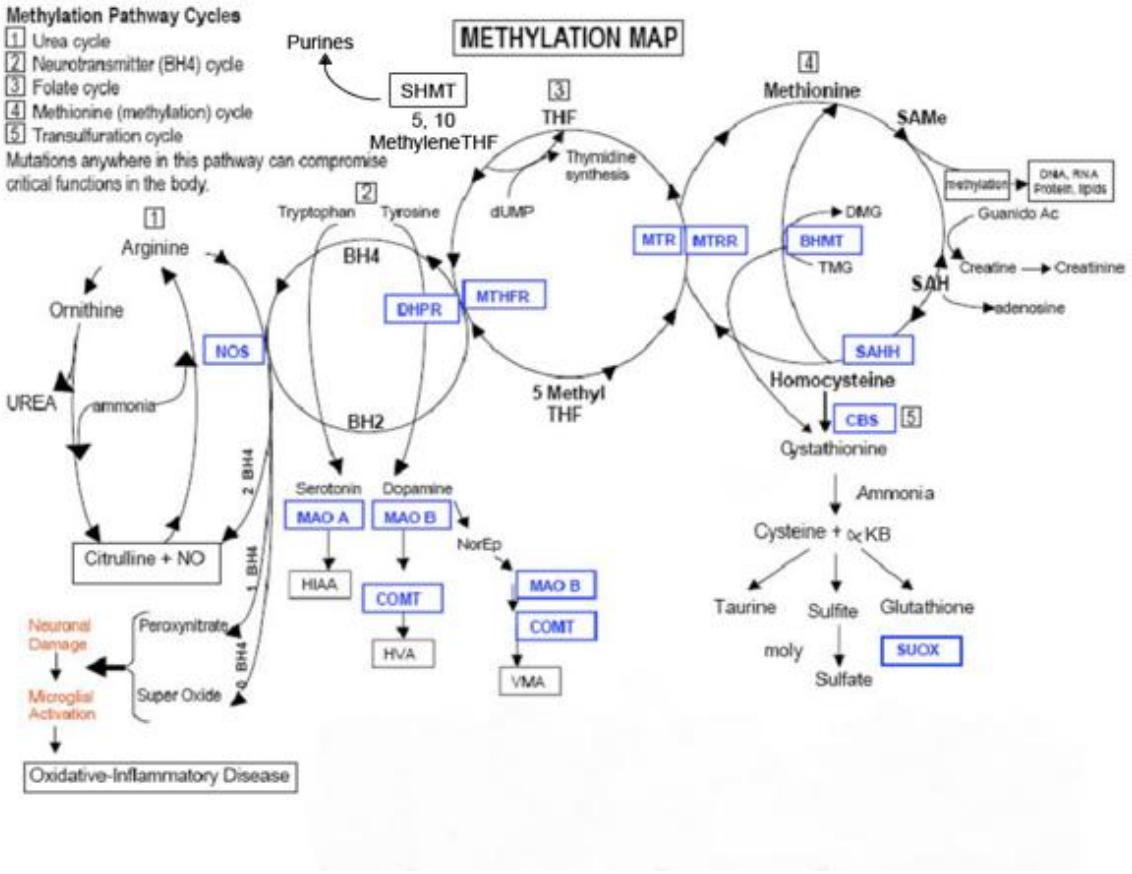


Figure 6: The Methylation Pathway is a confluence of important biochemical pathways in your body.

A major source of methyl groups in your body is the amino acid methionine. It comes from meat and other protein sources in your diet. It functions in cycle 4 of the pathway. Methionine contains the methyl group that is donated in most of your body's methylation reactions. It also contains sulfur that is used by your transsulfuration pathway. Methionine, in addition, functions as a free radical scavenger and an antioxidant.

Methionine acquires an adenosyl group that converts it into S-adenosylmethionine (SAMe). SAMe is your body's main methyl group donor. SAMe gives up its methyl group in many methylation reactions. After this, it becomes S-adenosylhomocysteine (SAH). When the methionine cycle is going in the clockwise direction, which is its progressive direction, SAH gives up its adenosyl group and becomes homocysteine. Homocysteine can then re-methylate into methionine. Methionine then goes through this cycle repeatedly to produce an optimal number of methyl groups for all the methylation reactions happening in your body. Methylation happens over a billion times a second in your body, biochemicals passing methyl groups one to another.

