SMART LIFE FORUM

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Dr. Richard Kunin, M.D.

Methylation and Megavitamins

Cubberley Center, 4000 Middlefield Road, Room H1, Palo Alto
Thursday, December 21, 2006 at 7:00 pm

Future Speaker:
January 19,2007: Robert Lustig, MD, What's Really Behind the Childhood Obesity Epidemic

Meet Dr. Richard Kunin

Inspired by Dr. Linus Pauling's work with vitamin C and antioxidants in orthomolecular medicine, Dr. Kunin has worked for over 40 years in the development of a more physiological approach to medicine. His 1973 discovery of manganese as a cure for drug-induced dyskinesia (muscle- movement disorder caused by drug therapy) was the first orthomolecular research to verify the efficacy of mineral therapy. His studies on the effects of niacin (1975) were first to identify prostaglandins in the niacin flush and aspirin as an antidote.

Dr. Kunin's 1974 innovation, The Orthocarbohydrate Diet™ was the first clinical research of individualized carbohydrate-protein-fat effects on mood, energy, and weight control. The "Listen To Your Body Diet" was published in his best-selling books "MegaNutrition" (1980) and MegaNutrition for Women (1983).

For the past 30 years Dr. Kunin has promoted a scientific approach to orthomolecular medical practice, based on laboratory testing of vitamins, minerals, amino acids, fatty acids, enzymes, and hormones. These are molecules that fit into the biochemistry and physiology of the body and regulate the process of adaptation for health and resistance to disease. Toxic molecules, including chemicals, pesticides, allergens and microbes are also measured along with all other appropriate medical tests. The recent availability of DNA testing has given new meaning to the concept of 'biochemical individuality' and supports the use of individualized nutrition, including megadose vitamin therapies.

Dr. Kunin was an invited presenter at the first Defeat Autism Now (DAN) conference in 1995, when the current epidemic of autism and developmental disorders was just gaining attention. He reported on his results of clinical laboratory testing that revealed higher than expected numbers of children with high homocysteine at the 1999 DAN conference; however the numbers were inconclusive and homocysteine has turned out to be an unreliable marker of methylation status. This has led to controversy about the role of homocysteine.

He did not publish his data at the time but this opened the door at DAN for acceptance of vaccine mercury hypothesis: that neurotoxic synergism between doses of mercury and aluminum from vaccines can block the methionine synthase enzyme complex, thus disrupting methylation and myelin synthesis at times of neonatal axon-receptor development. The convincing research of Drs. Richard Deth and Jill James has persuaded the DAN physicians that this is a plausible explanation for most of the current epidemic of autism. The schedule of vaccines containing adjuvant mercury (thimerosal) and aluminum was increased in the 1990s from 7 to 23 injections, thus exceeding the EPA limit of safety.

Clinical research into autism led also to consideration of the possible role of ischemia as a neonatal insult in its own right and this has led to a renewed interest in the impact of ischemia in all aspects of medical practice, and particularly in diseases of aging. Testing for blood factors, such as fibrinogen, homocysteine, lipoprotein(a) and LDL sub-types is proving valuable for all chronically ill patients. Cellular nutrition requires adequate blood circulation.

Dr. Kunin founded the Society for Orthomolecular Health Medicine in 1994 to honor the memory of Dr. Linus Pauling, and to promote a health-oriented and physiological strategy of medical practice, one that views mutation, nutrition, pollution, and stress in diagnosis and genomic nutrition, detoxification and adaptation as guidelines to rational treatment. While this approach is sometimes considered to be "alternative" it is sup-

ported by basic science and addresses physiological factors that enhance the healing power of the body, an area largely overlooked and under-utilized by mainstream medicine.

