FUNCTIONAL MEDICINE UPDATE
January 2007
ISSN 1092-1761
Vol. 27, No. 1

25 Years of *Functional Medicine Update*

Although it has been known by several different names throughout its history, 2007 will mark the 25th year of publication of *Functional Medicine Update*. As this milestone approaches, Dr. Bland summarizes the current production and administration of FMU, and looks forward to what the year ahead will bring. A new website, www.JeffreyBland.com is introduced.

Hot Breaking News

A research team from the University of Helsinki has recently published the findings from a study on vitamin D insufficiency in elderly women. The aim of the study was to examine how serum 25-hydroxy vitamin D concentrations respond to different doses of vitamin D3 supplementation, and also to determine the smallest efficient dose to maintain serum 25-hydroxy vitamin D concentration above the insufficiency level. Because insufficiency is typically accompanied by high intact parathyroid hormone (S-iPTH), the team also studied which dose would be efficient in decreasing S-iPTH concentration in the study subjects. The study authors noted a clear dose response in serum 25-hydroxy vitamin D to different doses of vitamin D3. In the study subjects, the recommended dietary intake of 15 µg was found to be adequate in maintaining an S-25-OHD concentration of around 40-55 nmol/L during winter, however if it is determined that the optimal level of S-25-OHD should be higher, higher vitamin D intakes will be needed. It was interesting to note that subjects with lower vitamin D status at baseline responded more efficiently to supplementation than those with more adequate status. The results of this study also showed that over a 12-week vitamin D supplementation with a dose as high as 20 µg/d, S-iPTH concentration was not normalized. The authors suggest the supplementation period may have been too short to affect PTH secretion. REF #1

There has been some confusion about the role of fish consumption in a healthy diet. While is has been acknowledged that consuming fish may have health benefits, such fish may also contain contaminants, which may pose health risks. An article that evaluates these risks and benefits was recently published in the *Journal of the American Medical Association*. The authors of the article thoroughly researched and analyzed reports published through April 2006 that evaluated (1) intake of fish or fish oil and cardiovascular risk, (2) effects of methylmercury and fish oil on early neurodevelopment, (3) risks of methylmercury for cardiovascular and neurologic outcomes in adults, and (4) health risks of dioxins and polychlorinated biphenyls in fish. The authors conclude that for major health outcomes among adults, based on both the strength of the evidence and the potential magnitudes of effect, the benefits of fish intake exceed the potential risks. For women of childbearing age, benefits of modest fish intake, excepting a few selected species, also outweigh risks. REF #2

The modern Western diet imposes an acid load on the body via acid-generating proteins. The effect of this diet-induced metabolic acidosis on bone mass is controversial. Epidemiologic studies have suggested a relationship among acidogenic diets and decreases in bone mineral density (BMD), as well as increased fracture incidence. A research group in Switzerland recently conducted a study to test the hypothesis that the acidogenic Western diet provides at least part of the pathophysiological basis of osteoporosis by evaluating the bone mass response to chronic alkali ingestion in humans without renal disease. Their findings showed that chronic alkali treatment resulted in a significant increase in lumbar spine and hip BMD. This study was published in a recent issue of the *Journal of the American Society of Nephrology*. REF #3

Acidosis influences the homeostasis of calcium, partly due to the influence on renal mechanisms. A number of studies from the literature have reported a relation between an increase in the body's acid load and an increase in renal calcium losses. The elderly have a decreased renal function that affects the capacity of the kidneys to excrete acid. Because of this and their generally lower intake of fruit and vegetables, the elderly constitute a risk group for acid conditions and an increased secretion of calcium and possibly magnesium. Recent evidence also suggests that metabolic acidosis can evoke a modest increase in cortisol production. Since cortisol promotes development of visceral obesity, and has a direct negative impact on insulin function throughout the body, even a modest sustained upregulation of cortisol production may have the potential to increase risk for insulin resistance and type 2 diabetes. REF #4-5

Clinician/Researcher of the Month

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Dr. S. Jill James is currently a Professor of Pediatrics at the University of Arkansas for Medical Sciences, and also an Adjunct Associate Professor in both the Department of Biochemistry and Molecular Biology and the Department of Pharmacology and Toxicology at the same institution. Dr. James has an extensive publication record, and has received substantial research grants from organizations that include the American Cancer Society, the Food and Drug Administration, the National Institutes of Health, the Environmental Protection Agency, and the Autism Research Institute. Her research interests include folic acid metabolism, oxidative stress, gene-environment interactions, plasma metabolic profiles, and polymorphisms in the folate/methionine/glutathione pathway.