When homocysteine does not become re-methylated and stays in the methionine cycle, it may transit down the transsulfuration pathway. The properly functioning transsulfuration pathway makes glutathione from this sulfur-bearing part of the original methionine molecule. Glutathione is, in its own right, the most important antioxidant detoxification molecule. As its name implies, the transsulfuration pathway processes the sulfur molecules in your body and is central to your detoxification of heavy metals and other toxins. The transsulfuration pathway is depicted in cycle 5 of Figure 6.

There are two pathways by which homocysteine can acquire a methyl group and become methionine again. One is 'the long route', the reaction involving

methionine synthase (MTR) and methionine synthase reductase (MTRR), which works in cycles 3 and 4. The other is 'the shortcut'. The shortcut is easier to activate, produces less detox when it is activated, and also provides methyl groups. The shortcut pathway is activated first.

Betaine Homocysteine Methyltransferase

The betaine homocysteine methyltransferase (BHMT) pathway is the pathway that appears to go directly from homocysteine to methionine in cycle 4.
The BHMT enzyme catalyses the transfer of a methyl group from trimethylglycine (TMG), also called betaine, to homocysteine. TMG becomes dimethylglycine (DMG) and homocysteine is then converted to methionine.

The phospholipids, phosphatidyl serine, phosphatidyl ethanolamine, and phosphatidyl choline feed directly into the BHMT pathway. In addition, phospholipids are key components of cell membranes. Many substrates in the shortcut pathway are critical for neurologic function and contribute to cell membrane integrity. These are the first supplements added to your program.

Using the BHMT enzyme to go from homocysteine to methionine will not help to generate RNA and DNA building blocks. You need these building blocks for wound healing, to replace tissues, or to expand T cell clones in response to infection. So, the long route is important to activate at some point, but it involves

more interference from genetic mutations and produces more detox symptoms when this is done.

Appropriate broad spectrum nutritional supplementation should be in place or coming shortly. Appropriate supplementation implies neither too much nor too little of any substrate. Excessive amounts of a substrate can unbalance pathway function as badly as too little. Some clinicians give unbalancing amounts of a substrate in an attempt to drive a reaction or remove a symptom. This trades long term recovery for putative short term gain. The treatment may end up without convincing direction.

Your supplementation needs to be reasonably precise to address the extremely intertwined and complex biochemical interactions of your whole body. For clinical purposes, certain critical pathways are highlighted, but recovery is a whole body phenomenon. Subsequent biochemical testing hopefully shows pathways that are coming into balance, and your progress should reflect this as well.

At the same time that you are carefully attempting to activate the shortcut pathway, you are also trying to increase the lithium level in your body. Expect to find yourself low in lithium by a hair, urine, or blood test. It is likely that you have the symptoms you have because of mutations in your methylation pathway. Several of the mutations in this pathway are associated with lithium loss from the

body. They are MTR, MTHFR C677T, SHMT, and CBS. As you increase the level of lithium in your body, you may find that you need to add potassium also.

Lithium enhances the uptake of B12 and folic acid into your cells. As such, it is critical to methyl group production. At the same time that you are activating the shortcut pathway, you are holding B12 supplementation to minimal amounts until you see from the Hair Elements Analysis test in particular, and the Urine for Toxic Metals and Essential Elements test to some degree, that lithium has increased in your body. Too much B12 before this time can further deplete lithium and lead to a stalemate. After lithium has come more into balance, you add B12 carefully so as not to deplete lithium again, and in doing this, you begin the activation of the long route, the pathway that uses methionine synthase (MTR) and methionine synthase reductase (MTRR).

Methionine Synthase and Methionine Synthase Reductase

The folate cycle, cycle 3 in Figure 6, is the source for the methyl group that re-methylates homocysteine back into methionine when the long route is activated. When the methionine cycle moves in a clockwise direction, the folate cycle moves counterclockwise. Then tetrahydrofolate (THF) becomes 5,10 methylene tetrahydrofolate (5,10 methylene THF). When 5,10 methylene THF is acted on by the enzyme methylene tetrahydrofolate reductase (MTHFR), it becomes 5 methyl tetrahydrofolate (5 methyl THF). It is 5 methyl THF that passes its methyl group to hydroxycobalamin, vitamin B12. Hydroxy B12 then is methylated, becoming

methyl B12. Methyl B12 donates its methyl group to homocysteine, thus turning homocysteine back into methionine, and methyl B12 back into hydroxy B12.