Main Presentation

Methylation refers to a family of biochemical reactions that involve controlled transfer of a methyl group, made up of a carbon atom and three hydrogen atoms, abbreviated CH3. Such movement of carbon atoms goes on in every cell and tissue of the body, for methylation is involved in hundreds of chemical reactions that regulate cell energy, healing, immunity and genetic expression of DNA and RNA. All of these reactions are responsive to environmental conditions. Thus methylation is a central feature of adaptation to the ever-changing physical and chemical conditions of life.

As a result of methylation, hundreds of molecular products change physically and functionally in the microscopic world of cellular biochemistry. For example the amino acid, methionine, carries an available but inactive methyl group on its sulfur atom. However, within the confines of the cell, methionine encounters adenosine as ATP and magnesium which are energized by a transferase enzyme, thus forming adenosylmethionine, or SAMe. This natural alchemy energizes the methionine so as to release its methyl group into the orbit of cellular enzymes, appropriately called methyltransferases. There are about 400 known methyl transferase reactions that produce vital products that affect our health, quality of life and survival.

The best known methylation products are:
1) Creatine, 2) Carnitine, 3) Coenzyme Q, 4) Calmodulin; all required to regulate energy and activity in every cell of the human body. Methylation also converts the phospholipid, ethanolamine to 5) choline (trimethyl-ethanolamine), essential for cell membrane structure and repair, including 6) myelin, the substance that insulates nerve fibers. Choline is also essential for the production of brain-regulating neurotransmitters: 7) acetylcholine, 8) dopamine, 9) nor-epinephrine, and 10) epinephrine. 11) Melatonin, the neuro-transmitter that initiates sleep and regulates the circadian sleep-waking rhythms is also a product of methylation, specifically of the neurotransmitter, serotonin. 12) And sarcosine, formed by methylation of the amino acid glycine, has recently attracted research attention as a treatment for schizophrenia.

And there is more, for the transfer of a methyl group from folic acid to cobalamin (B12) and thence to methionine is required in order to regenerate tetrahydro-folate, THF, which is required for methylation of the nucleic acid, uridine, which thus becomes 13) thymidine, the specific nucleic acid required for production of lymphocytes, active against viruses, cancer and microbial enemies. Failure to produce adequate thymidine hampers 14) methylation of DNA and RNA, thus depriving these genetic materials of protection against mutation. In short, methylation is an absolute requirement for immunity, fertility, and protection against birth defects, accelerated aging and susceptibility to cancer.

Methylation is also essential for production of 15) Polyamines, regulators of cell growth, mitosis, and healing. The chemistry involves decarboxylated SAM, which reacts with decarboxylated ornithine to form spermidine and then spermine in successive reactions with methyl-thioadenosine, which is decarboxylated SAM. Thus the methylation pathway produces a family of products that regulate cell division, fertility, growth, and healing.

16) Homocysteine, is a potentially toxic intermediate in the methylation process. When S-adenosyl-methionine (SAM) donates its methyl group, it becomes S-adenosyl-homocysteine (SAH), a free radical able to combine with other reactive molecules within the cell or in the blood stream. Inside the cell homocysteine is likely to react with copper for their mutual attraction is strong enough to pull copper out of its binding sites in enzymes, including tyrosinase, and possibly even the cytochrome enzymes of the mitochondria. This would hamper electron flow and lower cell energy and may explain the fact that patients with chronic fatigue states tend to have high homocysteine levels. Of course, it is well known that homocysteine also causes vasospasm, evidently by direct attack on the vascular endothelium, sufficient to dislodge cells and induce blood coagulation mechanisms.

Within the vasculature homocysteine also reacts with other homocysteine molecules, thus forming an inert dimer, homocystine, that is excreted in the urine, where it sometimes precipitates, causing kidney stones. Homocysteine can safely react with albumin and other proteins in the blood stream and the blood vessel wall. On the other hand, it can activate blood clotting by reacting with sulfur atoms in plasminogen, fibrinogen and lipoprotein(a), which amplifies coagulation mechanisms and may complicate illnesses by increasing the tissue-damaging effect of plasminogen to plasmin, which is a protease enzyme.

