

---

---

# Exercise for the Mind

---

Fall 2006

---

## METHYL MAGIC !

by *Stanford Field*

### WHY IS METHYLATION IMPORTANT?

Methylation ( the chemical transfer of a  $\text{CH}_3$ - group) is an essential metabolic process that takes place in each of the cells of the body. **Adequate methylation is required to attain a state of maximum physical and mental health.** Conversely, lack of sufficient methylation is associated with poor health that is reflected in conditions such as heart disease, stroke, cancer, loss of memory, depression, chronic fatigue, arthritis, autoimmune diseases and aging.

This report will discuss the physiology of specific methylation reactions, how to determine whether adequate methylation is occurring and the nutrients that are required by the body to achieve methylation.

### EVENTS LEADING TO THE DISCOVERY OF THE IMPORTANCE OF METHYLATION

**Mid-1800s:** European pathologists discovered that blood clots formed layers on the internal lining of arteries. These layers became calcified into tough, hardened arteries. That disease became known as "arteriosclerosis."

**1920s-1930s:** The amino acid "methionine" was discovered, and it was subsequently found to be essential for human life. Afterward, the amino acid "homocysteine" was discovered, but its importance was not known for many years.

**1933:** At the Massachusetts General Hospital, an eight-year old boy, with a rare inborn error of metabolism, died of a stroke. An autopsy showed that he had advanced

arteriosclerosis throughout his body, especially in the arteries of the heart, neck and legs. This provocative case could not be explained and was buried in the archives and forgotten.

**1950s:** A methionine derivative, s-adenosylmethionine (SAM) was discovered at the National Institutes of Health in the United States. SAM was made from methionine, a source of a methyl group, adenosine triphosphate (ATP—the energy and adenosine source) and liver enzymes to catalyze the methylation reaction. Subsequently, it was found that **SAM mediated (carried out) nearly all methylation reactions in humans** (and probably other primates). Primates are humans, apes, monkeys and related mammals.

**1960s:** In Ireland, the disease called "homocystinuria" was discovered. Homocystinuria is a metabolic disorder characterized by the dislocation of the lenses of the eyes, chronic fatigue, mental retardation, psychiatric disturbances, and thromboembolic episodes. Thromboembolism occurs when a blood vessel is blocked by a clot (embolus) carried into the bloodstream from the site of formation of the clot (as in major surgery). A clot in the carotid arteries leading to the brain, for example, is likely to cause a stroke and death in parts of the brain.

In homocystinuria, the liver is unable to dispose of homocysteine because of a genetic error in the enzyme that converts homocysteine into cystathionine which would then be metabolized to useful products. Homocysteine accumulates to levels that are 10-100 times what is normally found. Homocystine (the condensation of two homocysteine molecules) also accumulates, and it is

**Exercise for the Mind** is written by Stanford Field (BS chemical engineering [Penn State], 1951; MS meteorology [US Naval Postgraduate School], 1955). His chemical engineering career was in the oil and petrochemical industries. In 1993, he retired from Stanford Research Institute where he had been Director of Energy Programs. Since that time, he has been avidly studying biochemistry and physiology with the aim of staying healthy. This document is written to add to the general knowledge of interested readers. The publication has neither profit nor political motives.

Too soon old,  
Too late schmart

Getting schmart now,  
Getting old later

↑  
Knowledge

detected in the urine (homocystinuria) as the body desperately tries to rid itself of homocysteine.

**1960s:** Pathologists in the United States (most notably being Kilmer McCulley, MD) began to connect the dots accumulated over the previous century. The eight-year old boy had probably died of homocystinuria. Subsequent animal experiments verified it. **Dr. McCulley developed the homocysteine theory which predicts that a dietary imbalance between too much methionine (an amino acid derived from protein) and a deficiency of methylating nutrients (needed to detoxify excess homocysteine) is the underlying cause of death and disability from vascular disease.**

**1950 –2000:** The developments in biochemistry gradually led to the realization that the transfer of a methyl group occurred in many biochemical reactions that were critical to many aspects of health.