The active site on the cobalamin molecule first houses the hydroxy radical, releases it, then acquires a methyl group, and then releases that. This site can become oxidized very rapidly. It needs to be reduced again before it can be useful. So the presence of pro-oxidant conditions in your cells slows down the production of methyl groups. This may explain some adverse.reactions to ozone therapy. The enzyme methionine synthase reductase (MTRR) functions to keep this important site on the cobalamin molecule reduced. MTRR expedites the methylation of B12 and hence the production of methyl groups.

Antioxidant molecules are a particularly important component of your cell's environment. They must keep hydroxycobalamin reduced. A pro-oxidant environment shifts the equilibrium of MTR, driving substrates down the transsulfuration pathway. This process increases the production of glutathione, a potent antioxidant. This mechanism is adaptive for generating an antioxidant environment in your cells, however it does not contribute to your methyl group supply. So antioxidants are important if you are trying to optimize methyl group production.

There are at least six locations on the genes that encode for MTRR that impact enzyme activity. The Nutrigenomic test studies the following locations: MTRR

A66G, H595Y, K350A, R415T, S257T, and finally A664A, the location that Dr. Amy refers to as MTRR 11. MTRR 11 seems related to increased detoxification of heavy metals.

MTRR A66G produces a mild down-regulation of enzyme activity if only one gene is affected, but a significant down regulation if both of the two genes have SNPs. The other four locations, MTRR H595Y, K350A, R415T, and S257T produce profound down regulations of enzyme activity even if only one gene is affected. The solution in all cases is increased B12 of the appropriate kind for the individual involved. Profound down-regulations may require surprising amounts of B12.

Methylene Tetrahydrofolate Reductase

Methyl group production is also impacted by mutations in two genes encoding for MTHFR. A mutation in the gene at position C677T and/or position 3 decreases the activity of the enzyme and reduce the amount of 5, 10 methylene THF that becomes 5 methyl THF. 5 methyl THF is critical for the re-methylation of homocysteine, so these down regulating SNPs are significant.

MTHFR C677T has come into mainstream therapeutics because of its intimate association with chronic illness. Many chronically ill people are MTHFR C677T+ , and some get relief from methyl folate and methyl B12 administration. For others, it is not so simple, not only because of other mutations in the methyl group

producing pathways that interfere, but also because the causes of chronic illness are multifactorial. Besides their being genetic precursors, infectious and environmental factors also are involved. Each of these factors makes its contribution to how sick you get, and may make the impact of the other worse.

MTHFR+ interferes with methyl group production. Methylation is necessary for mounting an immune response, so you are more vulnerable to infectious disease. Beyond that, MTHFR+ impacts the transsulfuration pathway that makes glutathione, your body's main detoxification antioxidant for removal of mercury and other heavy metals and toxins. A problem with MTHFR+ function reduces your production of glutathione, which impairs your ability to excrete toxins. This leads to a negative feedback situation in which toxic metal accumulation inhibits another key enzyme in the methylation process, methionine synthase (MTR). MTR is totally inhibited by nanogram levels of mercury, lead, cadmium, arsenic, and aluminum, the consequence of which is increased toxin accumulation. Such toxins enhance their own retention. They reduce glutathione production and subsequently methylation pathway enzyme function, which further reduces glutathione production and methylation pathway enzyme function, etcetera. So MTHFR+ may start off a cascade of events which can really lay you low.

Folinic acid and 5 formyl tetrahydrofolate (5 formyl THF), are the immediate precursors to 5,10 methylene THF. Folinic acid is a form of folate found in many supplements. Giving folinic acid will not enhance methyl group production when

mutations at MTHFR C677T or 3 are present. Therefore only supplementing 5 methyl THF itself makes this substrate available to MTR.

