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

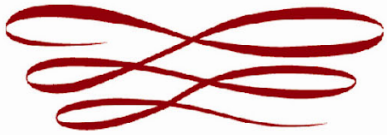

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Table of Contents

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, 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, premenstrual 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 practice. Pharmaceutical firms dominate medical education, therapeutics, research, professional publications and the mainstream media. And I had no idea that the stranglehold 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 have 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 but 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 insights about lab results and is persistent 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!

To see what is in it for you, read further. First, ***you learn 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. They 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 Facebook. You find them on Dr. Amy's forum or on her Facebook page. You will 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.

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.

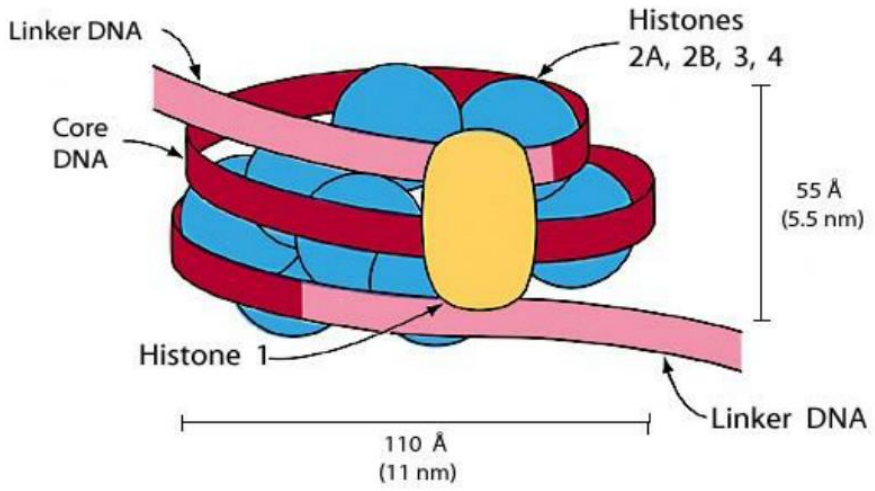

Figure 1: The DNA in the nucleus of the cell
is stored around structures called histones.

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***.

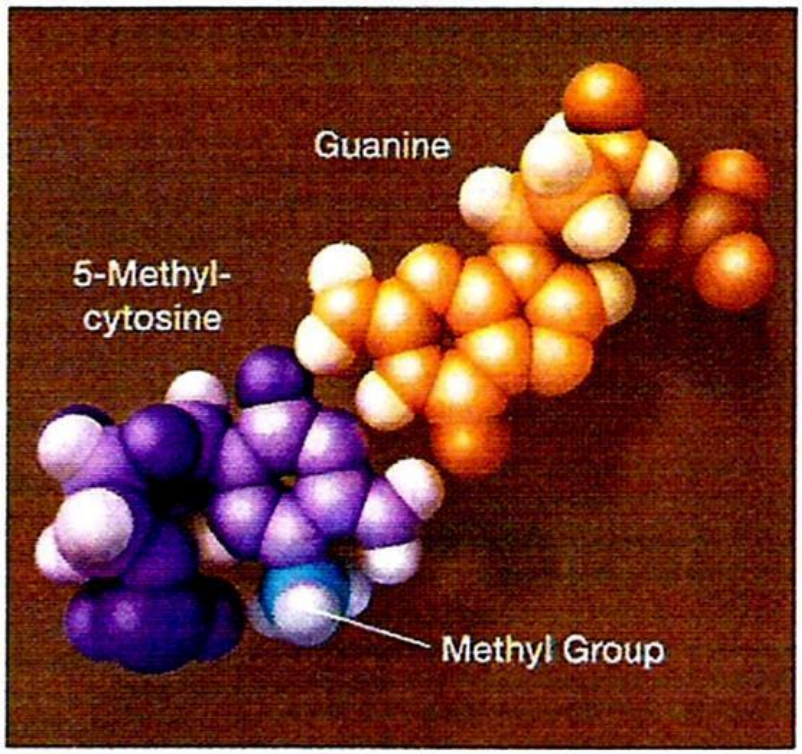

Figure 2: Epigenetic modification of the cytosine base in DNA by a methyl group.