When homocysteine binds to the arterial endothelium it can provoke spasm of the muscle layer, thus raising blood pressure but also lowering blood flow in major arteries. Chambers and MacGregor reported an average decrease in arterial flow of 85 percent due to elevated homocysteine induced by methionine loading. The vasospasm effect lasts over four hours, long enough to cause ischemia, apoptosis (programmed cell death) and permanent organ damage, even in healthy young adults.

The good news is that the drop in arterial blood flow after the large methionine load was cut by two-thirds simply by pre-treatment with 1000 mg of vitamin C. A 500 mg dose of vitamin C proved inadequate. Thus, it is likely that vasoconstrictive ischemia is an important mechanism by which homocysteine causes hypertension, atherosclerosis and arterial aneurysm. It is also likely that homocysteine-induced apoptosis is a major part of the aging process.

On the other hand, homocysteine is not all bad. In the first place, by accepting a methyl group from the folate-cobalamin methylation pathway, homo-cysteine can be restored to methionine and SAM. And by combining with serine, homocysteine can be converted to cystathionine and then to transmethylation products of the methylation cycles, namely, 18) cysteine, 19) glutathione, 20) taurine and 21) sulfate—all valuable components of antioxidant adaptation and detoxification.

Methylation is commonly impaired by pollutants and genetic mutations.

Judging by the extremely high rate of mutation of genes affecting methylation observed in my own practice, I think it is likely that inefficient methylation is an increasing problem in the past century. It is sobering to consider that advanced countries, such as Hungary, France and USA have much higher rates of MTHFR mutation (about 30%) compared to China (about 10%). I think it is very likely that we are adapting to environmental pollution by means of rapid genetic adaptation—at the expense of the unlucky individuals who lack efficient p-450 enzymes or adequate glutathione synthesis.

I think the methylation pathway, governed by folic acid B12, acts as a pro-evolutionary pathway by up-regulating mutation in response to environmental stresses, such as famine, drought, global warming or cooling, and especially chemical pollution and heavy metals. It is very likely that accelerated mutation could be the basis for survival of the species, selected from the surviviors of the toxic holacaust.

Summary:

Methylation is a diet dependent process in which carbon atoms from food are transferred to homocysteine, thus regenerating methionine, SAMe, glutathione and dozens of other substances vital to healthy adaptation.

Methylation support is especially important because of mercury pollution of both ocean and freshwater fish and the effects of acid rain, which increase the solubility of mercury and decrease the availability of selenium and other mineral antidotes. And it is also an increasing problem due to the remarkable frequency of mutations that affect enzymes upon which methylation depends. Most patients with chronic illness, especially those that are resistant to treatment, carry mutations that weaken the efficiency of vitamins folic acid and B12. In fact, genetic testing for hundreds of my patients shows over 90% carry mutations of MTHFR (folic acid) and over 98% are mutated for MTR (B12).

These results are so extreme as to provoke extreme skepticism and concern that we already caught up in an unrecognized epidemic! However, if these observations are confirmed under better controlled conditions, the world is faced with the first genetic epidemic in medical history, one that changes our conception of evolution, human potential and the nature of health and disease. At the least, such a GENETIC EPIDEMIC challenges us to revise our understanding of health and disease.

Megavitamins and Methylation

The fact that mutations of MTHFR and MTR are extremely common, especially among those with chronic illness, is offset by the fact that most of these people are improved by use of mega- doses of folic acid and cobalamin and/or their activated forms, folinic acid, and methylcobalamin. Doses of 1 to 10 mg of each are in use and with often spectacular benefits, particularly in treating nerve-related conditions such as autism, schizophrenia, depression and neuropathy. In one compelling case report, a 50 year old woman failed to recover from painful pedal neuropathy after daily injections of cobalamin 1mg but had a sustained recovery after monthly intra-thecal injections of cobalamin.