Cystathionine beta synthase

A mutation in the genes encoding for the cystathionine beta synthase (CBS) enzyme that are tested in the Nutrigenomic profile results in increased CBS enzyme activity. CBS is depicted at cycle 5 in Figure 6. The methionine and folate cycles are readily depleted of their substrates by this increased activity. CBS acts as a gate between homocysteine and the transsulfuration pathway. Normal genetic expression moves the conversion from homocysteine to cystathionine slowly and leaves enough homocysteine to convert back into methionine.

Nutrigenomic testing looks at three CBS locations: C699T, A360A, and N212N. A mutations at the C699T location can increase enzyme activity ten-fold, and a mutations at N212N is rare but even more up-regulating. It is as if the gate is constantly open. This allows the support that is used for the methionine and folate cycles, originally intended to make methyl groups, to increase the activity of the CBS enzyme and send substrates into the transsulfuration pathway. This open gate is not a neutral situation. It is critical to methyl group formation that CBS activity be restrained. The methionine and folate cycles must have adequate materials which act both to start and to continue the function of the

cycles. Those materials must be prevented from draining into the transsulfuration pathway.

SAMe helps to stabilize and modify CBS activity, as do nutritional supplements such as CBS+ RNA. Overenthusiastic Vitamin B6 supplementation can increase CBS enzyme activity, as will elevated glucose, excess cortisol, or excess protein intake in your diet. CBS up regulation frees up nitrogen molecules that were complexed in protein in the methionine cycle, wasting them from your body and increasing the production of the neurotoxin ammonia.

Immune system activation and/or bacterial infection increase the inflammatory cytokine TNF-alpha, which increases CBS activity. Pro-oxidant conditions in your body and inflammation can also increase CBS activity.

Individuals with CBS up-regulations are less able to tolerate both sulfur donors as well as lipid based support. Part of the reason for this intolerance to sulfur support, including sulfur based chelation such as DMSA or DMPS, is because the net result of CBS up-regulation is the problematic open gate at the start of the transsulfuration pathway. Intermediates of the methylation cycle are converted into toxic sulfur byproducts by increased transsulfuration pathway activity.

When sulfur groups are tied up in amino acids such as homocysteine, methionine, SAMe, SAH, and cysteine, the sulfur is not free to create havoc in

your body. But, by virtue of increased CBS activity, the sulfur groups that were complexed as part of the methylation cycle in the form of amino acids, are released into your system as sulfites, which are toxic to your body and deplete much needed molybdenum.

Serine Hydroxymethyltransferase

Serine hydroxymethyltransferase (SHMT) also has a significant and immediate impact on methyl group formation. It is depicted in cycle 3 in Figure 6. SHMT shifts the emphasis of the methylation cycle toward the building blocks needed for new DNA synthesis and away from the processing of homocysteine to methionine. While DNA building blocks are important, SHMT mutations affect your ability to regulate this enzyme and interfere with the delicate balance of methyl group production. This may cause accumulations in homocysteine as well as imbalances in other methylation cycle intermediates in your body. This mutation diverts methylation cycle intermediates toward purine formation, thus reducing methyl group production.

The net effect of SHMT mutations is to shift the focus of the methylation cycle toward the formation of thymidine, a purine. Supplementing nucleotides including purines takes the pressure off of your body to produce them. In addition, SHMT activity is regulated by the amount of iron in your body, as well as by the level of 5 formyl THF. The use of lactoferrin and low dose 5 formyl THF shifts the focus of the methylation cycle back to the production of methyl groups.

Now you have a lot of information pertaining to which gene mutations most profoundly impact your body's ability to make methyl groups. So, what do you do with it exactly? How do you translate this into improved health?

Some things are not simple, but in the next chapter, we give you some help with this.

Know Your Genetics

Genetics based supplementation is a complex and heady task, but considering the alternatives, you may opt to take it up. By looking at diagrammatic representations of the methyl group producing pathway, knowing your own genetics, and relating what you know about the impact of genetic mutations on the formation of methyl groups, you can formulate some hypotheses about what your methyl group production status may be. Then you perform biochemical testing to uncover what the situation in your body actually is. When the tests come back and you have considered them, you can target nutritional supplementation to optimize methyl group formation and methylation function in your body.

This is a process that is done over and over again as your body changes and you progress toward wellness. The vitamins, minerals, and other substrates in your body come into balance, and then need to be rebalanced again as you go along and your internal conditions change. It is a process. It is a complicated process viewed all at once, but broken down into steps, what to do becomes more apparent. This method provides guidelines for you that clearly indicate which direction is up.