### METHYLATION REACTIONS RELATED TO NEUROENDOCRINE FUNCTION

Sensory inputs from all parts of the body (external as well as internal) flow to the brain as electromagnetic energy (in both serial and parallel flows) where the information is integrated and stored. This sensory information is received by cells (at their membranes) and results in **perception** which is the awareness of the stimulus. The electromagnetic signals received by neurons act in concert with chemical neurotransmitters to effect various physiological actions.

- **Production of Acetylcholine:** The reaction of choline (**trimethylaminoethanol** — a compound containing three methyl groups) with an acetyl group (abundant from acetyl coenzyme A in the energy generation system of each cell), forms acetylcholine which is the main chemical neurotransmitter of the cholinergic nervous system. In such a system, an electromagnetic impulse, traveling along an axon at the speed of light, reaches a nerve ending and causes the liberation of acetylcholine into the synapse (the space between neurons). That neurotransmitter then stimulates a receptor on the dendrite of the receiving neuron which causes an action to be taken. Acetylcholine controls all muscle movements in the body including the heart, lungs and digestive tract, and acetylcholine also plays a vital role in memory.

Acetylcholine has to be removed from the synapse before the next message can be transmitted. In an instant, the enzyme acetylcholinesterase metabolizes the acetylcholine into acetic acid and choline for recycling.

When scientists wanted to invent a toxic substance for war, they developed “nerve gas” which deactivates the acetylcholinesterase which results in excessive acetylcholine build-up in the synapses. That causes the receiving muscles and organs to work hard and fast until the convulsions cause exhaustion and death.

The organophosphate and carbamate pesticides that are part of our toxic world, kill insects by deactivating acetylcholinesterase. The pesticides that we unknowingly

inhale and ingest with our food are directly descended from research for chemical warfare.

- **Production of Epinephrine (adrenalin):** The adrenal glands, located on the kidneys, are the source for norepinephrine and epinephrine (catecholamines) — time out for some etymology: “ad renal” means “adhered to the kidney” and “epi nephron” means “upon the kidney.” The “nor” in norepinephrine comes from German scientists. “nor” means “nitrogen ohne radical.” In English, that means “nitrogen without a radical [methyl group]”. So, when cortisol induces the enzyme that **adds the methyl group to norepinephrine**, the “nor” can be dropped and norepinephrine becomes epinephrine.

On an electromagnetic signal from the sympathetic nervous system, the adrenal glands release stored epinephrine and norepinephrine directly into the bloodstream (typical of a hormone) to produce a reactive or emergency (“fight or flight”) physiological effect. This all occurs in an instant.

Under the stimulation of a modest fall in plasma glucose from 90 mg/dl (normal) to 60 mg/dl (hypoglycemic) that occurs slowly, epinephrine concentration in the plasma rises from 30-40 pg/ml (basal) to 230 pg/ml (hypoglycemic). Glucose is rapidly mobilized from storage in the muscles and liver and sent to the brain as the first priority. Eventually, the hypoglycemia is mitigated and glucose is brought back into a temporary balance that becomes longer lasting when food is eaten.

- **Detoxication of Excess Neurotransmitters:** When an extraordinary sensory stimulus is **perceived**, the need to react can result in an instantaneous electromagnetic impulse that results in the rapid release of a neurotransmitter from storage into a synapse and the subsequent creation of additional neurotransmitter. An example would be any life-threatening situation. When the threat has diminished or gone, the neurotransmitter is reabsorbed into storage (re-uptake). However, the excess beyond the storage capacity must be detoxified to restore balance. Two important enzymes are used to effect the detoxication: (1) monoamine oxidase [MAO] and (2) catechol oxygen methyltransferase (COMT).
- **Detoxication of Excess Steroid Hormones:** Steroid hormones include adrenocorticoids (cortisol, aldosterone, dehydroepiandrosterone [DHEA]), estrogens (estrone, estradiol, estratriol), progesterone, and androgens (testosterone, dihydrotestosterone [DHT] and androstenedione).  
The steroid hormones act on target cells to regulate gene expression and protein biosynthesis. The steroid hormones are present in

extremely low concentrations, but they exert potent physiological effects.