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 erythematosus, 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 also. 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.

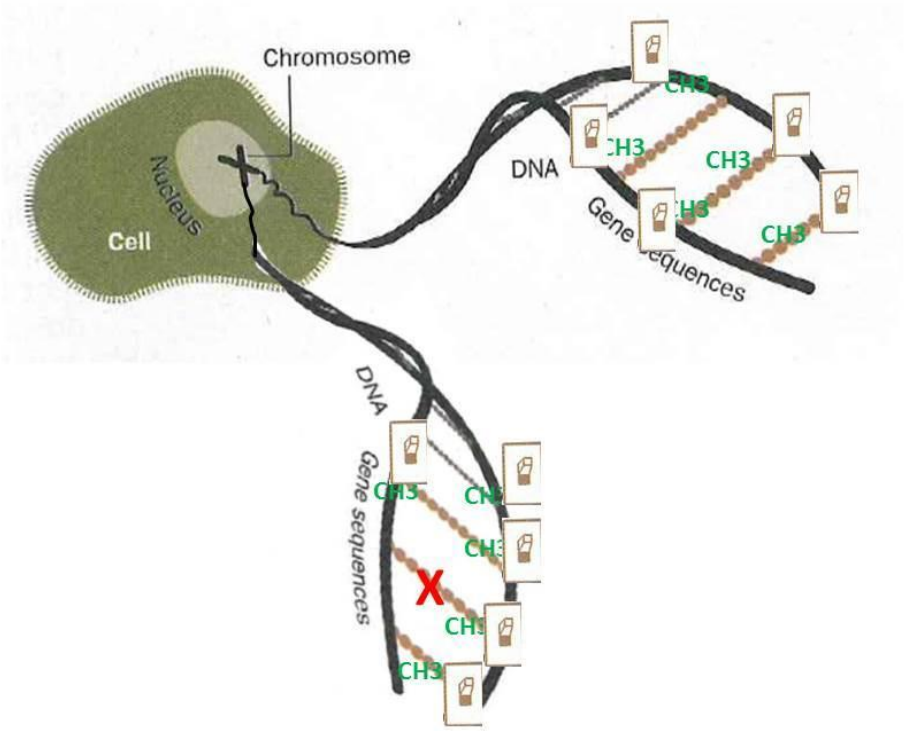

Figure 3: Epigenetic marks sit on your genes telling them to switch on or off.

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.

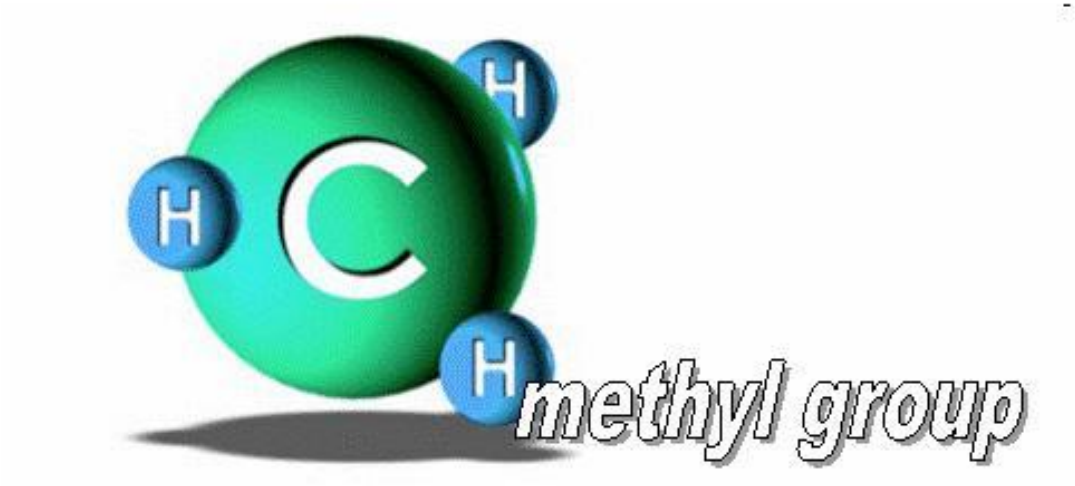

Figure 4: The small but mighty methyl group.