The URL' s for many supports are available to you on knowyourgenetics.com. They include links to Dr. Amy's Nutrigenomics Discussion Group, the books she has written which are posted online, the many videos of her lectures which are also there, her workbooks, supplement lists, etc. You are given access to a tremendous amount of information about how to proceed.

In addition, I can consult for you within the context of my private practice and give you and your test results individual attention. I also conduct a Mastermind Program every Tuesday evening at 5:00 PM Pacific Time in which I answer your questions and help to move you forward. The contact information is available if you email my office at nancymullanmd@aol.com, and on my web site, www.NancyMullanMD.com.

Dr. Amy has an additional complimentary service that she describes below:

As part of my goal of paying it forward and providing information at no cost, I am sharing this link to http://knowyourgenetics.com that includes up-to-date information to consider when supporting your Methylation Cycle. The link to http://knowyourgenetics.com is a **free service** that offers suggestions that may be applicable **regardless of what genetic test you have run**. Please feel free to use this site and have open access to the information. However, as always when implementing any supplement program, please work with and defer to your doctor.

Again, this program is applicable **regardless of the test you have run** to get your nutrigenomic results. The Methylation Pathway Analysis (MPA) program focuses on 30 SNPs (mutations) which I have found to be central in promoting and supporting a healthy methylation cycle.

Those of you who have previously run the test through HHI and have already received a methylation pathway analysis can input your data to receive updated information. This link also helps to make the ordering process easier, as it includes a master supplement list. Even if you have not run the Nutrigenomic test that I have designed, in most cases, **regardless of the test you have run** to get your nutrigenomic results, if the SNPs are the same, this program may aid in your ability to better understand how to best support a healthy methylation cycle.

Recall that every cell in your body contains identical DNA, which is why blood, saliva, hair, and fingernails, can be used to evaluate your personal DNA. There are approximately 25,000 genes in the human body that code for proteins, but it is not practical to look at all 25,000 genes. While every cell in the body contains the information about your total genetic profile, tests that look at genetics choose specific genes to evaluate and look for changes or mutations. **I personally believe in looking only for changes in the DNA in well-defined nutritional pathways** in which it is clear how to add natural supplements to bypass imbalances. I feel that whether you have a test that gives you 30 or 1000 or 5000

markers, this is still only a fraction of the total number of genes in your body, and frankly, having more markers is not the issue. The real question is whether the information that you have is in a pathway that has been characterized so you know what can be done to help restore your body to health. **The nutritional pathway that this program focuses on is something I call "The Methylation Cycle"**. The methylation cycle is a well-defined nutritional pathway in the body. When you look at the suggested nutritional support, you are working to increase the ability of the entire Methylation Cycle to run properly, keeping in mind that it has been functioning to some degree in spite of any mutations in particular genes. Nutrigenomics is just one aspect of the many factors that determine your health. I see complex health conditions as multifactorial in nature. That means that while your nutrigenomics are a piece of the puzzle, they are not the whole picture. The environmental burden of toxins you are exposed to, along with infectious agents such as viruses, bacteria, fungal infections, parasites, and yeast, and the stress on your system, all impact your overall health.

AGAIN, the link to http://knowyourgenetics.com is a free service that offers suggestions that may be applicable regardless of what genetic test you have run. Please feel free to use this site and have open access to the information. However, as always when implementing any supplement program, please work with and defer to your own doctor.

3 Mistakes Not to Make with MTHFR+

Most often MTHFR+, Lyme Disease, and other causes of chronic illness overlap. There are certain stock things that clinicians do when they are confronted with these illnesses that may or may not be right for you. Most often these clinicians are not acquainted with genetics, epigenetics, methyl groups, methylation or any of the issues described above. They may know to test for MTHFR, but not know what to do after that. This section highlights some common problems that come up when you are attempting to get treatment, and is an effort to help you avoid them.

Mistake # 3: Trying to teach your doctor anything.

You may be one of the fortunate few who has an open-minded doctor. Good for you. You can bring him books and other information, and while he will smile and accept them, you have no clue if the material you hand him is getting read, let alone digested and integrated into his knowledge base well enough for him to be able to help you with it. Most doctors get their serious education at seminars put on by professional organizations for professionals like themelves. They may conclude that if the information is really important enough for them to learn, their local hospital or medical society would be presenting it.