When there is a build-up of excessive steroid hormones, the body also uses the enzyme, **catechol oxygen methyltransferase (COMT)**, to attach a **methyl group** in the first part of the detoxification process.

#### METHYLATION REACTIONS RELATED TO DNA

- **Methylation is Required to Repair DNA:** A major factor in aging is damaged DNA. This damage prevents a cell from adequately reproducing proteins that are required for life. Furthermore, lack of **methylation** of DNA causes DNA chain breaks and mutations that are associated with cancer. However, damaged DNA can be repaired, and one of the requirements for that repair is to have adequate methylation activity.

This is to understand some of the biochemistry of DNA methylation: the enzyme DNA methyltransferase facilitates the DNA methylation reaction by positioning s-adenosylmethionine (SAM) and the cytosine base of DNA very close to each other.

#### MORE METHYLATION

- **Methylation in the Energy System:** The brain consumes 10-15 times as much energy as the somatic portion of the body per unit of weight. To put it another way: the brain consumes ~ 20% of the body's energy use to analyze all incoming sensations, to secrete neurotransmitters, and to power all electromagnetic communications among neurons. The brain is always awake and active to power the nervous system. So what about methylation?

**The methylation of guanidinoacetic acid forms creatine.** During times of energy surplus, creatine is phosphorylated to phosphocreatine using energy in the form of adenosine triphosphate (ATP) which is converted to adenosine diphosphate (ADP). Conversely, when energy demand increases, phosphocreatine is converted to creatine to provide the energy for the conversion of ADP to ATP. So, phosphocreatine provides the incremental energy for use during peak energy demands. This is how electric utility systems work by using natural gas and fuel oil from storage to meet peak electricity demands.

Incidentally, in Alzheimer's Disease, phosphocreatine use for energy is highly inhibited (>95%), particularly by mercury which deactivates creatine kinase (the enzyme that converts creatine to phosphocreatine and vice versa).

- Creatine production is the largest demand for methyl groups in the body. Supplementation with creatine, especially under heavy energy demand conditions is especially important. Even if you are out hiking or playing tennis, putting creatine and/or phosphocreatine in your water bottle would help your energy system.

**Bottom line: supplementing with creatine reduces the demand for methyl groups for energy use and leaves more methyls available to lower homocysteine, detoxify, repair DNA and make melatonin for a good night's sleep.**

- **Methylation to Make Melatonin:** Melatonin is a hormone produced by the pineal gland (the size of a kernel of corn) in the center of the brain. It has been found in every animal and plant from human beings to the primitive one-celled algae that evolved more than three billion years ago.

Melatonin has many beneficial functions in the human body. For example, melatonin is found in high concentrations in the nucleus of cells where it is involved in the protection of DNA. Melatonin is deficient in Alzheimer's patients who produce less than half the melatonin of normal people of a comparable age. Melatonin is associated with longer life as shown in experiments with calorie-restricted rats. Those rats produced twice as much melatonin and lived substantially longer than the rats who were well fed.

People who go to bed at the onset of darkness and sleep 7-9 hours are in better health and live substantially longer than those who stay up subjected to the harmful electromagnetic radiation and excitement of late-night television. Melatonin production is inhibited not only by the light but also by the stimulative effect of the TV programming. Incidentally, excess caffeine has a similar negative effect on melatonin production.