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 their 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 5: 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 problems 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.

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, a condition 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. Obstetricians 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.

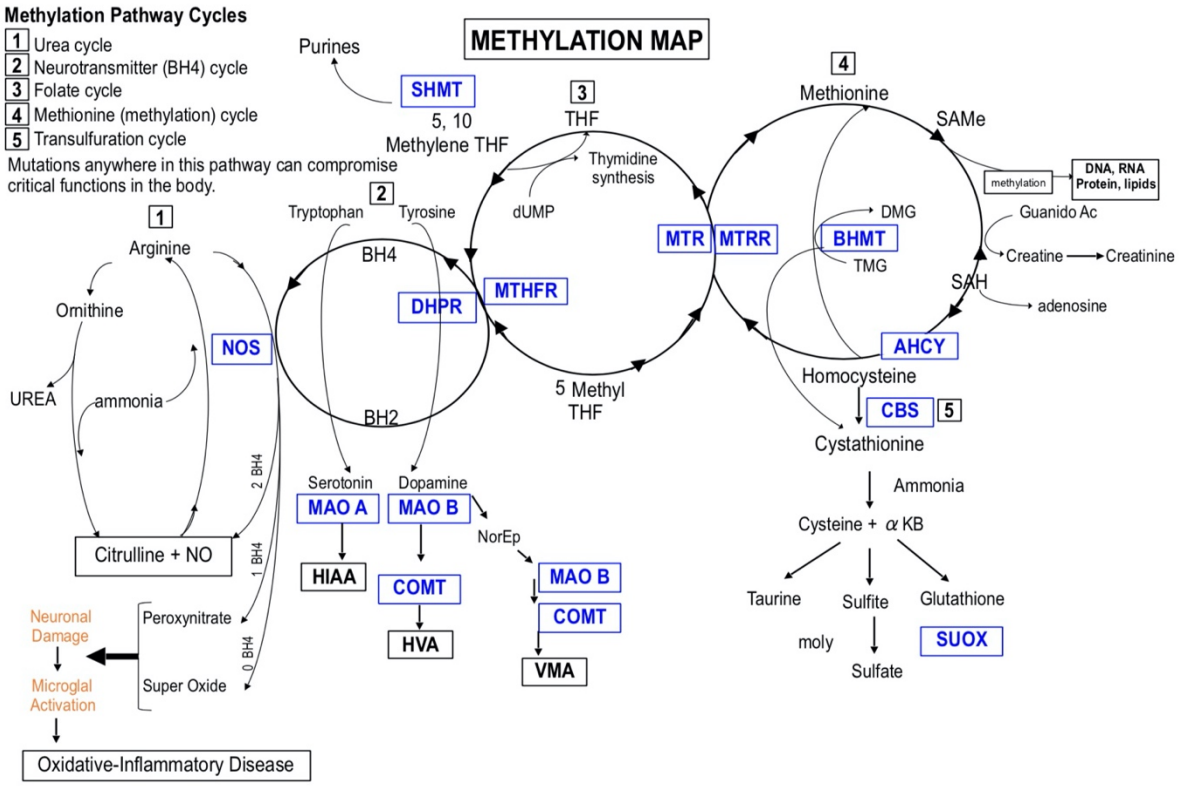

Figure 6: The Methylation Pathway is a confluence of important biochemical pathways in your body.

The 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 a 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 reactions happen over a billion times a second in your body! Over ONE BILLION TIMES A SECOND biochemicals pass methyl groups one to another in your body. The methyl group is a major player in your maintaining biochemical wellness and stability.