Your doctor may be busy right now trying to keep up with the changes in health care insurance. He may be working on how to keep you as his patient and get paid. There are a zillion reasons why he will take your material and lay it aside. Still, you need him, so just accept this.

Your doctor may tell you that he is willing to do the testing you ask for, but he really does not know much beyond that. Good for you. You have an honest, humble person there to help you. If you are using an additional clinician who is at a distance, or getting information from an online forum, there are going to be times when you need to go to a good local doctor to be examined and to find out just what is happening inside your body so that you can figure out what to do next.

Your doctor may undergo one of any number of transformations when you attempt to present him with information. He may get officious and stuffy, covertly or overtly tell you how much you don't know, or try to impress you with how little the information is worth. Or, he may just ignore you. Then again, he may change into something just short of a raving maniac when you bring up anything outside of his knowledge base. There are as many reactions out there as there are doctors. Stay calm. He still may be a good doctor. Just do not try to teach him anything.

Use your doctor for what he knows, not for what he doesn't know. It is his job to go out and learn what he needs to know to get you well. It is not your place to tell him. It is your place to find out what you need to know to get yourself well, and to use your doctor for what he can help you with, as opposed to what he cannot.

Mistake # 2: Pounding your body with any kind of intervention.

There are interventions that clinicians usually recommend for chronic disease, especially Lyme Disease and its related infections. They may be appropriate if you are mostly well, but they can be a total disaster if you are truly chronically ill. You know about some of these if you have been in the chronic disease community for any length of time at all.

Prolonged or multiple antibiotic administration can be one of the interventions that is suggested when a mainstream physician approaches Lyme Disease. If your methylation processes were online, your body would use its own immune system to combat the infection. You can destroy the lining of your gastrointestinal tract with prolonged and repeated antibiotics. Then you will not be able to absorb the nutrition in your food. And then what is your body supposed to run on?

You have to be healthy to tolerate pharmaceutical antibiotics. Even herbal antibiotics can be a challenge for you. You have to have good GI function and a range of good GI organisms present in your gut to tolerate antibiotic therapy.

Most of you have heard about patients who have gotten sick from antibiotic administration. Some of them have never recovered from how sick they have gotten.

If the flora in your gastrointestinal tract is already compromised, and you start pounding your body with antibiotics, you wipe out the bacteria that is supposed to be there, and instead promote the growth of opportunistic organisms like clostridia and candida yeast. These organisms are the cause of many symptoms in themselves. And once an organism like clostridia or yeast establishes itself in your GI tract, it can take years of maintaining the correct GI environment to get rid of it.

Other problematic interventions include intravenous injections. How problematic these are depends upon the state of your health and what the IV contains. There are substances that may help a mostly healthy person, but if you are mostly sick, they can put you on a roller coaster of symptoms. These IVs include in particular Vitamin C, glutathione, and Vitamin B6.

Vitamin C is a very helpful antioxidant. Injected intravenously, it is also very antiviral. Intravenous administration of Vitamin C can kill the virus that is in your system very efficiently. But the viruses in your body harbor metals, and when you kill them precipitously with an intravenous solution, those metals dump into your system. Unless you can detox them effectively, they get redistributed, and you

get symptoms of metal toxicity. This has nothing to do with a Herxheimer reaction or doing anything effective about any illness you may have. In addition, high dose intravenous Vitamin C can exacerbate underlying glucose-6-phosphate dehydrogenase deficiency that in itself can cause a world of symptoms, among them hemolytic anemia.

Glutathione is another popular intravenous injection. It may be helpful unless you have one of the genetic mutations that cause biochemical pathways to be unbalanced by the injection of a sulfur molecule into your bloodstream. Then you just get symptoms of sulfur toxicity and never get any benefit from the glutathione at all.

Plus, it is nearly impossible to get a nutritional IV without Vitamin B6. Vitamin B6 is a perennial favorite among doctors who use nutritional IVs. But B6 up regulates the CBS enzyme, the enzyme that functions in the first step of the sulfur detoxification pathway. B6 increases the activity of the CBS enzyme, which may unbalance this pathway and make it function less effectively. The CBS enzyme is also vulnerable to up-regulation by genetic factors and other biochemical issues, like blood sugar fluctuations. If you are chronically ill, it is best to keep the B6 in your system to just what you need, as opposed to high dosing B6.