The body makes melatonin from tryptophan in the diet. Tryptophan is an amino acid that is obtained from eating protein. The average protein content, in weight-percent, of various food types are: seafood 21%, nuts and seeds 17%, meats 15%, dairy and eggs 9%, grains 9% and vegetables 6%.

The chemical pathway is like this: tryptophan is converted to 5-hydroxytryptophan (5HTP); then to 5-hydroxytryptamine (serotonin); then to N-acetylserotonin which is **methylated** to N-acetyl-5-methoxyserotonin which is **melatonin**.

- **Oxidized Cholesterol is Dangerous:** Autopsies of young men killed in the Korean (early 1950s) and Vietnam (late 1960s) wars showed that the men had significant **atherosclerosis (cells of arteries combine with protein and lipids to make plaques which gather cholesterol to form a blockage which becomes calcified)**. The primary cause of the atherosclerosis was traced to the ingestion of **oxidized cholesterol which is inflammatory**. So, what were they eating?

They were eating **powdered eggs** and **powdered milk**. The water had been removed by **spray drying** to avoid the need to transport so much water for the long distances from the United States. The spray drying process is a continuous operation in which almost any pumpable liquid can be converted into free-flowing powder. The spraying drying operation is conducted at 400-700 degrees F. (higher than oven baking

temperatures). It is high enough to ensure that the **cholesterol in the eggs and milk will be oxidized**. Spray-drying at high temperatures is the cheapest way of removing large amounts of water. Incidentally, if you order scrambled eggs in restaurant and the eggs presented to you are uniformly yellow, it is likely that they were made from powdered eggs.

Many people, who do not want to eat meat or farmed fish because of a justified fear of ingesting toxic contaminants, turn to powdered whey protein or powdered egg protein which contains oxidized cholesterol if it was sprayed-dried at high temperature. **However, some whey protein is processed at ambient temperatures to avoid denaturing physiologically valuable proteins and preventing the oxidation of cholesterol. That is the whey to use!** To make the situation more understandable, a brief review of milk processing is in order.

Whey protein is a by-product of the cheese-making process. To make cheese, milk is poured into a cheese tub and a bacterial culture is added. The milk is heated to about 85 degrees F and enzymes (rennin and pepsin) are added to coagulate the milk. Within 30 minutes, the milk becomes thick (like a pudding). The mixture is cut with special knives and separated into two parts: the solid curds (cheese) and the watery liquid whey. The whey liquid is about ninety percent of the product, and the curds are ten percent.

The **most profitable and most dominant (heavily advertised) route** for making whey powder is for processors is to spray dry the liquid whey at high temperatures to remove the water. The dry, yellow powder (80% protein) is packaged for sale. **Each 40g of whey protein powder contains 30 mg of cholesterol that was oxidized at the high temperature of spray drying**. The cholesterol (fat-soluble) is in the whey because only a crude separation is made between the cheese (mostly fat) and the whey (mostly protein). **The intake of oxysterols contributes directly to arterial inflammation and the consequent atherosclerosis (blockage of coronary arteries with oxidized cholesterol and calcium plaques).**

Filtration processes that operate at ambient temperatures (40-90 degrees F) produces a flaky powder that is high in protein (90%) and has no oxidized cholesterol. This route is more expensive, less known and far healthier.

- **Other Whey Considerations:** Cows are injected with bovine somatotropin (also known as recombinant **growth hormone**) to increase their milk and meat production. **The growth hormone causes existing cancer to grow**. Somatotropin is a protein-based hormone and thus, essentially all of it is in the whey. The concentration found in the whey is up to 10,000 parts per trillion (pg/ml) which exerts strong physiological growth reactions on a cow. This is **far more** than enough to do the same to a human. Furthermore, **antibiotic residues** are detected in commercial milk. It is likely that they are also in the whey.

A better option to spray dried whey powder is to use a **liquid amino acid concentrate** (Twinlab Amino Fuel) that uses pancreatic enzymes to convert whey protein, egg protein and other animal protein into amino acids at low temperature. This avoids oxidizing cholesterol, but it does not solve the growth hormone contamination.