When homocysteine does not become re-methylated to stay in the methionine cycle, it may transit down the transsulfuration pathway, pathway 5 that comes off of cycle 4 at the 6:00 position. The transsulfuration pathway is depicted in Figure 6. The properly functioning transsulfuration pathway makes glutathione from homocysteine. Glutathione is, in its own right, the most important antioxidant detoxification molecule you make. 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. So, this particular biochemical

intersection impacts on the formation of methyl groups which you use over a billion times a second and glutathione which is your major antioxidant and detox molecule. When something goes wrong here, the impact on your body can be major.

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, so we try to activate the shortcut pathway first.

Betaine Homocysteine Methyltransferase

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

The phospholipids, phosphatidylserine, phosphatidylethanolamine, and phosphatidylcholine 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 should show 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. One of the mutations in this pathway, MTR, is associated with lithium loss from the body, but if you are chronically ill, you may have low lithium without that mutation being present. As you increase the level of lithium in your body, you may find that you need to add potassium. Iodine is often surprisingly low also. No matter whether you have Hashimoto's or not, you will not do well with low iodine. Unless you are trying to burn your thyroid out so you can take pharmaceutical thyroid for the rest of your life, iodine should be brought into the normal range in a very careful, thoughtful manner.

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 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 methylenetetrahydrofolate (5,10 methylene THF). When 5,10 methylene THF is acted on by the enzyme methylenetetrahydrofolate reductase (MTHFR), it becomes 5 methyltetrahydrofolate (5 methyl THF). It is 5 methyl THF that passes its methyl group to hydroxocobalamin, 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 hydroxocobalamin 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 downregulation of enzyme activity if only one gene is affected, but a significant downregulation if both of the two genes have SNPs. The other four locations, MTRR H595Y, K350A, R415T, and S257T produce profound downregulations 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 downregulations may require surprising amounts of B12.

Methylenetetrahydrofolate 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 there 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 further toxin accumulation. These 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 mutation at the C699T location can increase enzyme activity ten-fold, and a mutation 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+ Nucleotide. Overenthusiastic Vitamin B6 supplementation can increase CBS enzyme activity, as will elevated glucose, excess cortisol, or excess protein intake in your diet. CBS upregulation 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 upregulations 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 upregulation 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.

Many of you have been suffering with developmental disability or chronic illness for a long time. Most often you have been to doctors who may have helped a little or sometimes not at all. Some of you have even been made worse by the recommendations you have been given. New information, like the impact of MTHFR on your biochemistry, takes time to filter into the mainstream. The solutions for MTHFR issues are nutritional as opposed to pharmaceutical, so they may take even longer to see the light of day. You need answers now.

To start, get genetic testing of your methylation pathway. Use Dr. Amy’s Nutrigenomic testing. It is a blood test. Blood is more reliable than saliva. You get fewer no answers (N/A) for genes that they cannot find. Saliva testing is considerably less expensive, but sometimes you get (N/A) for important genes. 23andme Health and Ancestry DNA testing is widely used.

3 Mistakes Not to Make with MTHFR+

Most often MTHFR+, Developmental Delay 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 very much about 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 themselves. 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 or even 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, you will still need a good local doctor at times in order to be examined, get a mainstream diagnosis, and get their particular testing, so you can put all the information together and 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, overtly or covertly 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 thinks will 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 and its related infections. They may be appropriate. But they may also be a total disaster if you are truly chronically ill. You are aware of this if you have been in the chronic disease community for any length of time at all.

Prolonged or multiple oral antibiotic administration can be one of the interventions that is suggested when a mainstream physician approaches chronic illness. If your methylation processes were functioning, your body would use its own immune system to combat the infection. Unless your own immune system is working, prolonged, high dose, multiple oral antibiotics may not work anyway and you can destroy the lining of your gastrointestinal tract with this approach. Then you will not be able to absorb the nutrition in your food. Then how is your immune

system supposed to function? It won't. And you may go from bad to worse, and lose hope of anything ever getting you well.

You have to be healthy to tolerate oral 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.

If the flora in your gastrointestinal tract is already compromised, and you start pounding your body with oral 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 be very helpful, but if you have the wrong genetics for them, 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 toxic metals, and when you kill them precipitously with an intravenous solution, those toxins dump into your system.