Likewise, it is better that your immune system develops competence

from balanced, daily administration of the substances it needs. This supports both immune competence and sustainable detox. If your methyl group formation is optimized, your immune system will come online and many functions in your body will happen better. If you balance your transsulfuration pathway, your body makes its own glutathione. This glutathione is already inside the cell, exactly where it needs to be to function.

Especially if you are chronically ill, resist the temptation to overwhelm your body with anything. Just supply it with what is necessary for it to function optimally on a daily basis. And use biochemical testing to make sure you are going in the right direction. Then you find yourself on the slow but sure path to wellness.

Mistake # 1: Testing only the MTHFR gene and treating based on that.

The MTHFR gene is being widely discussed. More doctors are coming to know about it because it is located at a site that profoundly impacts making methyl groups, and methyl groups have come into prominence because of their epigenetic functions.

But, as was described above, a number of genes have an impact on making methyl groups, not just MTHFR. You need to use genetic testing that tells you about the whole methylation pathway so you can get that pathway balanced and functioning. It is distinctly non-optimal if your clinician tests only the MTHFR

genes. If these genes come back abnormal, and you are handed the current remedies, high dose methyl tetrahydrofolate and methyl B 12, your condition may be made significantly worse.

Some people can tolerate 5 methyl tetrahydrofolate and methyl B12 and do well on them. But you may not have the appropriate genetics to take significant methyl donor supplementation without developing symptoms that can take months or years to resolve. The more sick you are, the more possible it is that high dose methyl donors may be a chemical stressor for you. If you are sick enough, you may not recognize what made you worse. You may be told to stay the course, that what you are experiencing is part of the treatment. Ultimately, this is a mess.

You may now understand the importance of optimizing methylation. Among all the functions in your body, making methyl groups and methylating is the most critical next to breathing, absorbing food and fluid, and having a functioning energy production cycle. Unless you have the genetic regulation in your body functioning well, the interventions you make will not move you forward in a sustained way.

Some of you have serious, disabling disorders. These are complex problems and need to be handled precisely. You need to use techniques that have the capacity to actually get you well, to start you at A, and proceed to B, then to C, and

ultimately to wellness. You need to recover or you may spend your whole life handicapped.

You may be selling your recovery short

It is a mistake for you to choose an easy patchwork treatment while you neglect biochemical testing and a systematic approach. You will find that two years have slipped by and you are still disabled. This was not inevitable. This was by your own hand.

The people who get well are the ones who get genetic testing, do Hair Elements Analysis, Urine for Toxic Metals and Essential Elements, and Urine Amino Acids approximately every three to four months and then act based on those results. You need gastrointestinal testing approximately every 6-8 months. You get on the supplements that are indicated by the test results as soon as you are able to tolerate them, and you just keep taking those boring old supplements until you turn a corner and your realize that your symptoms are diminishing. You have energy. You can do the old moves again.

This is from the wife of a man with adult onset psychosis. He had just begun the protocol. This is not to say that there will not be twists and turns along the way, but it is certainly a hopeful response:

I am blown away by the improvement so far. We spent the other evening with our friend's family and my husband was completely composed and engaged in the conversation the entire evening for the first time in 5 years. That was the best gift ever. Awesome!

Getting results does not have to take forever. Here is another quick turn around from optimizing methylation:

You have opened my eyes to the absolute need to keep methylation central--a message I have never heard in the 10+ years my daughter has been sick. Personally consulting with you about her genetics and health and then following your prescribed protocol for her for these past few months have yielded results beyond any that we have experienced before. I would like to thank you for how vital a role you have played in all this and will continue to play as my daughter recovers her health.

It has taken me many months of hearing you say again and again "methylation first," and many months of hearing you say again and again "start slowly with what fits on the prong of a fork" to finally realize that slow and steady does indeed win the race. So please keep up your message, because you and Dr. Amy are some of the only voices out there saying these things.
Leslie Tsai, CA

More than a few people are recovering using Dr. Amy's protocol. It is well out of the realm of chance. There is genuine excitement here. It feels like a breakthrough. More customarily, after only about 18 months on a serious, careful regimen, you can have your life back. This is not forever and it is not too much to ask.