Another excellent option is to use **rice protein concentrate (Nutribiotic)**. The processing sequence follows: whole brown rice is ground into a fine flour. Filtered water is added to form a thick slurry. Enzymes are added in different stages to break down and separate the carbohydrate and fiber from the protein portion of the whole grain. All processing temperatures are kept below 90 degrees F. The concentrate is 80% protein with zero cholesterol and therefore, no oxidized cholesterol. There are no hormones and the rice protein is free of common food allergens normally associated with soy, milk and egg proteins.

There are other **protein concentrates that are made from vegetables, various brans and mushrooms**. They are in the beneficial category if they do not contain genetically modified material which allows greater pesticide residues. Also be certain that aspartame is not used as a sweetener in any of the protein that you eat. Now, back to the main subject of methylation.

- **Cell Communications are Enhanced by Methylation:** Cells are able to act in concert with one another and remain coordinated in their activities only as long as information is continuously passing back and forth among them (**electromagnetic biocommunication**). It is this constant and instantaneous (speed of light) communication process that provides each cell with essential feedback from the body as a whole organism and from the environment in which it lives. **The ability of cells to communicate instantly is vital to health.**

The skins of cells are composed of a **bi-layer of protein and phospholipids with antenna-like structures that receive electromagnetic signals**. These electromagnetic waves change the shape of membrane proteins to generate signals that regulate cellular activities. The communication speed and activity is dependent on the flexibility of the cell membranes. The most flexible membranes are found in cold water ocean fish whose fatty acids, when eaten, can make human membranes flexible. At the other end of the membrane composition spectrum are long-chain saturated fats and cholesterol that make cell membranes stiff and less able to communicate.

Some main components of flexible cell membranes are phospholipids. **The methylation of certain phospholipids increases membrane flexibility. For example, phosphatidylethanolamine is trimethylated by s-adenosylmethionine (SAM), in the liver, to form phosphatidylcholine which is a primary component of cell membranes.**

- **Control of Histamine Excess by Methylation:**

Histamine is chemical messenger that is stored in the mast cells and basophils of the immune system. It is released at sites of trauma, inflammation, allergic reaction and asthma. The release of histamine in trauma contributes to the dangerous lowering of blood pressure that can lead to shock. In inflammation and allergic reaction, histamine causes enlargement of blood capillaries and accompanying reddening of the skin. In asthma, histamine can choke and inflame the bronchial tubes, making it difficult to breathe. Using different receptors, histamine also controls gastric acid (HCl) secretion.

**When the need for histamine has ended, the excess histamine is deactivated by methylation to methylhistamine, and the immune system is brought back to balance.**

## THE SPECIAL CASE OF HOMOCYSTEINE

- **Homocysteine: Why is it dangerous?**

**Homocysteine is a powerful oxidant that attacks the lipid membranes of the endothelial cells that line the arteries and veins of the circulatory system.** Inflammatory mediators are then released that induce blood clotting factors at the site of damage. Platelets and fibrin form a mesh that is followed by cholesterol to form a patch for the injured area. However, the **cholesterol is promptly oxidized to oxysterols by homocysteine and associated thiolactone.**

A dangerous chain reaction of oxidation ensues, but that's not the end of it. Homocysteine blocks the production of nitric oxide in the cells that line the blood vessels. The loss of nitric oxide causes the cells to lose their pliability and to become stiff and thickened with calcium deposits. The entire aggregate forms a tough and hardened patch which seals the damage, but at the same time, blocks the blood flow. This phenomenon is labeled "arteriosclerosis."