Dr. Bland and Dr. James have a lengthy and thought-provoking discussion that begins with some background on the methionine transsulfuration pathway, which has been a focus of Dr. James' work throughout her career. Often working in a rat model and utilizing a lipotrope-deficient diet, Dr. James and her colleagues have studied how diet

affects this pathway. This work included a published 1994 study that suggests apoptosis may be very important in understanding multistage carcinogenesis (perhaps equally important to the dysregulation of physiological signals and mechanisms controlling cell proliferation). Data from this study supported the reasoning that the decrease in metabolic and hormonal trophic factors induced with dietary restriction could promote selective cell deletion via apoptosis. REF #6

In a study using human subjects published in 2000, Dr. James and her colleagues were able to demonstrate an important relationship: as homocysteine is elevated, S-adenosylhomocysteine (SAH) is also elevated. As the product of essential cellular methyltransferase, SAH (along with S-adenosylmethionine, the substrate) is an important indicator of cellular methylation status. Chronic elevation of SAH, secondary to the homocysteine-mediated reversal of the SAH hydrolase reaction, reduces methylation of DNA, RNA, proteins, and phospholipids. High affinity binding of SAH to the active site of cellular methyltransferases results in inhibition of the enzyme. This suggests that chronic elevation in plasma homocysteine levels, such as those associated with nutritional deficiencies or genetic polymorphisms in the folate pathway, may have an indirect and negative effect on cellular methylation reactions through a concomitant increase in intracellular SAH levels. REF #7

Dr. James discusses her extensive research on Down syndrome. There is a long-held belief among some professionals that maternal genetics are not associated with Down syndrome risk. In an article published in the *American Journal of Clinical Genetics* in 2004, Dr. James discusses an earlier published study in which she and her colleagues hypothesized that low folate status, whether due to dietary or genetic factors, could induce centromeric DNA hypomethylation and alterations in chromatin structure that could adversely affect DNA—protein interactions required for centromeric cohesion and meiotic segregation. The possibility of a genetic link stimulated several follow-up studies of the MTHFR 677C>T polymorphism, as well as several other allelic variants in the folate pathway, as possible genetic risk factors for having a child with Down syndrome. The follow-up studies were conducted in several different countries and yielded inconsistent results. In the article, Dr. James presents a possible metabolic explanation for the observed inconsistencies among different populations. REF #8

Dr. Bland and Dr. James return to the topic of homocysteine and discuss a 1998 study on postmenopausal women published in the *Journal of Nutrition*. A subclinical folate deficiency with decreased plasma folate was created among the study subjects, resulting in significantly elevated plasma homocysteine and urinary malondialdehyde, and lymphocyte DNA hypomethylation. The folate depletion also resulted in an increased ratio of dUTP/dTTP in mitogen-stimulated lymphocyte DNA and decreased lymphocyte NAD, changes suggesting misincorporation of uracil into DNA and increased DNA repair activity. The DNA hypomethylation was reversed in the study subjects. The results of the study indicated that marginal folate deficiency may alter DNA composition and that the RDA (recommended daily allowance) may not be sufficient to maintain low plasma homocysteine concentrations of some postmenopausal women. REF #9

In addition to research into the p53 tumor suppressor gene, Dr. James has also examined the methylation patterns of phosphatidylethanolamine to phosphatidylcholine and how that relates to construction of cellular membranes. Dr. James and her colleagues looked at this ratio in a study with children with cystic fibrosis (CF). Their objective was to determine whether excretion of choline phosphoglyceride (phosphatidylcholine and lysophosphatidylcholine) is increased in CF and whether loss of fecal choline phosphoglyceride is associated with altered plasma methionine cycle metabolites. The conclusions of this study were that choline phosphoglyceride excretion is increased in children with CF and is associated with decreased plasma methionine and increased homocysteine and S-adenosylhomocysteine. These findings suggest choline depletion and an increased choline synthesis by S-adenosylmethionine-dependent methylation in CF, as well as a metabolic link between phosphatidylcholine metabolism and the methionine-homocysteine cycle in humans. REF #10

Dr. James' most recent research has focused on Autistic Spectrum Disorder (ASD). She describes how her interest in ASD came about—a remarkable story in which she encountered a unique set of twins (one twin with Down syndrome and the other with autism). This meeting took place while she was conducting a study on Down syndrome, and it was then that Dr. James came to observe that the metabolic profiles of these dizygotic twins were virtually identical with respect to methionine cycle and transsulfuration metabolites. This serendipitous event led to further studies with autistic children, and the conclusion that an increased vulnerability to oxidative stress and a decreased capacity for methylation may contribute to the development and clinical manifestation of autism. REF #11

The diagnosis of autism is based solely on behavioral criteria that define deficits in social interaction, impairment in verbal and non-verbal receptive/expressive speech, and hyper-focused repetitive behaviors. Currently, there is no biochemical test for the presence of autism to support the behavioral diagnosis. Although abnormal methionine metabolism has been associated with other neurologic disorders, these pathways and related polymorphisms had not been evaluated in autistic children until Dr. James and her colleagues conducted a study.. The primary participants in this study were 80 autistic and 73 control children, but additional data about common polymorphic variants known to modulate these metabolic pathways was also evaluated in 360 autistic children and 205 controls. The results of this study were recently published in an issue of the *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*. REF #12

Dr. Bland and Dr. James conclude their discussion with a focus on the environment and the need for systematic testing of chemicals to determine neurotoxicity and a potential link to neurodevelopmental disorders such as autism. Through her research, Dr. James has come to demonstrate the environmental sensitivity of the transsulfuration pathway and the important role glutathione synthesis has in detoxification of heavy metals. Although larger population-based studies are needed, the hypothesis that a genetic component of autism could involve multiple susceptibility alleles that interact to create a fragile, environmentally sensitive metabolic imbalance is intriguing. If some children with autism are confirmed to have an abnormal metabolic profile, treatment for this form

of autism could be directed toward correcting the metabolic derangements and potentially ameliorating the autistic symptoms. REF #13-14

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