Chronic illness only sometimes gets resolved. Far more often it gets re-solved. Your genetic vulnerabilities do not go away. You must continue to bypass them with targeted supplementation. For example, anyone who needs 5 methyl tetrahydrofolate because of MTHFR+ needs it for life.

So, how can you get started on your own best solution?

Get genetic testing. Make use of all of the materials that have been made available to you. Take charge. Get it right. Right now, you may be taking the wrong supplements for your genetics. You may be avoiding all sulfur foods unnecessarily and to your detriment. You may be restricting protein intake too far. Some mistakes can stop your progress cold. Get a **Complimentary 15 Minute Conversation** and get input on what you are doing. My time is a premium value.

Many of you know that 15 minutes with me is a really valuable. Email me at NancyMullanMD@aol.com and ask for a **Complimentary 15 Minute Conversation**. I will send you a link to schedule one.

Don't let methylation biochemistry go by the wayside just because you don't understand it.

Don't let mistakes concerning methylation waste years when you can avoid them.

Come on the Mastermind Program that happens every Tuesday night at 5:00 PM Pacific Time and obtain information there. The call-in number is (559) 726-1300. Enter the access code 986935#.

If you think you are interested in using this protocol, email me at NancyMullanMD@aol.com for a **Complimentary 15 Minute Conversation** to talk it over and find out how to begin.

Bring about your best solution starting right now!

Biography

"Thank you for being such a caring and loving person. The sincerity in your voice says so much to those of us with chronic health issues.... So many times tears come into my eyes when you speak to us. I so appreciate your efforts. Thank you ever so much for all you do."

These are typical of the sentiments expressed toward Dr. Nancy Mullan after attending her weekly Tuesday Mastermind Program, getting a complimentary conversation with her, or engaging her as your medical and methylation genetics consultant.

Dr. Mullan received her undergraduate degree from the University of Pennsylvania and an MD from Tufts University. She completed an internship and residency in Psychiatry and a fellowship in Child Psychiatry at the University of Chicago Hospitals and Clinics. While there, she studied at the Chicago Institute for Psychoanalysis and taught at the Psychosomatic and Psychiatric Institute for Research and Training at Michael Reese Hospital. After coming to Los Angeles, Dr. Mullan joined the medical staff at Cedars-Sinai Medical Center

and taught at both UCLA and USC Schools of Medicine. She earned Psychoanalytic Certification from the Psychoanalytic Center of California.

Author, lecturer, clinician, with a passion for healing, and motivated to help people solve their chronic disease issues, Dr. Mullan has helped literally thousands of people to achieve their goals in treating MTHFR+, Lyme Disease, Chronic Fatigue Syndrome, Fibromyalgia, Psychiatric Disorders, Autism Spectrum Disorders, Heavy Metal Toxicity, and other syndromes.

Applying her understanding of Dr. Amy Yasko's protocol, her knowledge of genetics and nutritional supplementation, and working carefully with Dr. Amy, Dr. Mullan helps you negotiate the labyrinth of chronic illness to finally get symptom resolution.

Dr. Mullan has a deep, compassionate interest in you which comes through in her down-to-earth demeanor and candid approach to your care. She says, "Keep in touch," and she sincerely means it. She wants to stay right on top of your treatment to move it in a positive direction.

Dr. Amy Yasko and Dr. Mullan have an impressive track record for getting you to the other side of very frightening and intractable illnesses. Both doctors are tremendously invested in clinical innovation and finding what it is that will get YOU well. It makes their day!

Dr Mullan holds a weekly Mastermind Program on Tuesday evenings at 5:00 PM Pacific Time. The call in number is (559) 726-1300. Punch in access code 986935#. International access numbers are available.

If you are interested in Dr Mullan's private practice, please email her at nancymullanmd@aol.com.

Specialties:

Methylation

Genetics

Genetics Based Nutritional Supplementation

MTHFR +

Chronic Fatigue Syndrome

Lyme Disease

Psychiatric Disorders

Autism Spectrum Disorders

Women's Health

Thyroid Disorders

Gastrointestinal Disorder

Heavy Metal Toxicity