Supplementation with methylation end-products also proves beneficial, e.g. creatine, carnitine, coenzyme Q10, choline, DMAE, sarcosine, thymidine, serine. Supplementation assures a supply of these essential metabolites and also lightens the burden of providing continuous supply of methyl groups for hundreds of other products.

The importance of methylation is clinically documented with human patients. In particular, fairly brief exposure to nitrous oxide (N20) anesthesia for as little as 60 - 90 minutes can cause demyelination and permanent brain and spinal cord injury.
(N Engl J Med. 2003 Jul 3;349(1):45-50. Comment in: N Engl J Med. 2003 Jul 3;349(1):5-6. N Engl J Med. 2003 Oct 9;349(15): 1479-80; author reply 1479-80.)
Adverse effect of nitrous oxide in a child with 5,10-methylenetetrahydrofolate reductase deficiency.
Selzer RR, Rosenblatt DS, Laxova R, Hogan K.

Other megadose vitamins also support the needs of the

methylation system. Niacin is required for synthesis of serine, which is derived by glycolysis through 3-phosphoglycerate to phosphopyruvate in a NAD dependent reaction and then by transamination to phosphoserine, which requires pyridoxine (B6). It is likely that these rate-limiting reactions are stimulated by the presence of megadoses of B3 and B6. Pyridoxine is also required for SHMT (serine hydroxy methyl transferase) the enzyme that transfers methyl from serine to THF to generate methyelene THF.

Riboflavin is required to transfer formaldehyde in folic acid cycle and larger doses enhance the MTHFR enzyme, especially in the 30 percent of trhe population with thermolabile mutation. Vitamin C is also required for optimum function of MTHFR, especially important in the face of pollutants, such as chloramines, chloride and fluoride, which are detoxified by vitamin C at megadose levels. Selenium is required by the very same MTHFR enzyme and megadose selenium can even substitute for the MTHFR enzyme in the absence of the enzyme! Magnesium is required by Methionine Adenosyltransferase (MAT) in production of SAM. Adenosine is required in the same reaction and supplementation may enhance the MAT activity, especially since mutations of MAT are not rare.

Megadose vitamins folic acid and B12 are all the more rational in response to the widespread and increasing pollution of ecosystem by heavy metals, particularly mercury, lead, aluminum and antimony, which block the folic acid-B12 and glutathione dependent methionine synthase complex.

On the other hand, methyl-accepting molecules, such as niacin and niacinamide, and amino acid, glycine, also regulate hypermethylation, when over-eating of meat (methionine) or sugar (serine) favor over-production of methylated products. Exercise may provide much of its health benefits by regulation of methyl metabolism. 'Runner's High' is almost certainly a case in point: a good work-out shunts the plethora of methyl groups generated by high protein and excess carbohydrate into creatine, thus converting the sluggish, couch-potato feeling into one of vigor and euphoria.

Until recently it was accepted that the largest consumer of methyl groups is muscle, which requires creatine phosphate to assure stable energy supply. Creatine is generated by way of methylation of guanido-acetate, derived from fragments of arginine and glycine. Old research estimated that creatine synthesis required up to 70 percent of the methyl groups cycled through the system. However the calculations did not credit dietary creatine as a significant source of creatine. Recent estimates run about equal division of methyl groups between creatine and phospholipid synthesis, with about ten percent left over for carnitine, Coenzyme Q, calmodulin, neurotransmitters, myelin and polyamine synthesis—and a few other methylated specialty products, including steroid receptors and methylated DNA, RNA and histones. Methylation is continuous, diverse and incredibly busy.