- **What Causes Unsafe Homocysteine Levels?**

The homocysteine theory is based on the fact that a dietary **imbalance between too much methionine** (an essential amino acid) and a **deficiency of methylating nutrients** (B6, B12, folic acid and methyl donors such as trimethylglycine [also known as betaine] and trimethylaminoethanol [also known as choline]) **is an underlying cause of death and disability from vascular disease.** The recommended intake of methionine for a 160 pound person is about 1000 mg/d. One half pound of fish or meat contains 1200 mg of methionine. High protein diets that are effective for weight loss are also a source of excess methionine.

- **Homocysteine and Arteriosclerosis**

The buildup of homocysteine in the body leads to the overproduction of homocysteine thiolactone — a highly reactive form of homocysteine that causes low-density lipoproteins (LDL) to become aggregated. The LDL-homocysteine thiolactone aggregates are released into the

bloodstream from the liver. Then these aggregates are taken up by macrophages of the artery wall to form foam cells of early arteriosclerotic plaques. These foam cells degrade the LDL-homocysteine aggregates and release fat and cholesterol into the developing plaques. The foam cells also release homocysteine thiolactone into surrounding cells of the artery wall. As a result, highly reactive oxygen radicals accumulate within cells and damage the cells lining the arteries. The damage to the arteries evokes blood clot formation and the formation of fibrous tissue which becomes encrusted with calcium deposits (arteriosclerosis)

## DETOXICATION

To maintain a strong, healthy body, it is necessary to continuously detoxicate normal metabolic poisons. Methylation is an important part of that process. Furthermore, it is absolutely necessary to minimize the accumulation of environmental chemicals that are poisoning us. Detoxication in the body takes place in two distinct phases:

Phase I of the detoxication process takes lipophilic (fat-soluble) molecules and makes them water-soluble (polar). This task is effected by oxidoreductase enzymes that transfer electrons to and from fat-soluble toxins. These enzymes are collectively called the "cytochrome P450 enzyme system." They are typically found anchored to the membranes of the endoplasmic reticulae and the mitochondria within cells. Cytochrome P450 enzymes are responsible for all molecules that require conversion to water-soluble forms including food-related toxins, most drugs, steroid hormones, neurotransmitters, eicosanoids, bile acids and caffeine. Food pesticides and fungicides have been shown to inhibit cytochrome P450 enzymes.

The water-soluble molecules from Phase I detoxication are reacted with chemicals in the Phase II group that are catalyzed by Phase II enzymes called "transferases." The transfer reactions that occur in Phase II detoxication are typically referred to as "conjugation" reactions because of the joining together of Phase I-activated toxins and Phase II chemical groups. There are five basic types of conjugation reactions in Phase II. They are as follows:

- Sulfation — Uses glutathione (a tripeptide consisting of glutamic acid, glycine and cysteine) and other sulfur sources such as methyl sulfonyl methane (MSM) and dimethyl sulfoxide (DMSO). Glutathione is generally regarded as the most important thiol (—SH) in humans. Glutathione can cause cancer cells to redifferentiate to normal cells. Glutathione is part of the chemotaxis effect that allows immune system phagocytes to engulf and digest microorganisms, cellular debris and foreign particles.
- Methylation — Uses methyl groups from molecules such as trimethylglycine (TMG),

trimethylaminoethanol (choline), dimethylaminoethanol (DMAE), and dimethylsulfoxide (DMSO). **Methylation deficiency has been linked to schizophrenia, Alzheimer's disease, Parkinson's disease, depression, cancers and general aging.**

- Glucuronidation — Uses glucuronic acid from a chemical such as calcium-D-glucarate.
- Acetylation — Uses an acetyl group from a chemical such as acetic acid (vinegar). The body's energy system has an abundant supply of acetyl groups in the form of acetyl coenzyme A.
- Acylation — Uses one of three amino acids (glycine, glutamine or taurine).

Best wishes for a healthy life,

Stanford Field  
20730 Celeste Circle  
Cupertino, CA 95014

408-255-1784

[toolateschmart@yahoo.com](mailto:toolateschmart@yahoo.com)