Unless your methylation pathway is working efficiently enough to make glutathione, you won't be able to detox toxins effectively and they will cause symptoms. This has nothing to do with a Herxheimer reaction or doing anything positive about any illness you may have.

IV Glutathione is often given with or following Vitamin C. This may help mop up the immediate toxic spill, but you need to be making your own glutathione to continue the cleanup as you shed virus. So, you need a functioning methylation pathway to get the benefit from these IV's.

Glutathione has sulfur in it. If 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 IV glutathione may really make you sick. You get symptoms of sulfur toxicity and never get much benefit from the glutathione at all.

Beyond that, 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 upregulates the CBS enzyme, an 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 upregulation 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. 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 activate and many functions in your body will perform 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 multiple significant 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 methyltetrahydrofolate and methyl B 12, your condition may be made significantly worse.

Some people can tolerate 5 methyltetrahydrofolate 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 right up there along with respiration, absorbing food and fluid, and having a functioning energy production cycle. Unless you have the genes in your body methylated well so that they function optimally, the other 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 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 genetic and 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 done by your own hand.

The people who get well are the ones who get tested and get on the supplements that are indicated by the test results. You keep taking the supplements indicated by the most current testing until you turn a corner and you 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 his was 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.

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 methyltetrahydrofolate 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. You may be getting the wrong advice.

Why stumble around in the dark? You can go for weeks trying a solution that is flat out wrong for you, and then try another one that doesn't work any better.

Some mistakes can stop your progress cold. You end up feeling lost and desperate. You lose hope. I help people just like you all of the time.

Get an Exploratory Conversation with me. In this 30-minute conversation, I will listen to the issues you have, look at the lab tests you email me, tell you what I think, and leave you feeling relieved. What I tell you will make sense. You will feel that there is a path forward, that you have a doctor who 'gets it.'

There is a reduced fee for this conversation. It is quick and easy and does not involve filling out long forms or becoming a patient. I can clarify your confusion and pull you out of the muddle.

We will

- talk about the symptoms that you are having
- get some ideas about what may be causing them
- review the interventions you have already tried
- assess why they may not have moved you forward, and
- discuss what you need to do next to make progress.

Together we can work on your solution.

Contact me at NancyMullanMD@aol.com and ask for this time with me.

I look forward to being able to help.

Biography

Some people call Dr. Nancy Mullan the **MTHFR genetic medicine expert**.

Dr. Mullan works with people who have the MTHFR mutation and the chronic health issues it can cause. She uses diet and genetics based nutritional supplementation to help you increase energy, feel strong and vital, and to reconnect with love and joy. Dr. Mullan has a passion for precision and getting it right. She says, "Pharmaceutical symptom removal is not a solution, although it can be useful. The underlying cause of your problem needs to be addressed." She further states, "Chronically ill people are desperate for symptom resolution. Your lives are devastated by disease processes. I want to offer you something better than mainstream solutions." And she does this. She negotiates the labyrinth of chronic illness to finally get you to symptom resolution.

Dr. Mullan has studied at a number of exceptional institutions: the University of Pennsylvania, Tufts University School of Medicine, and the University of Chicago Hospitals and Clinics. She excels at integrating the results of biochemical and genetic testing into sustained clinical improvement. She has succeeded with patients who confounded the specialists at Massachusetts General Hospital, the

Mayo Clinic, the Cleveland Clinic, Stanford, and many well-known integrative medical doctors. When recommending her, her patients say, “This is the woman you need to talk to. She really knows how to handle tough clinical problems.”

With deep and compassionate interest, Dr. Mullan relates to you with a candid and down-to-earth demeanor. She has an impressive track record for getting you to the other side of very frightening and intractable illnesses. She is tremendously invested in clinical innovation and finding what it is that will get you well.

Dr. Mullan’s specialty areas are MTHFR+, Methylation Genetics, and genetics based nutritional supplementation. Within this context, she most often works with people who have Chronic Fatigue Syndrome, Psychiatric Disorders, Developmental Delay, Autism Spectrum Disorders, Gastrointestinal Disorder, and Heavy Metal Toxicity.

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