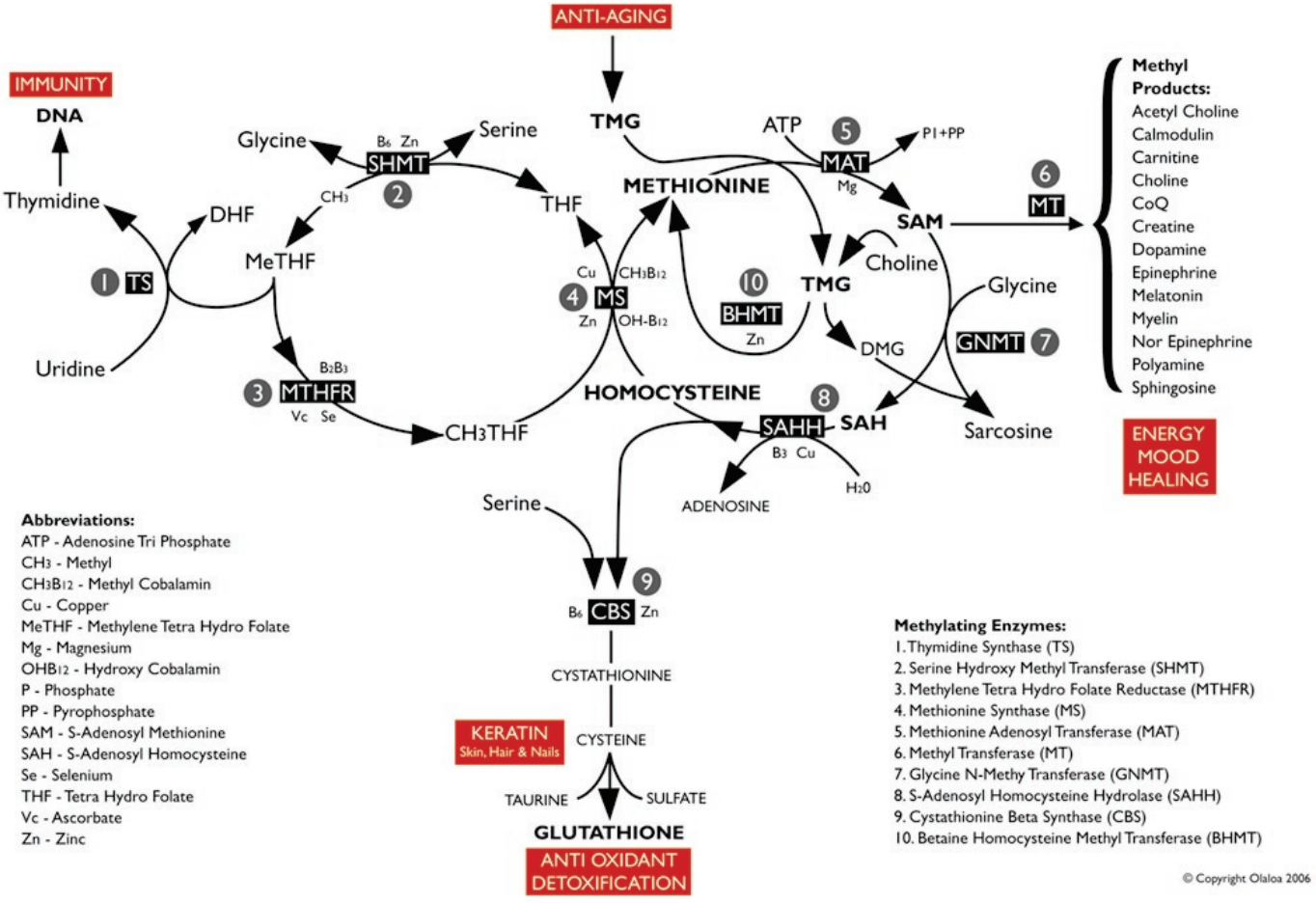
Heavy metal pollution increases requirement for sulfur-binding vitamins, i.e. thiamine, biotin and alpha-lipoic acid, which are inactivated by heavy metal-binding. ALA synthase blockade by lead and other heavy metals increases requirement for Zinc and B6 for synthesis of porphyrin, used for production of blood and for the heme component of cytochromes and oxidase enzymes, including cystathionione beta-syynthase. Higher than normal doses of zinc and pyridoxine and also of copper can reverse numerous related symptoms. However it is always wise to induce intestinal metallothioneins by supplementing with zinc for a week before treating with copper. Free copper, not bound to alubumin, ceruloplasmin and/or amino acids, is a peroxidizer and can cause adverse symptoms. This can be challenging.

Megavitamins B3, B6, C and B2 act in tryptophan-niacin-NAD-ribose system, which is responsive to megadose niacin, pyridoxine, and vitamin C and this therapy has been featured in orthomolecular medicine since the double-blind research reports with in-hospital schizophrenic patients by Hoffer, Osmond and Smythies half a century ago. The use of this megavitamin therapy has become synonymous with the title, orthomolecular, in the orthodox medical mind. However, Dr. Abram Hoffer's adrenochrome theory has been unfairly neglected though it is amply reported in his books and papers in the Journal of Orthomolecular Medicine (bibliography on-line). Kunin summarized the early megavitamin-schizophrenia studies in Roots of Orthomolecular Medicine (Ed. Huemer, 1998) and published an earlier research, on the use of aspirin to block the niacin flush reaction, in the Journal of Orthomolecular Medicine (1974). At that time Kunin proposed that a niacin-responsive prostaglandin derivative might be the link between the niacin skin flush and the benefits of niacin in treating schizophrenic patients. That theory has since been confirmed by Horrobin, who identified PGD2 as the specific agent of the niacin flush reaction.

Megavitamins are potentially therapeutic for:

1. Genetotropic enzyme blocks (cf Ames review)
2. Methylation: Vitamins B6, folic acid, B12, Betaine, and B2.
3. Malnutrition
4. Malabsorption
5. Antioxidant action (C, E, A, folic, B12)
6. Anti-Coagulation
7. Toxic metals and chemicals (assists detox; restores enzyme activity)

8. Trigonelline(B3) neuroprotective, neuro-regenerative, cancer growth inhibition
9. Retinol vs SAHH (enzyme inhibition)
10. Vitamin C-pentose effect (Dihydroascorbate stimulates)
11. Vitamin C- (protects against endothelial damage-low blood flow caused by homocysteine)
12. Antidote toxic medication (B2 vs phenothiazines; CoQ vs statins)
13. CoQ (anti-aging, anti-fatigue, anti-cancer effect)
14. Carnitine (protects myocardium from ischemia; antidote aspirin, valproic acid, phenols)
15. B6 (tranquilizer, analgesic) (at expense of potency)
16. B6 pyridoxamine chelation of copper and iron
17. Lipoic acid (Anti-aging, neuroregenerative, diabetes, erective impotency)
18. Carnosine (antioxidant, neuroprotective, cataracts)
19. Thiamine (offsets thiaminase in soy, tea and fish)
20. Thiamine, Biotin, Lipoic (detox & offset heavy metals)
21. Thiamine anti-lipidemic.
22. Vitamin K (enhances healing of bone, linings of ducts and vessels, digestion, mood)
23. Zinc (Rx copper overload and Wilson's)
24. Inositol hexaphosphate (IP-6) chelates copper and iron radicals
25. Betaine (substitutes for MTHFR-methionine synthase enzymes).
26. Magnesium (antihistamine, laxative, Rx ischemia, cardiac arrhythmia and asthma)
27. n3-EFA (arthritis, dermatitis, allergy, auto-immune, schizophrenia)
28. Glycine (tranquilizer, detox as hippurate, sedative)
29. Tryptophan (sedative, anti-depressant)
30. Tyrosine (anti-depressant, anti-addiction, Rx ADD)
31. Glutamine (immune support)
32. Arginine (vasodilator, Rx impotency, hypertension, ASHD.
33. And many more applications



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